MGH having 20 allergists on staff, and BWH having 29 allergists on staff.

Within each of these institutions, allergen extracts are mixed separately by using aseptic techniques based on current USP chapter <797> guidelines but not consistent with proposed USP changes. Most commercial extracts are 50% glycerinated, and dilutions are made with sterile saline containing phenol. Studies of the sterility of allergen extracts have demonstrated that bacterial contamination is extremely rare (1 in 2,085).[9] There have been no case reports in the published literature of infections resulting from AIT injections. To our knowledge, only 1 prior study, that by Lay et al,[6] examined infectious risk and AIT. This retrospective study examined 26,795 injections administered to 272 patients over a 6-year period and found that no patients experienced fever or SSTI at the site of injection. Additionally, they found that no patients required antibiotics or other medical treatment for infection. Our study examined a significantly larger population of patients across 2 large allergy practices.

The strengths of this study include the large sample size (>130,000 AIT injections in >3,000 patients), the 10-year study period, and use of high-quality EHR data, which reduces the possibility of misclassification. Although we do not have a closed health system, our methods would have identified infections that might have been diagnosed in other practices within our health care system (eg, urgent care clinics or primary care office).

A potential limitation is that minor localized infections might have gone unreported and would not be captured in this analysis; however, any major complications would have been captured. Another limitation is that these data were collected retrospectively from the EHR using ICD-9 codes. Although ICD-9 codes have been validated to identify SSTIs,[8] identification of systemic infections with ICD-9 codes are less clear. However, we used a broad array of ICD-9 codes and adapted codes used from a prior study (Stevenson et al[7]) to identify postoperative systemic infections. Ultimately, we reviewed all suspected cases with a formal chart review. A final limitation is that racial/ethnic minorities might have been underrepresented in our cohort.

In conclusion, in this large retrospective cohort study of risk of infection with AIT, we did not find any cases of SSTIs or systemic bacterial infections from AIT injections. These findings suggest that the sterility and safety practices in place during the study period are adequate to prevent adverse infectious outcomes related to the preparation and administration of AIT.

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Increasing visits for anaphylaxis and the benefits of early epinephrine administration: A 4-year study at a pediatric emergency department in Montreal, Canada

To the Editor:

It was recently reported that at least 1.6% of the population will experience anaphylaxis in their lifetime and that 60% of the individuals who had anaphylaxis were not equipped with life-saving epinephrine.[1] Although it has been reported that food allergy and other allergic conditions have increased worldwide,[2] it is not clear whether anaphylaxis rates among children have increased in recent years. Furthermore, no study has assessed the effect of administration of prehospital epinephrine on the subsequent risk of administration of multiple doses of epinephrine (≥2) in the emergency department (ED).

As part of the Cross-Canada Anaphylaxis REgistry (C-CARE), individuals presenting to EDs or emergency medical services with anaphylaxis were recruited and followed longitudinally. Here, we describe the annual percentage of ED visits due to anaphylaxis between April 2011 and April 2015 at the Montreal Children's Hospital and assess factors associated with the use of multiple (≥2) doses of epinephrine in the ED. Although this report is limited to a single site, C-CARE includes multiple sites across Canada, but these have not participated long enough to contribute 4 years of data.

Anaphylaxis was defined as involvement of 2 organ systems and/or hypotension in response to a potential allergen.[3] Prospective recruitment involved identification of cases of anaphylaxis at the time of ED presentation by the treating physician. After consent was obtained, the physician completed a standardized questionnaire regarding patients' demographic factors, comorbidities, characteristics of the reaction, and management. The study lead (M.B.S.) and study coordinator, using International Classification of Diseases, Tenth Revision codes to identify any cases of anaphylaxis that were not identified prospectively, reviewed all visits to the ED between April 2011 and April 2015 and these cases were also included. Anaphylaxis severity was classified according to a modified grading system published by Brown.[4]

TABLE I. Percentage of anaphylaxis among all pediatric ED visits

Variable	Year 1	Year 2	Year 3	Year 4
Date	April 2011-2012	April 2012-2013	April 2013-2014	April 2014-2015
Anaphylaxis/ED cases	167/81,677	218/78,650	239/82,862	341/84,850
Percent of all ED visits, % (95% CI)	0.2 (0.18-0.24)	0.28 (0.2-0.3)	0.29 (0.25-0.33)	0.41 (0.36-0.45)
Difference vs year 1, % (95% CI)		0.07 (0.02-0.12)	0.08 (0.03-0.13)	0.19 (0.13-0.24)
Difference vs year 2, % (95% CI)			0.01 (−0.04 to 0.06)	0.13 (0.08-0.19)
Difference vs year 3, % (95% CI)				0.11 (0.06-1.7)

TABLE II. Use of medication either inside or outside of the ED for management of anaphylaxis

	% (95% CI)			
Medication	Outside ED	Inside ED	Inside/outside ED	Inside/outside in moderate/severe cases
Epinephrine	32.4 (29.5-35.5)	44.3 (41.1-47.5)	71.5 (68.5-74.3)	74.7 (71.4-77.8)
Antihistamines	42.0 (38.8-45.2)	43.9 (40.8-47.1)	73.3 (68.5-74.3)	72.4 (69.0-75.6)
Steroids	0.6 (0.3-1.4)	24.6 (21.9-27.5)	25.2 (22.5-28.1)	26.7 (23.6-30.1)
≥2 doses of epinephrine	—	4.5 (3.3-6.7)	—	—

Statistical analysis was conducted using R version 2.12.0 (R Core Team [2013]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were used to assess the percentage of anaphylaxis cases among all ED visits, patients' demographic characteristics, triggers, severity of reaction, and medications administered. For categorical variables, percentages were presented with 95% CI. Age was presented as medians with interquartile ranges (IQRs). Univariate and multivariate logistic regression models were compared to assess confounders and to determine sociodemographic factors, anaphylaxis triggers, comorbidities, and prehospital management associated with (1) reaction severity and (2) use of multiple doses of epinephrine in the ED (≥2).

The McGill University Health Centre Ethics Review Board approved both prospective and retrospective data collection.

Overall, a total of 965 anaphylaxis cases were identified (50% prospectively). The percentage of anaphylaxis cases among all ED visits more than doubled over the 4-year period from 0.20% (95% CI, 0.18-0.24) to 0.41% (95% CI, 0.36-0.45), with the largest annual increase between 2013-2014 and 2014-2015 (0.11%) (Table I).

The median age of patients with anaphylaxis across all 4 years of recruitment was 5.8 years (IQR, 2.4-11.6 years; median age of prospective cases, 5.2 years [IQR, 1.9-11.3 years] vs 6.2 years [IQR, 2.9-11.7] for retrospective cases). Almost half the patients reported a known food allergy, whereas asthma and eczema were reported in almost 20% of the patients (see Table E1 in this article's Online Repository at www.jacionline.org). Most cases (85.3%; 95% CI, 82.0-87.5) were referred to an allergist after the ED visit or had already consulted an allergist.

The major trigger was food, which accounted for more than 80% of all anaphylaxis cases, with peanut (22.2%; 95% CI, 19.4-25.3) being the most predominant (see Table E2 in this article's Online Repository at www.jacionline.org). Most reactions were of moderate severity (see Table E3 in this article's Online Repository at www.jacionline.org). The percentage of mild, moderate, and severe reactions among all cases of anaphylaxis was relatively stable. No fatalities occurred in our population. Asthma (odds ratio [OR], 2.3; 95% CI, 1.2-4.5) and eczema (OR, 2.1; 95% CI, 1.1, 4.2) were associated with severe reactions. More than 25% of moderate/severe anaphylaxis cases did not receive epinephrine inside or outside the hospital (Table II). Only 50.7% (95% CI, 45.9-55.4) of those who had an epinephrine autoinjector used it before arrival to the ED.

Factors associated with increased likelihood of receiving multiple doses of epinephrine in the ED were older age (OR, 1.1; 95% CI, 1.0-1.2), a severe reaction (OR, 17.3; 95% CI, 6.1-49.2), and anaphylaxis cases triggered by peanuts (OR, 2.9; 95% CI, 1.1-8.5), tree nut (OR, 7.2; 95% CI, 2.6-20.2), and milk (OR, 5.2; 95% CI, 1.4-20.0). The only factor associated with a reduced risk for multiple ED epinephrine doses was use of epinephrine before ED arrival (OR, 0.2; 95% CI, 0.0-0.6) (see Table E4 in this article's Online Repository at www.jacionline.org).

Our results are limited to one pediatric center, but they suggest a worrisome increase in anaphylaxis rate that is consistent with the worldwide reported increase.[2] Our annual estimates between 2012 and 2015 are higher than previously published US estimates[5] (difference = 0.09%, 95% CI, 0.05-0.18; 0.10%, 95% CI, 0.06-0.1; and 0.20%, 95% CI, 0.17-0.27, respectively).[5] Both our study and US studies reveal that a higher percentage of pediatric ED visits are due to anaphylaxis in North America compared with European centers.[6] This likely reflects differences in the prevalence of food allergies between North America and Europe.[7] Similar to other studies, food is the most common trigger of anaphylaxis in our study (82.1%), with peanut responsible for 22.2% of the cases.[2] The overall volume of visits and the volume of specific diagnoses to the ED did not change substantially between 2011 and 2015. The setting, health system, and ambulance transfer guidelines or practices did not change during the study period. In line with other studies, asthma and eczema were associated with a more severe reaction.[8]

An important observation in our study is that administration of epinephrine, before arrival in the ED, is independently associated

with a decreased likelihood of requiring multiple doses of epinephrine in the ED, suggesting that prompt epinephrine administration is beneficial. However, because of ethical considerations, it is not possible to randomize children to prehospital administration of epinephrine versus no epinephrine, precluding definitive conclusions on the benefit of prehospital epinephrine. Our results are in line with a previous observation suggesting that use of epinephrine in the community reduces epinephrine use in the hospital.[9]

Similar to other studies, we found associations between administration of multiple doses of epinephrine and more severe reactions and older age.[10] Older patients may verbalize symptoms better, leading to more rapid administration of epinephrine. Peanut, tree nut, and milk triggers were also found to be independently associated with the administration of 2 or more doses of epinephrine in the ED. This association might be related to the tendency of these allergens to lead to more severe anaphylaxis and anaphylaxis fatalities.[10]

Our study has some potential limitations. We describe the experience at only one Canadian pediatric hospital, which may not represent the entire population. In addition, the high percentage of visits due to anaphylaxis in our study compared with other studies might be related to differences in the catchment populations. However, given that Canadians have more ED visits related to non–life-threatening conditions in general compared with other industrialized countries, this should inflate the denominator and yield more conservative estimates. There is a potential for misclassification bias given that data for 50% of the patients were collected retrospectively. However, demographic and clinical characteristics were similar between prospective and retrospective cases, reducing the probability of misclassification. Another potential limitation is that we did not measure height and therefore were unable to calculate body mass index and were unable to determine whether older patients received more doses of epinephrine because it was appropriate for their size. In addition, parents and physicians may have become more adept at recognizing anaphylaxis, contributing to the continuous annual increase that we observed over 4 years. Finally, data were not available for the specific time interval between prehospital administration of epinephrine and arrival in the ED, which prevented us from examining the benefit of early versus later administration of epinephrine.

In conclusion, our study demonstrates that anaphylaxis accounts for an increasing percentage of all pediatric ED visits. Furthermore, we report that early use of epinephrine before ED arrival is associated with a lower likelihood of requiring multiple doses of epinephrine in the ED.

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Limited thymic recovery after extracorporeal photopheresis in a low-body-weight patient with acute graft-versus-host disease of the skin

To the Editor:

Survival after hematopoietic stem cell transplantation (HSCT) for T-lymphocyte immunodeficiency approaches 80% to 90%, has improved over time, and is best in younger patients without pre-existing severe infection.[1]

A serious complication associated with poor outcome is acute graft-versus-host disease (aGvHD), which is more likely to develop, with a worse prognosis, in cases of unrelated donor or HLA-mismatched transplantation. The incidence of aGvHD is 35% to 80% of all HSCT recipients, most frequently affecting skin with a characteristic maculopapular rash initially affecting the soles and palms before involving the trunk and limbs. Severity is graded I to IV depending on the extent of skin affected, level of skin damage, and extent of liver and intestinal dysfunction.[2] Grades II to IV require treatment, and grade III to IV disease negatively affects prognosis. aGvHD and steroid treatment are

TABLE E1. Demographic characteristics and atopic comorbidities

	% (95% CI)				
Variable	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**All 4 years**
Prospectively identified	47.3 (39.6-55.2)	48.2 (41.4-55.0)	42.3 (36.0-48.8)	48.1 (42.7-53.5)	46.6 (43.5-49.8)
Age (IQR)	4.5 (2.3-10.1)	5.9 (2.1-11.1)	6.3 (2.9-12.6)	6.0 (2.4-11.5)	5.8 (2.4-11.6)
Sex: male	50.9 (43.1-58.7)	61.0 (54.2-67.4)	56.5 (49.9-62.8)	56.0 (50.6-61.3)	57.1 (53.9-60.2)
Food allergy	52.9 (44.8-60.8)	26.7 (20.9-33.3)	57.8 (51.2-64.1)	49.9 (44.4-55.3)	47.2 (44.0-50.4)
Asthma	22.3 (16.2-29.8)	18.6 (13.7-24.6)	17.4 (12.9-22.9)	18.8 (14.8-23.4)	19.0 (16.5-21.6)
Eczema	17.8 (12.4-24.9)	13.3 (9.2-18.9)	13.6 (9.6-18.8)	20.2 (16.2-25.0)	16.6 (14.3-19.2)

TABLE E2. Anaphylaxis triggers and reaction history

	% (95% CI)				
Trigger	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**All 4 years**
Food trigger	85.5 (79.1-90.3)	80.6 (74.6-85.6)	79.1 (73.3-83.9)	82.4 (77.9-86.2)	82.1 (79.5-84.4)
Peanut	30.3 (23.0-38.6)	20.6 (15.0-27.5)	20.6 (15.2-27.2)	20.3 (15.8-25.6)	22.2 (19.4-25.3)
Tree nut	15.5 (10.2-22.7)	14.8 (10.1-21.2)	13.8 (9.3-19.7)	18.1 (13.9-23.2)	13.4 (11-16)
Milk	7.0 (3.6-12.9)	6.3 (3.3-11.3)	7.9 (4.7-13.0)	6.4 (3.9-10.1)	6.8 (5.2-8.9)
Egg	5.6 (2.6-11.2)	7.4 (4.2-12.6)	6.9 (3.9-11.7)	4.3 (2.3-7.5)	5.8 (4.3-7.7)
Sesame	2.8 (0.9-7.5)	2.9 (1.1-6.9)	2.6 (1.0-6.4)	1.4 (0.5-3.9)	2.3 (1.4-3.6)
Venom	3.0 (1.1-7.2)	3.2 (1.4-6.8)	1.3 (0.3-3.9)	1.2 (0.4-3.2)	2.0 (1.2-3.1)
Drug	2.4 (0.8-6.4)	4.1 (2.0-8.0)	3.3 (1.6-6.7)	3.5 (1.9-6.2)	3.2 (2.2-4.6)
Unknown	6.0 (3.1-11.0)	4.1 (2.0-8.0)	13.8 (9.8-19.0)	9.7 (6.8-13.4)	9.8 (8.1-11.9)
Reacted to peanut among those with known peanut allergy	51.3 (35.0-67.3)	31.2 (19.1-46.4)	32.2 (20.1-45.8)	39.5 (28.7-51.4)	37.6 (31.2-44.3)
Reacted to tree nut among those with known tree nut allergy	52.2 (31.1-72.6)	46.7 (22.3-72.6)	54.2 (33.2-73.8)	24.4 (12.9-40.6)	32.3 (23.2-42.7)
Reacted to milk among those with known milk allergy	55.6 (22.7-84.7)	35.0 (16.3-59.1)	45.0 (23.8-68.0)	34.4 (19.7-52.3)	37.1 (27.3-48.0)
Reacted at home	54.1 (46.0-62.0)	56.1 (48.4-63.6)	56.7 (49.1-64.0)	48.3 (42.4-54.2)	53.0 (49.5-56.5)
Anaphylaxis in the context of exercise	7.9 (4.2-14.1)	9.3 (5.3-15.7)	6.7 (3.3-12.6)	6.2 (3.7-10.0)	7.3 (5.5-9.6)

TABLE E3. Anaphylaxis reaction severity

	% (95% CI)				
Reaction	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**All 4 years**
Mild	29.3 (22.7-40)	23.4 (18.1-29.7)	21.3 (16.4-27.2)	21.7 (17.5-26.5)	23.3 (0.2-26.1)
Moderate	64.1 (56.2-71.2)	73.9 (67.4-79.4)	76.6 (70.6-81.7)	73.0 (67.9-77.6)	72.5 (69.6-75.3)
Severe	6.6 (3.5-11.7)	2.8 (1.1-6.2)	2.1 (0.8-5.1)	5.3 (3.2-8.4)	4.1 (3.0-5.6)

Mild anaphylaxis: Combination of symptoms involving the skin and subcutaneous tissues (ie, urticaria, erythema, and angioedema) as well as oral pruritus, nausea (ie, gastrointestinal involvement), or nasal congestion, sneezing, rhinorrhea, and throat tightness (ie, respiratory involvement).
Moderate anaphylaxis: Presence of any of the previous symptoms as well as crampy abdominal pain, diarrhea or recurrent vomiting, dyspnea, stridor, cough, wheeze, or "light headedness."
Severe anaphylaxis included cyanosis, hypoxia (saturation <92%), respiratory arrest, hypotension, dysrhythmia, confusion, or loss of consciousness.[6]

TABLE E4. Univariate and multivariate logistic regression for ≥2 doses of epinephrine used in anaphylaxis in the ED

Reaction, % (95% CI)	Univariate OR	Multivariate OR
Age	1.06 (1.00-1.11)	1.1 (1.03-1.2)
Sex: male	1.41 (0.74-2.69)	1.41 (0.74-2.69)
Asthma	1.42 (0.70-2.90)	1.42 (0.70-2.90)
Eczema	1.23 (0.56-2.74)	1.23 (0.56-2.74)
Use of epinephrine outside ED	0.25 (0.09-0.71)	0.25 (0.04-0.6)
Use of antihistamines outside ED	0.5 (0.23-0.94)	0.5 (0.20-1.18)
Use of antihistamines inside ED	3.6 (1.39-9.21)	3.6 (1.39-9.21)
Severe anaphylaxis	12.4 (5.62-27.29)	17.3 (6.1-49.2)
Anaphylaxis triggered by peanut	2.15 (1.11-4.19)	2.9 (1.1-8.5)
Anaphylaxis triggered by tree nut	3.5 (1.22-10.03)	7.2 (2.6-20.2)
Anaphylaxis triggered by milk	1.7 (0.57-4.87)	5.2 (1.4-20.0)
Anaphylaxis associated with exercise	0.8 (0.18-3.45)	0.9 (0.15-5.2)
Anaphylaxis at home	1.2 (0.62-2.40)	1.2 (0.62-2.40)