

Short- and long-term management of cases of venom-induced anaphylaxis is suboptimal



Ashley Tritt, BSc ^{*}; Sofianne Gabrielli, MSc [†]; Sarah Zahabi, BSc ^{*}; Ann Clarke, MD, MSc, FRCPC [‡]; Jocelyn Moisan, MD, MSc [§]; Harley Eisman, MD ^{||}; Judy Morris, MD, MSc [¶]; Lea Restivo, MD [#]; Greg Shand, MSc ^{**}; Moshe Ben-Shoshan, MD, MSc [†]

^{*} Faculty of Medicine, McGill University, Montreal, Quebec, Canada

[†] Division of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, McGill University Health Centre, Montreal, Quebec, Canada

[‡] Division of Rheumatology, Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[§] Regional Medical Director of Emergency Medical Services of Outaouais, Outaouais, Quebec, Canada

^{||} Department of Emergency Medicine, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada

[¶] Department of Emergency Medicine, Sacre-Coeur Hospital, Montreal, Quebec, Canada

[#] Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada

^{**} Division of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, Montreal Children's Hospital, Montreal, Quebec, Canada

ARTICLE INFO

Article history:

Received for publication March 15, 2018.

Received in revised form April 4, 2018.

Accepted for publication April 6, 2018.

ABSTRACT

Background: Venom-induced anaphylaxis (VIA) accounts for severe reactions. However, little is known about the short- and long-term management of VIA patients.

Objective: To assess the short- and long-term management of VIA.

Methods: Using a national anaphylaxis registry (C-CARE), we identified VIA cases presenting to emergency departments in Montreal and to emergency medical services (EMSs) in western Quebec over a 4-year period. Data were collected on clinical characteristics, triggers, and management. Consenting patients were contacted annually regarding long-term management. Univariate and multivariate logistic regressions were used to identify factors associated with epinephrine use, allergist assessment, and administration of immunotherapy. **Results:** Between June 2013 and May 2017, 115 VIA cases were identified. Epinephrine was administered to 63.5% (95% confidence interval [CI], 53.9%–72.1%) of all VIA cases by a health care professional. Treatment of reactions without epinephrine was more likely in reactions occurring at home and in nonsevere cases (no hypotension, hypoxia, or loss of consciousness). Among 48 patients who responded to a follow-up questionnaire, 95.8% (95% CI, 84.6%–99.3%) were prescribed epinephrine auto-injector, 68.8% (95% CI, 53.6%–80.9%) saw an allergist who confirmed the allergy in 63.6% of cases, and 81.0% of those with positive testing were administered immunotherapy. Among cases with follow-up, seeing an allergist was less likely in patients with known ischemic heart disease.

Conclusion: Almost 30% of patients with suspected VIA did not see an allergist, only two thirds of those seeing an allergist had allergy confirmation, and almost one fifth of those with confirmed allergy did not receive immunotherapy. Educational programs are needed to bridge this knowledge-to-action gap.

© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction that involves at least 2 organ systems and/or the presence of hypotension in response to a potential

allergen, and the condition is increasing in prevalence.^{1–4} Studies suggest that, although venom-induced anaphylaxis (VIA) cases represent less than 5% of all anaphylactic reactions in the general population, they account for the most severe cases, yet data regarding incidence, clinical characteristics, and management of VIA are limited.^{4–6}

The diagnosis of VIA is based on detailed, comprehensive history of systemic symptoms, corroborated with skin-prick testing (SPT) and, potentially, venom-specific immunoglobulin E (IgE) levels.⁵ In addition, recently established European guidelines recommend assessing serum tryptase within 1–2 hours after development of systemic symptoms, and at baseline to confirm anaphylaxis and to rule out an underlying mastocytosis, which requires a different

Reprints: Ashley Tritt, BSc, Montreal Children's Hospital, Department of Allergy and Immunology, 1001 Decarie Boulevard, Montreal, Quebec, H4A3J1, Canada; E-mail: ashley.tritt@mail.mcgill.ca.

Disclosures: Authors have nothing to disclose.

Funding Sources: This project was supported by the Allergy, Genes, and Environment Network of Centres of Excellence (AllerGen NCE) and by Health Canada.

<https://doi.org/10.1016/j.anaai.2018.04.006>

1081-1206/© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

treatment algorithm.^{7–10} According to current North American and European guidelines, VIA requires prompt administration of epinephrine as well as venom immunotherapy to decrease the risk of recurrence.^{11–13} However, little research exists regarding patients', caregivers', and clinicians' uptake of management guidelines of VIA. At the time of this study, there were no known studies assessing follow up and management of VIA patients as well as treatment using venom immunotherapy. The goal of our study was to collect and evaluate the immediate (ie, treatment at the time of reaction) and long-term (ie, prescription of epinephrine auto-injector, assessment by an allergist, and use of confirmatory tests and immunotherapy) management of suspected VIA cases.

Methods

The Cross-Canada Anaphylaxis Registry (C-CARE) is a cross-country initiative that aims to bridge knowledge gaps related to anaphylaxis rates and management across Canada. C-CARE enrolls anaphylactic cases presenting to emergency departments (EDs) and out-of-hospital emergency medical services (EMSs). We utilized the C-CARE database to identify VIA cases presenting to 2 EDs in Montreal: the Montreal Children's Hospital (MCH) and Sacré-Coeur Hospital (HSC), and to EMSs in western Quebec (Outaouais region), from June 2013 to May 2017. The 2 centers are tertiary care hospitals, each assessing approximately 80,000 and 60,000 ED visits annually, respectively, whereas the EMSs have 30,000 ambulance calls per year.

In the EDs at the MCH and HSC, prospective data were collected at the time of patient presentation, as described in previous studies.^{14,15} As with our other studies, a software program previously developed was used to record all suspected allergic reactions in the EMS setting.⁶ Cases of anaphylaxis were identified by the treating physician/paramedic. A standardized form was completed by health care professionals in both the ED and EMS settings to collect patient information, including age, sex, clinical background, medication use, and clinical characteristics of the reaction, such as the suspected trigger, symptoms, route of exposure, time interval between exposure and development of clinical symptoms, as well as management, including the use of epinephrine, antihistamines, and steroids. For ED patients, data on admission to hospital/intensive care unit, prescription of an epinephrine auto-injector, referral to an allergist, and requisition for tryptase levels were also collected. For EMS patients, these data were collected through chart review, medical documentation, and/or follow-up questionnaire conducted with consenting participants.

The standardized forms completed by the ED physicians and EMS providers were evaluated by 3 members of our research team (S.G., G.S., and M.B.S.), and only cases that met the definition of anaphylaxis were included.² In addition, charts of missed VIA cases were identified and reviewed using *International Classification of Disease, 10th revision* codes referring to either anaphylaxis or allergic reaction to ensure no cases were missed, as previously described.^{6,14,15} EMS records were also verified for any missed cases. For patients not recruited prospectively at the MCH but provided consent when assessed at the allergy clinic we collected data on reaction and long-term management based on chart review. A modified grading system described by Brown and outlined in our previous studies was used to classify anaphylaxis severity.^{6,14–17} Consenting adults or the patients' parents and/or legal guardians were contacted annually to complete a standardized form querying on epinephrine auto-injector prescription, assessment by allergist, use of confirmatory tests (skin tests and blood tests for specific immunoglobulin E [IgE] levels), and the use of venom immunotherapy.

All statistical analyses were done using R version 3.2.2 (R Core Team 2013; R Foundation for Statistical Computing, Vienna, Austria). Percent and 95% confidence interval (binomial or multinomial for

variables with more than 2 categories) data were used for patient demographics, reaction severity, allergy assessment, and management of VIA cases. Univariate and multivariate logistic regression models were compared with estimate factors associated with use of epinephrine, assessment by an allergist, and administration of immunotherapy. The study was approved by the McGill University Health Center and Sacré-Coeur ethics review boards.

Results

Between June 2013 and May 2017, 115 VIA cases were identified: 14% from the MCH; 10% from the HSC; and 77% from the EMS of western Quebec. Three of 115 cases of VIA were recurrent reactions, 2 of which occurred at a different timepoint (>3 days from the index reaction), and 1 was a biphasic reaction (occurred within 3 days of the index reaction). More than half of the cases (60%) were prospectively recruited. There was a male predominance (66.1%), and the majority (80.0%) of patients were adults (Table 1). Approximately half (51.8%) of the reactions occurred at home. More than half of the reactions were classified as moderate and a third as severe (manifested by desaturation <92%, cyanosis, respiratory arrest, hypoxia, dysrhythmia, confusion, or loss of consciousness) (Table 1).¹⁶ There were no fatal cases of VIA in our study population.

Epinephrine was received in the majority of cases of VIA (78.3% [95% CI, 69.4%–85.2%]); more than one third of patients (37.4% [95% CI, 28.7%–46.9%]) received epinephrine before management by a health care professional, and almost two thirds of patients (63.5% [95% CI, 53.9%–72.1%]) received epinephrine by a health care professional (Table 2); 26 cases received epinephrine both before assessment and by a health care professional. Fewer than half of the patients (42.6%) received an antihistamine before management by a health care professional (Table 2). Management by a health care professional included an antihistamine and/or short-acting inhaled β -agonist in less than one fifth of VIA cases (14.8% and 13.9%, respectively). Among moderate and severe cases (99 cases), the majority (81.9% [95% CI, 72.5%–88.6%]) were treated with epinephrine either before or after an encounter with a health professional; more than half (56.3% [95% CI, 30.6%–79.2%]) of the mild reactions (16 cases) were treated with epinephrine (Table 2). Reactions treated

Table 1
Demographics and Characteristics of Patients

	Percent (95% CI)
Number of reactions per number of patients: 115 of 112	
Site of reaction presentation	
MCH (16 of 115)	13.9% (7.0%–21.5%)
HSC (11 of 115)	9.6% (2.6%–17.2%)
EMS (88 of 115)	76.5% (69.6%–84.1%)
Prospectively identified cases (69 of 115)	60.0% (50.4%–68.9%)
Age in years [median (IQR)]	44.8% (25.6%–59.2%)
Adults (≥ 18 years) (92 of 115)	80.0% (71.3%–86.7%)
Male sex (76 of 115)	66.1% (56.6%–74.5%)
Comorbidities	
Asthma (12 of 114)	10.5% (5.8%–18.0%)
Eczema (1 of 115)	0.9% (0.05%–5.5%)
Food allergy (6 of 89)	6.7% (2.8%–14.6%)
Heart disease (4 of 114)	3.5% (1.1%–9.3%)
Previously prescribed medications	
β -blockers (6 of 111)	5.4% (2.2%–11.9%)
NSAID use regularly (8 of 111)	7.2% (3.4%–14.1%)
Reaction occurring at home (58 of 112)	51.8% (42.3%–61.3%)
Reaction severity	
Mild (16 of 115)	13.9% (5.2%–24.0%)
Moderate (60 of 115)	52.2% (43.5%–62.2%)
Severe (39 of 115)	33.9% (25.2%–44.0%)

Abbreviations: CI, confidence interval; EMS, emergency medical services; IQR, interquartile range; HSC, Sacré-Coeur Hospital; MCH, Montreal Children's Hospital; NSAID, nonsteroidal anti-inflammatory drug.

Table 2
Management of Allergic Venom Reactions

	Percent (95% CI)
Administered before management by health care professional	
Epinephrine (43 of 115)	37.4% (28.7%–46.9%)
Antihistamine (49 of 115)	42.6% (33.5%–52.1%)
Short-acting inhaled β -agonist (1 of 115)	0.9% (0.05%–5.5%)
Steroids (3 of 115)	2.6% (0.7%–8.0%)
Administered by health care professional	
Epinephrine (73 of 115)	63.5% (53.9%–72.1%)
Antihistamine (17 of 115)	14.8% (9.1%–22.9%)
Short-acting inhaled β -agonist (16 of 115)	13.9% (8.4%–21.9%)
Steroids (9 of 115)	7.8% (3.9%–14.7%)
Moderate and severe reactions	
Received epinephrine (81 of 99)	81.9% (72.5%–88.6%)
Mild reactions	
Received epinephrine (9 of 16)	56.3% (30.6%–79.2%)
All reaction severities	
Received epinephrine (90 of 115)	78.3% (69.4%–85.2%)

Abbreviation: CI, confidence interval.

Table 3
Odds Ratio of Factors Associated With Management of VIA Without Epinephrine

	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)
Age at reaction	0.99 (0.99–1.00)	0.99 (0.99–1.00)
Treatment by health care team		
Short-acting inhaled β -agonist	0.78 (0.63–0.96) ^a	0.82 (0.66–1.00)
Antihistamine	0.95 (0.77–1.18)	
Severe reaction	0.81 (0.69–0.94) ^a	0.79 (0.68–0.93) ^a
Comorbidities		
Asthma	1.05 (0.82–1.34)	0.95 (0.75–1.20)
Eczema	0.81 (0.36–1.82)	
Known food allergy	0.80 (0.57–1.12)	
Heart disease	1.04 (0.69–1.57)	
β -blocker use	1.13 (0.80–1.59)	1.19 (0.89–1.61)
Daily NSAID use	1.36 (1.01–1.82) ^a	
Conditions of reaction		
During exercise	0.97 (0.75–1.25)	1.31 (1.13–1.53) ^a
While at home	1.26 (1.09–1.47) ^a	
Location		
EMS	0.95 (0.79–1.13)	1.02 (0.84–1.24)

Abbreviations: CI, confidence interval; EMS, emergency medical services; NSAID, non-steroidal anti-inflammatory drug; VIA, venom-induced anaphylaxis.

^aStatistically significant.

without epinephrine were more likely to occur while at home (adjusted odds ratio [aOR] for age, severity of reaction, asthma, location, and use of nonsteroidal anti-inflammatory drugs [NSAIDs] and inhaled short-acting β -agonists): 1.32 (95% CI, 1.13–1.53). Reactions treated without epinephrine were less likely among those with severe reactions (aOR, 0.79 [95% CI, 0.68–0.93]) (Table 3).

Follow-up information was obtained for a total of 48 of the 112 patients in the study. Follow-up data were unavailable for the remaining 64 of 112 patients who could not be reached. Of the 48 patients, follow-up information was obtained by telephone in 40 prospective patients, and through chart review in 8 consenting retrospective patients (Fig 1). The response rate was 66.7% (40 of 69 prospective cases of VIA) (Table 4). There were no substantial differences between patients for whom follow-up information was obtained and those for whom follow-up management data were unavailable, other than a slightly younger patient population in those with follow-up data (eTable 1). The average length of follow up was 2.89 years.

Among patients with follow-up information ($n = 48$), 33 (68.8% [95% CI, 53.6%–80.9%]) were assessed by an allergist (Table 4); of these patients, 27 (81.8% [95% CI, 63.9%–92.4%]) underwent allergy testing, including SPT and/or in vitro venom-specific IgE levels. Tryptase levels (all within normal limits) were obtained after the reaction in less than 20% (8 of 48) of patients (16.7% [95% CI, 8.0%–30.8%]); only 1 patient had a tryptase level during the reaction with repeat levels afterward. Of the 27 patients in whom allergy testing was performed, testing was negative in 6 (22.2% [95% CI, 9.4%–42.7%]). Nineteen of 48 patients (39.6% [95% CI, 27.1%–54.8%]) providing follow-up information had a confirmed allergy to non-bees (including wasps and/or hornets), and 2 (4.2% [95% CI, 0.0%–19.4%]) to both bees and non-bees; there were no patients with a confirmed allergy to bees alone. Twenty-seven patients providing follow-up data (56.3% [95% CI, 43.8%–71.5%]) had an unconfirmed allergy, either due to lack of testing performed (6 cases), lack of assessment by an allergist (15 cases), or negative allergy tests, despite a documented allergic reaction to an insect sting (6 cases). Of the 6 patients with negative test results, only 3 had tryptase levels assessed to rule out mastocytosis and none had a repeated venom skin test done. Of the patients with available follow-up data, almost all (95.8% [95% CI, 84.6%–99.3%]) were prescribed an epinephrine auto-injector, and nearly one third (35.4% [95% CI, 22.6%–50.6%]) were administered venom immunotherapy. Among patients with positive test results, the majority (81.0%) received venom immunotherapy (17 of 21 cases).

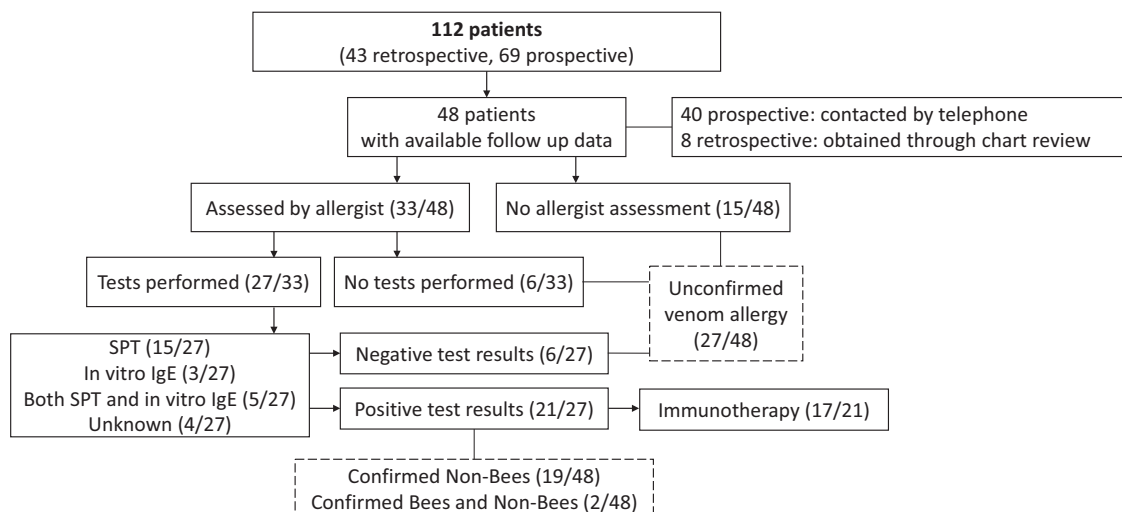
**Figure 1.** Diagnosis and management of patients with venom-induced anaphylaxis (VIA).

Table 4
Follow Up and Management of VIA Cases

Variable (numerator/denominator)	Percent of patients (95% CI) ^a
Patients with follow-up data (either prospective or retrospective) among all patients (48 of 112)	42.9% (33.7%–52.6%)
Patients responding to follow up among prospective patients (40 of 69)	66.7% (53.2%–78.0%)
Length of follow up, in years (mean, standard deviation)	2.89 (1.08)
Age at reaction, in years (median, IQR)	39.6 (12.8–56.2)
Sex (% males) (32 of 48)	66.7% (51.5%–79.2%)
Reaction severity	
Mild (7 of 48)	14.6% (2.1%–30.4%)
Moderate (25 of 48)	52.1% (39.6%–67.9%)
Severe (16 of 48)	33.3% (20.8%–49.2%)
Asthma (7 of 47)	14.9% (6.7%–28.9%)
Location	
MCH (15 of 48)	31.3% (18.8%–45.8%)
HSC (4 of 48)	8.3% (0.0%–22.9%)
EMS (29 of 48)	60.4% (47.9%–75.0%)
Follow-up assessment by an allergist (33 of 48)	68.8% (53.6%–80.9%)
Assessed with tests (27 of 33)	81.8% (63.9%–92.4%)
Positive test results (21 of 27)	77.8% (57.3%–90.6%)
Negative test results (6 of 27)	22.2% (9.4%–42.7%)
No tests performed (6 of 33)	18.2% (7.6%–36.1%)
Confirmed venom allergy in patients who saw an allergist (21 of 33)	63.6% (45.1%–79.0%)
Among the 27 patients who underwent testing	
SPT (15 of 27)	55.6% (40.7%–76.1%)
IgE ^b (3 of 27)	11.1% (0.0%–31.6%)
Both SPT and IgE ^b (5 of 27)	18.5% (3.7%–39.0%)
Unknown which tests performed (4 of 27)	14.8% (0.0%–35.3%)
Trypase (8 of 48)	16.7% (8.0%–30.8%)
Allergy status	
Confirmed non-bees (19 of 48)	39.6% (27.1%–54.8%)
Confirmed bees only (0 of 48)	0.0% (0.0%–15.3%)
Confirmed both bees and non-bees (2 of 48)	4.2% (0.0%–19.4%)
Unconfirmed (27 of 48)	56.3% (43.8%–71.5%)
Unconfirmed due to lack of testing (6 of 27)	22.2% (7.4%–43.5%)
Unconfirmed due to negative testing (6 of 27)	22.2% (7.4%–43.5%)
Unconfirmed due to no follow up (15 of 27)	55.6% (40.7%–76.8%)
Management	
Prescribed epinephrine (46 of 48)	95.8% (84.6%–99.3%)
Desensitization via immunotherapy among all patients with follow up (17 of 48)	35.4% (22.6%–50.6%)
Desensitization via immunotherapy among patients with positive testing (17 of 21)	81.0% (57.4%–93.7%)

Abbreviations: IgE, immunoglobulin E; IQR, interquartile range; HSC, Sacré-Coeur Hospital; MCH, Montreal Children's Hospital; SPT, skin-prick testing.

^aUnless noted otherwise.

^bIn vitro IgE.

Seeing an allergist was less likely in patients with known ischemic heart disease (aOR, 0.54 [95% CI, 0.31–0.95]) while controlling for age, sex, asthma, location, and reaction severity (Table 5).

Discussion

We have conducted the first study to assess short- and long-term management of VIA patients. Although current recommendations state that cases of VIA should be referred for further assessment, our study has revealed that, among those patients for whom we obtained long-term follow-up data, almost one third (15 of 48) were not seen by an allergist after a venom-induced reaction, and, among those assessed, 6 of 33 (20%) were not evaluated appropriately through the use of confirmatory tests. In patients who underwent allergy testing, 6 of 27 (22%) of those with suspected venom allergy remained unconfirmed due to negative results. Further, despite recommended repeat testing in those with negative results,¹⁸ none of these negative tests were repeated. Consistent with the clinical guidelines recommending epinephrine as the drug of choice for

Table 5
Odds Ratios of Factors Associated With Management of VIA Cases

Variable	Univariate OR (95% CI)	Multivariate OR (95% CI)
Factors associated with seeing an allergist		
≤18 years old	1.16 (0.88–1.52)	1.54 (0.87–2.73)
Sex (male)	0.91 (0.69–1.21)	0.95 (0.71–1.26)
Severe reaction	1.10 (0.83–1.46)	1.21 (0.88–1.65)
Asthma	0.88 (0.60–1.29)	0.95 (0.63–1.42)
EMS	0.92 (0.70–1.43)	1.09 (0.73–1.64)
Ischemic heart disease	0.48 (0.29–0.81) ^a	0.54 (0.31–0.95) ^a
Factors associated with undergoing immunotherapy		
≤18 years old	0.97 (0.73–1.29)	1.17 (0.79–1.73)
Sex (male)	1.06 (0.79–1.43)	1.11 (0.85–1.46)
Severe reaction	1.13 (0.85–1.52)	1.02 (0.75–1.39)
Asthma	0.79 (0.54–1.16)	0.89 (0.61–1.29)
Saw allergist	1.67 (1.29–2.17) ^a	1.61 (1.20–2.16) ^a
EMS	1.16 (0.88–1.54)	1.37 (0.93–2.01)
Ischemic heart disease	0.70 (0.40–1.21)	0.91 (0.51–1.60)

Abbreviations: EMS, emergency medical services; OR, odds ratio; VIA, venom-induced anaphylaxis.

^aStatistically significant.

acute venom-induced anaphylactic reactions,^{19,20} epinephrine was prescribed to almost all patients with suspected and/or confirmed VIA. However, despite being the “gold standard” for venom allergy management, almost 20% of patients with confirmatory testing did not receive immunotherapy.

Our findings are consistent with previous studies that discussed inadequate management of anaphylaxis and suboptimal adherence to clinical guidelines, recommending allergy assessment after a severe allergic reaction.^{21–23} In resource-limited settings, the decision to refer and the possibility of follow up with an allergist often depends on local access to a specialist as well as long wait times for assessment. Patient age and social determinants may contribute to noncompliance to follow up, and multiple months of waiting to see a specialist may impact a patient's decision to seek allergy consultation.^{24–26} The large percentage of patients not assessed for VIA may be due to patient-related factors, such as other priorities or inability to take time off from work, or other factors related to the Canadian health care system, including the low number of allergists in Canada and long wait times for specialist assessment.^{24,25}

Studies suggest that patients with cardiovascular disease are at increased risk of fatal anaphylaxis.^{27,28} Cardiac mast cells are key contributors to atherosclerotic plaques, and medications for heart disease may exacerbate anaphylaxis or make it more difficult to treat.²⁹ The decreased rate of allergy referrals in patients with ischemic heart disease may be due to concern regarding concurrent use of angiotensin-converting enzyme inhibitors (ACE-Is) and/or β -blockers and venom immunotherapy.^{30–34} However, a recent North American practice parameter update concluded that the benefits of venom immunotherapy outweigh the risks in patients taking these medications, supporting that patients with ischemic heart disease and suspected VIA should be referred for allergy assessment for further investigations and possible treatment.¹¹

Although testing with SPT and/or venom-specific IgE may be recommended for allergy confirmation, we found that a significant proportion (almost 20%) of patients with suspected VIA who were assessed by an allergist did not undergo further investigation, possibly due to mild reaction severity, decreased patient compliance, and/or resource-limited settings with no available venom testing in some areas of Quebec. It has been reported that a false-negative test can occur in 15% of cases, as we found 6 of 27 cases with negative testing despite a clinical history consistent with VIA.^{5,12,18,35,36} These cases may also indicate idiopathic anaphylaxis or another

unknown trigger, such as food, a common trigger for anaphylaxis, or the presence of mastocytosis. Studies suggest that, in these cases, tests should be repeated; however, this recommendation was not followed in our cohort (no repeated testing documented).

Despite recommendations for tryptase testing in the acute setting and at baseline, we found that almost no patients actually had tryptase testing during the allergic reaction and only 20% had tests at baseline. This finding is similar to that in a study from the United Kingdom in which tryptase was measured in less than one third of patients.⁸ Tryptase assessment is particularly important when skin tests or blood tests are negative, to rule out the presence of underlying mastocytosis.^{18,36} However, tryptase testing may not be available in all laboratories across Quebec. At the HSC, tryptase testing is only available through outsourcing to another location; however, availability of the test is not well known and is thus seldom used by the primary care ED community.

The decision to initiate venom immunotherapy is a commitment on behalf of the patient and the allergist, as treatment often lasts at least 5 years.^{5,12,13,37} However, despite established guidelines, we found that almost 20% of patients with confirmatory testing were not administered immunotherapy despite established guidelines. It is possible that patients may choose to forego venom immunotherapy due to discomfort with regular injections as well as difficulties adhering to frequent medical appointments, which can be time-consuming and inconvenient for patients. In resource-limited health care systems, such as those in Quebec, the cost of venom immunotherapy together with availability of the health care provider must be considered in addition to accessibility of immunotherapy in a nonurban setting.

There are several limitations to our study. Despite being the only study assessing the immediate and long-term management of prospectively followed VIA cases, our results are limited to a relatively small sample size that may not reflect the catchment population. However, the similarity in sociodemographic (with the exception of a slightly younger age in nonresponders) and clinical characteristics between responders and nonresponders suggests that this did not bias our results. Furthermore, our sample was representative of tertiary care adult and pediatric care as well as regional and community centers. Still, our study may have several potential biases. A significant proportion of the patients in our study were identified through EMSs, including in remote and rural regions of Quebec, most of which are near wooded areas. These patients may be more likely to be exposed to insects, and thus more likely to be stung in areas far from a health care facility. Hence, our results may not reflect the practice in more urban areas, with greater access to EDs. However, in a separate univariate regression analysis adjusting for the location of patients (ie, presenting to ED or EMS), we did not identify that this had an effect on the use of epinephrine or immunotherapy (Table 5). Treatment with immunotherapy was more likely in patients who saw an allergist, but this is self-explanatory. In addition, our findings are subject to misclassification bias. Patients' and physicians' documentation did not often differentiate between types of non-bee culprits (eg, in many cases, patients were defined as allergic to both yellow jackets and hornets, or to wasps in general). To reduce the risk of misclassification bias, we used the dichotomous variable of bee and non-bee, although this may not appropriately reflect the true culprit.

In conclusion, our findings reveal low adherence to current guidelines regarding long-term management of VIA cases. Educational programs bridging knowledge-to-action gaps and promoting adherence to guidelines are crucial to manage VIA appropriately.

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.anai.2018.04.006>.

References

- [1] Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004;113:832–836.
- [2] Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–397.
- [3] Ben-Shoshan M, Clarke AE. Anaphylaxis: past, present and future. *Allergy*. 2011;66:1–14.
- [4] Asai Y, Yanishevsky Y, Clarke A, et al. Rate, triggers, severity and management of anaphylaxis in adults treated in a Canadian emergency department. *Int Arch Allergy Immunol*. 2014;164:246–252.
- [5] Matron PK, Timms V, Fitzsimons R. Identifying and managing Hymenoptera venom allergy. *Nurs Stand*. 2016;30:44–51.
- [6] Kimchi N, Clarke A, Moisan J, et al. Anaphylaxis cases presenting to primary care paramedics in Quebec. *Immun Inflamm Dis*. 2015;3:406–410.
- [7] Brown SG, Blackman KE, Hedde RJ. Can serum mast cell tryptase help diagnose anaphylaxis? *Emerg Med Australas*. 2004;16:120–124.
- [8] Buka RJ, Knibb RC, Crossman RJ, et al. Anaphylaxis and clinical utility of real-world measurement of acute serum tryptase in UK emergency departments. *J Allergy Clin Immunol Pract*. 2017;5:1280–1287, e2.
- [9] Krishna MT, Ewan PW, Diwakar L, et al. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. *Clin Exp Allergy*. 2011;41:1201–1220.
- [10] Akin C, Valent P. Diagnostic criteria and classification of mastocytosis in 2014. *Immunol Allergy Clin N Am*. 2014;34:207–218.
- [11] Golden DB, Demain J, Freeman T, et al. Stinging insect hypersensitivity: a practice parameter update 2016. *Ann Allergy Asthma Immunol*. 2017;118:28–54.
- [12] Bonifazi F, Jutel M, Bilo BM, Birnbaum J, Muller U. Hypersensitivity EIGoV. Prevention and treatment of Hymenoptera venom allergy: guidelines for clinical practice. *Allergy*. 2005;60:1459–1470.
- [13] Sturm GJ, Varga EM, Roberts G, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. *Allergy*. 2017;73:744–764.
- [14] Gabrielli S, Clarke AE, Eisman H, et al. Disparities in rate, triggers, and management in pediatric and adult cases of suspected drug-induced anaphylaxis in Canada. *Immun Inflamm Dis*. 2017;6:3–12.
- [15] Lee AY, Enarson P, Clarke AE, et al. Anaphylaxis across two Canadian pediatric centers: evaluating management disparities. *J Asthma Allergy*. 2017;10:1–7.
- [16] Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol*. 2004;114:371–376.
- [17] Ben-Shoshan M, La Vieille S, Eisman H, et al. Anaphylaxis treated in a Canadian pediatric hospital: incidence, clinical characteristics, triggers, and management. *J Allergy Clin Immunol*. 2013;132:739–741, e3.
- [18] Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Insect sting allergy with negative venom skin test responses. *J Allergy Clin Immunol*. 2001;107:897–901.
- [19] Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126:477–480, e1–42.
- [20] Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis—a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115:341–384.
- [21] Wasserman S, Chad Z, Francoeur MJ, et al. Management of anaphylaxis in primary care: Canadian expert consensus recommendations. *Allergy*. 2010;65:1082–1092.
- [22] Ciccarelli A, Calabro C, Imperatore C, Scala G. Hymenoptera venom allergy. A closer collaboration is needed between allergists and emergency physicians. *Eur Ann Allergy Clin Immunol*. 2017;49:15–17.
- [23] Fiedler C, Miehe U, Treudler R, Kiess W, Prenzel F. Long-term follow-up of children after venom immunotherapy: low adherence to anaphylaxis guidelines. *Int Arch Allergy Immunol*. 2017;172:167–172.
- [24] Harrington DW, Wilson K, Rosenberg MW. Waiting for a specialist consultation for a new condition in Ontario: impacts on patients' lives. *Health Policy*. 2014;9:90–103.
- [25] Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: a review from the patient's perspective. *Ther Clin Risk Manag*. 2008;4:269–286.
- [26] van Dijk CE, de Jong JD, Verheij RA, Jansen T, Korevaar JC, de Bakker DH. Compliance with referrals to medical specialist care: patient and general practice determinants: a cross-sectional study. *BMC Fam Pract*. 2016;17:11.
- [27] Triggiani M, Patella V, Staiano RI, Granata F, Marone G. Allergy and the cardiovascular system. *Clin Exp Immunol*. 2008;153(suppl 1):7–11.
- [28] Mueller UR. Cardiovascular disease and anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2007;7:337–341.
- [29] Lieberman P, Simons FE. Anaphylaxis and cardiovascular disease: therapeutic dilemmas. *Clin Exp Allergy*. 2015;45:1288–1295.
- [30] Pitsios C, Demoly P, Bilo MB, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy*. 2015;70:897–909.
- [31] Stoevesandt J, Hosp C, Kerstan A, Trautmann A. Hymenoptera venom immunotherapy while maintaining cardiovascular medication: safe and effective. *Ann Allergy Asthma Immunol*. 2015;114:411–416.
- [32] Tunon-de-Lara JM, Villanueva P, Marcos M, Taytard A. ACE inhibitors and anaphylactoid reactions during venom immunotherapy. *Lancet*. 1992;340:908.

- [33] White KM, England RW. Safety of angiotensin-converting enzyme inhibitors while receiving venom immunotherapy. *Ann Allergy Asthma Immunol*. 2008; 101:426–430.
- [34] Muller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. *J Allergy Clin Immunol*. 2005;115:606–610.
- [35] Bilo BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN. Hypersensitivity EI GoIV. Diagnosis of Hymenoptera venom allergy. *Allergy*. 2005;60:1339–1349.
- [36] Bilo MB, Brianzoni F, Cinti B, Napoli G, Bonifazi F. The dilemma of the negative skin test reactors with a history of venom anaphylaxis: will this always be the case? *Eur Ann Allergy Clin Immunol*. 2005;37:341–342.
- [37] Boyle RJ, Elremeli M, Hockenhull J, et al. Venom immunotherapy for preventing allergic reactions to insect stings. *Cochrane Database Syst Rev*. 2012;(10): CD008838.

Supplementary Data

eTable 1

Demographics of Patients Reached for Follow up Compared With Patients Not Reached for Follow Up

Variable (% , 95% CI)	Patients with follow-up data (n = 48)	Patients without follow-up data (n = 64)	Difference
Age at reaction [mean (SD)]	36.4 (23.2)	46.6 (18.1)	–10.2 (–18.2 to –2.1)
Sex (% male)	66.7% (51.5%–79.2%)	67.2% (54.2%–78.1%)	–0.5% (–18.7%–17.6%)
Reaction severity			
Mild	14.6% (2.1%–30.4%)	12.5% (1.6%–26.6%)	2.1% (–12.6% to 16.8%)
Moderate	52.1% (39.6%–67.9%)	53.1% (42.2%–66.8%)	–1.0% (–20.8% to 18.7%)
Severe	33.3% (20.8%–49.2%)	34.4% (23.4%–48.0%)	–1.0% (–19.8% to 17.7%)
Asthma	14.9% (6.7%–28.9%)	4.7% (1.2%–14.0%)	10.2% (–3.1% to 23.5%)
Location			
MCH	31.3% (18.8%–45.8%)	0.0% (0.0%–7.3%)	31.3% (16.3%–46.2%)
HSC	8.3% (0.0%–22.9%)	10.9% (4.7%–18.3%)	–2.6% (–15.4% to 10.9%)
EMS	60.4% (47.9%–75.0%)	89.1% (82.8%–96.4%)	–28.6% (–46.3% to –11.0%)

Abbreviations: CI, confidence interval; EMS, emergency medical service; HSC, Sacré-Coeur Hospital; MCH, Montreal Children's Hospital; SD, standard deviation.