



Characteristics of venom allergy at initial evaluation

Is fire ant hypersensitivity similar to flying Hymenoptera?

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ABSTRACT

Background: Hymenoptera venom allergy (HVA) is a well-established cause of anaphylaxis; however, studies comparing patients with imported fire ant (IFA) to flying hymenoptera (FH) allergies are lacking.

Objective: This study sought to characterize the initial presentation and examine differences between patients with IFA and FH reactions.

Methods: A multiyear (2007–2014), observational, single-institution analysis of patients referred for evaluation of HVA was performed. Data was obtained via physician interview, chart review and specific IgE results.

Results: 175 patients were enrolled with no difference between FH and IFA patients when analyzing mean age, sex or likelihood to seek emergency department (ED) care. Asthma was similar in all groups at 21%. ED treatments were also similar (epinephrine: 32/150, 21%; antihistamines: 141/155, 91%; corticosteroids: 67/148, 45%). Reaction severity correlated with likelihood of ED visit ($P < .001$), use of epinephrine ($P < .001$) and corticosteroid use ($P < .05$). Patients presenting to the ED with anaphylaxis received epinephrine in 27/73 (37%) of cases. Overall, 149/175 (85%) patients in our cohort were confirmed to be sensitized to hymenoptera. Of those with positive testing 127/149 (85%) chose to pursue VIT.

Conclusion: IFA and FH patients have many similarities at presentation. Asthma occurred 2.5 times more frequently in our cohort compared to the general US population. Epinephrine administration in our cohort was suboptimal. Children have initial reactions and are treated in the ED similarly to adults, with a notable (although not statistically significant) reduced use of epinephrine. The majority of patients seen in the ED and subsequently followed up in an allergy clinic had their venom allergy confirmed and initiated life-saving immunotherapy.

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Introduction

Hymenoptera venom allergy (HVA) is a well-established cause of anaphylaxis, comprising 10% of anaphylaxis cases.¹ In most areas of the United States, HVA concerns revolve around flying hymenoptera (FH). However, in the southern regions of the country, where imported fire ants (IFAs) are endemic, fire ant attacks are extremely common. In fact, IFAs are the leading cause of venom concerns, comprising 59% of venom immunotherapy (VIT) and 42% of insect hypersensitivity visits in allergy clinics located in endemic areas.²

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In the general population, IFA stings have been reported to occur at an annual frequency of 13% to 58%.^{3–7} Partridge et al¹⁰ reported that approximately 40% of children are stung monthly during the summer months. Clemmer et al³ found a 55% annual attack rate in children younger than 10 years. Patients new to an IFA endemic region experience IFA sting rates of 51% within the first few weeks of arrival.¹¹ In patients with confirmed IFA allergy undergoing VIT, one might expect a decreased rate of stings because of a heightened rate of avoidance counseling and tactics. However, even in these identified and counseled patients, decreased frequency of stings is not observed.¹²

Most systemic reactions (SRs) occur after a single IFA sting.¹³ In a retrospective medical record review of patients experiencing a SR secondary to insect stings in IFA endemic regions, 38.3% of SRs were secondary to IFA stings compared with 49.2% for FH, 4.2% for scorpion, and 8.3% for other insects.¹⁴ Up to 17% of the general population in an endemic region has specific IgE to IFA compared

with 10% to yellow jacket and 7.5% to peanut.¹⁵ In patients with a history of atopy, the rate of positive skin test results to IFAs is as high as 23% in individuals without a history of IFA SRs.¹⁶ Sensitization may be age dependent, with the highest rate of sensitization (64%) seen in children 6 to 10 years old.¹⁰

VIT has been proven safe and effective in patients with histories of SRs to both FH and IFAs.^{17–23} In light of the ubiquitous nature of IFA stings and the lifesaving therapy that VIT has to offer, it is surprising to find that only two-thirds of allergists in IFA endemic regions perform venom testing and offer VIT.²⁴

Currently, data involving patients with reactions to IFAs compared with FH are lacking. Specifically, there are limited data on the clinical features and treatment of venom allergy at initial presentation to the emergency department (ED). Within these limited data sets, there have been no direct comparisons among varied types of hymenoptera.^{8,9} Our study sought to characterize the initial presentation and ED management of patients with HVA, examine differences between patients with IFA and FH reactions, and correlate their presentation with subsequent allergy evaluation and consideration of VIT to help guide clinical management.

Methods

This was a multiyear, observational, single-institution analysis of patients referred for evaluation of HVA. The study was approved by the Wilford Hall Ambulatory Surgical Center Institutional Review Board. Patients who presented with concern for HVA to the allergy clinic at Wilford Hall Ambulatory Surgical Center were offered enrollment from 2007 to 2014. Once enrolled, information was obtained via physician interview and medical record review. Baseline characteristics collected included demographic information; comorbid conditions, such as asthma or coronary artery disease; medication use, specifically β -blockers or angiotensin-converting enzyme inhibitors; and the culprit stinging insect(s). Further information was gathered, including the initial reaction severity, treatments sought, ED interventions when applicable, specific IgE results, and whether VIT was ultimately pursued. For the purposes of this study, test results were considered positive if they had a specific IgE level equal to or above 0.35 kU_A/L or positive skin test results to the venom in question. Skin prick test results were considered positive if the wheal was 3 mm or larger, with surrounding erythema. Intradermal test results were considered positive if the wheal was 5 mm or larger with surrounding erythema. Skin testing and immunotherapy were performed using venom in the case of FH or whole-body extract for IFA.

The initial reaction severity data were categorized and labeled as grades A through E. For the purposes of this study, grade A was defined as a simple large local reaction, grade B was a cutaneous SR, grade C was a reaction that involved the cutaneous system plus gastrointestinal or respiratory symptoms, grade D included reactions that involved hypotension or hypoxia, and grade E was a serum

sickness-like reaction. ED treatment information was obtained via patient report and ED records (when available) and included whether the patient received epinephrine, antihistamines, and/or steroids. Treatment decisions regarding allergy testing and offering VIT were individualized and made at the primary allergist's discretion.

Patients were grouped for analysis based on type of venom reactions, age, and severity of initial reaction. Analysis based on culprit insect leading to a venom reaction was performed (eg, FH-only reactors, IFA-only reactors, reactors to both IFA and FH). Age analysis compared patients 16 years and younger with adults (17 years and older). The severity of reactions was broken down based on the categorization model discussed above.

Categorical data were summarized using percentages and analyzed using χ^2 tests or Fisher exact test, whichever was most appropriate. Means (SDs) were used as summary statistics for continuous variables and were analyzed using the *t* test and analysis of variance (ANOVA) with a Tukey adjustment or the Wilcoxon test, whichever was most appropriate. Significance for results was established as $P < .05$. All statistical analysis was performed using JMP statistical software, version 13.0 (SAS Institute Inc).

Results

Baseline Characteristics

A total of 175 patients were enrolled, and 77 (44%) were males. FH reactions were reported by 38 patients (22%), IFA reactions were reported by 124 patients (71%), and reactions to both FH and IFA were reported by 13 (7%). Table 1 summarizes the baseline characteristics. The type of venom reaction was not associated with sex differences among the 3 insect groups. No statistically significant differences were found between patients with reactions to FH compared with IFAs when analyzing mean age (mean age, 31 vs 27 years; age range, 6–63 years vs 2–75 years; $P = .14$). However, those with both FH and IFA reactions were found to be statistically older than those with IFA-only reactions (mean age, 39 vs 27 years; age range, 11–64 years vs 2–75 years; $P = .01$). The pediatric population constituted 34 of the 175 patients (19%) in the total cohort.

Asthma was noted in 36 patients (21%) in the cohort. No differences among the groups were found regarding prevalence of asthma. Two patients (3%, 1 with FH and 1 with IFA reactions) were taking a β -blocker, and 10 patients (6%) were taking angiotensin-converting enzyme inhibitors (2 with FH and 8 with IFA reactions) at time of enrollment. None of our enrolled patients had a history of coronary artery disease.

Initial Reaction Severity

The 3 insect groups were compared based on their initial reaction severity (Table 2). In our population, the type or number of venoms that a patient was sensitized to did not correlate with the severity of their initial reaction ($P = .26$). The cohort included a total

Table 1
Baseline Characteristics of Participants at Time of Enrollment

Characteristic	Total (N = 175)	FH cohort (n = 38)	IFA cohort (n = 124)	FH and IFA cohort (n = 13)	P Value
Male	77 (44)	16 (42)	55 (44)	6 (46)	.96 ^a
Age, y					
Mean (SD)	28 (14)	31 (14)	27 (14)	39 (16)	.14 for FH vs IFA, .01 for FH and IFA vs IFA, and .24 for FH and IFA vs FH
Range	2–75	6–63	2–75	11–64	
Age <17 y	34 (19)	6 (16)	27 (22)	1 (8)	
Asthma	36 (21)	7 (18)	26 (21)	3 (23)	.92 ^a
β -Blocker use	2 (3)	1 (3)	1 (1)	0 (0)	
ACE inhibitor use	10 (6)	2 (5)	8 (6)	0 (0)	

ACE = angiotensin-converting enzyme; FH = flying Hymenoptera; IFA, imported fire ant.

^aP values comparing IFA, FH, and both.

Table 2
Initial Reaction Severity

Grade	No. (%) of reaction				P value
	Total (N = 175)	FH cohort (n = 38)	IFA cohort (n = 124)	FH and IFA cohort (n = 13)	
A (large local reactions)	9 (5)	3 (8)	6 (5)	0	.26 ^a
B (systemic cutaneous only, eg, hives/angioedema)	26 (15)	4 (11)	22 (18)	0	
C (cutaneous and other system)	114 (65)	27 (71)	78 (63)	9 (69)	
D (hypotension or hypoxia)	24 (14)	3 (8)	17 (14)	4 (31)	
E (serum sickness–like reaction)	1 (1)	0	1 (1)	0	

Abbreviations: FH, flying Hymenoptera; IFA, imported fire ant.

^aThere was no statistical significance in regard to reaction severity across all groups.

of 9 patients (5%) who sought allergy care for a history of large local reactions (grade A). Cutaneous SRs (grade B) were reported in 26 patients (15%) of our cohort. Overall, the most common reaction was a grade C (114/175 [65%]), which was a cutaneous SR with gastrointestinal or respiratory symptoms that did not involve hypoxia or hypotension. Severe, grade D reactions occurred in 24 patients (14%) in our cohort. One patient in the IFA group sought care after experiencing a serum sickness–like reaction. Children and adults were compared and had no significant differences in the severity of their initial reactions ($P = .63$).

Emergency Care

Specific ED intervention data were not available in some patients, and specific data points were excluded from analysis. Whenever possible, the limited data available for a patient were included. Complete ED treatment data were obtained for 19 of the 38 patients (50%) with FH reactions, 96 of the 124 patients (77%) with IFA reactions, and 9 of 13 coreactive patients (69%). There were 150 patients who sought ED care and recalled whether epinephrine was administered. Of those, only 32 (21%) received epinephrine. There were 155 patients who sought ED care and recalled whether an antihistamine was administered. Of those, 141 (91%) received an antihistamine. There were 148 patients who sought ED care and recalled whether a steroid was administered. Of those, 67 (45%) received a steroid. There were 73 patients who presented to the ED with a grade C or D reaction that also had epinephrine administration information. Of those patients, 27 received epinephrine in the ED when they arrived for treatment. Overall, 37% of patients presenting to the ED who met the criteria for anaphylaxis after receiving an insect sting received the recommended therapy of epinephrine.

Emergency treatment was analyzed for differences based on the patient's insect reaction history (IFA only, FH only, both IFA and FH) (Fig. 1A). A total of 104 of the 175 patients (59%) sought ED care, and patients from each insect group were equally likely to seek ED care ($P = .73$). In addition, the treatments received in the ED did not vary by insect group (epinephrine use: $P = .74$; antihistamine use: $P = .95$; steroid use: $P = .75$).

Emergency care was next analyzed for differences based on age (Fig. 1B). The likelihood of seeking ED care for the pediatric cohort was similar to adults (62% vs 59%; $P = .76$). A secondary 2-way ANOVA was performed to assess whether there were differences in children and adults who sought care compared with severity of the reactions and no variations were found. In addition, the treatments received in the ED did not vary between children and adults (epinephrine use: $P = .11$; antihistamine use: $P = .60$; steroid use: $P = .99$). Given the small sample size, it is notable that children were administered epinephrine approximately half (11%) as often when compared with their adult counterparts (24%); however, the study was not sufficiently powered to achieve a significant P value.

Finally, reaction severity data were compared with likelihood of seeking ED care, epinephrine use, steroid use, and antihistamine

use. Overall, patients with more severe reactions were statistically more likely to present to the ED ($P < .001$). They were also more likely to have epinephrine administered ($P < .001$) and steroids prescribed ($P < .05$). No correlation was found between antihistamine use and severity of reaction. On secondary 2-way ANOVA analysis, these findings were independent of age.

Specific IgE Analysis and Immunotherapy

Overall, 149 of the 175 patients (85%) in our cohort were confirmed to have specific IgE to FH, IFA, or both. Table 3 summarizes the patient's venom testing data and VIT initiation rates with comparisons between the insect groups. Differences were found in the likelihood of positive test results found between the FH and IFA groups as well as between the FH group and those with reactions to both ($P < .05$). Positive specific IgE test results was confirmed in 149 of the total 175 patients (85%), 26 of the 38 patients in the FH group (68%), 110 of the 124 patients in the IFA group (89%), and 13 of the 13 patients in the coreactive group (100%).

Furthermore, 127 of the 175 total patients (73%) in our cohort initiated VIT. Patients with positive test results ($n = 149$) were offered VIT at the discretion of their primary allergist. Of those with positive test results, 127 of 149 (85%) chose to pursue VIT. When the patients who tested positive ($n = 149$) were divided based on insect group, all categories were equally likely to select initiation of immunotherapy (FH, 21/26 [80%]; IFA, 95/110 [86%]; both, 11/13 [85%]).

Discussion

This is the first study, to our knowledge, to compare patients with HVA reactions by correlating their initial ED course with subsequent specific IgE testing and determination to pursue VIT. In comparing those with histories of reactions to IFA, FH, and both, many similarities were confirmed. Baseline characteristics were similar with no predilection for sex regardless of type of venom hypersensitivity. Despite the potential for children to be at increased risk for IFA reactions based on their increased sting rate, we did not find any statistically significant correlation between age and seeking care for HVA in our cohort. It is notable that increased age is associated with a statistically significant increase of having both an IFA and FH allergy, which is likely a reflection of the increased lifetime exposure to a variety of stings over time.

Interestingly, our data revealed an asthma rate of 21% in venom allergic patients. Compared with data from the Centers for Disease Control and Prevention, this is 2.5 times more frequent than the rate in the general US population of 8.3%.²⁵ This finding is in contrast to an ED analysis by Rudders et al,⁸ who reported an asthma rate of 6% in patients presenting to the ED for treatment of stinging insect reactions. In another ED analysis of stinging insects, Clark et al⁹ reported a general atopic rate of 33% to 39% but did not differentiate among food allergies, allergic rhinitis, or asthma. A safety report of patients receiving IFA whole body extract immunotherapy found a prevalence of asthma in 21% in those without a history of SRs to subcutaneous immunotherapy and 29% in those with SRs to

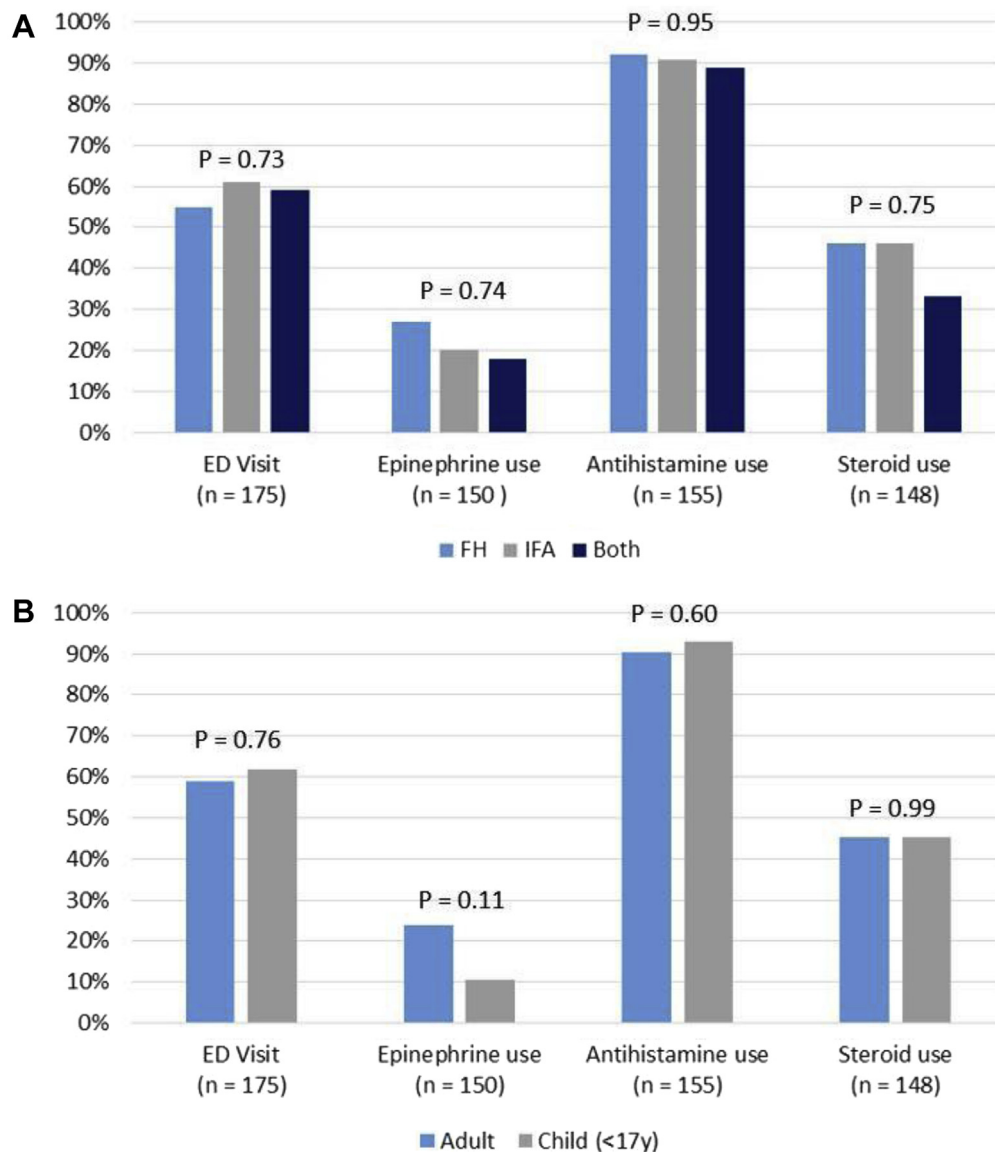


Figure 1. A, Insect analysis of emergency care. B, Age analysis of emergency care.

subcutaneous immunotherapy.¹³ To our knowledge, this is the only published study that specifically reports on asthma rates in an IFA reactive group. Additional studies are needed to confirm that asthma is associated with increased risk of HVA reactions.

This study found no difference in the severity of initial reactions, the likelihood of ED presentation, or treatment in the ED with epinephrine, antihistamine, and steroid use between the HVA groups regardless of age. The lack of differences between children and adult reactions, initial presentation, and treatment in the ED was unexpected. We hypothesized that the parents of children would be more likely to seek care in the ED for more minor

reactions and that the ED staff would be more likely to treat children with epinephrine. Although not statistically significant, the finding that children were administered epinephrine approximately half (11%) as often as adults (24%) in the ED was surprising. This finding is in stark contrast to rates of epinephrine administration for food-induced anaphylaxis reported by the Mount Sinai Pediatric ED and Massachusetts General Hospital ED, which ranged from 63% to 79%.^{26,27} The reason for such a discrepancy remains to be elucidated but may be attributable to the cultural environment in the ED at the academic centers where the studies were performed. Our report is the first known study to date, to our knowledge, that

Table 3
Follow-up sIgE Testing and VIT Initiation Rates

	No. (%) of cases				P value
Variable	Total	FH cohort	IFA cohort	FH and IFA cohort	
Confirmation of sIgE	149/175 (85)	26/38 (68)	110/124 (89)	13/13 (100)	.05 for FH vs IFA, .20 for FH and IFA vs IFA, and <.05 for FH and IFA vs FH
Positive sIgE test results ^a and initiated VIT	127/149 (85)	21/26 (80)	95/110 (86)	11/13 (85)	.47 for FH vs IFA, .86 for FH and IFA vs IFA, and .78 for FH and IFA vs FH

Abbreviations: FH, flying Hymenoptera; IFA, imported fire ant; sIgE, specific IgE; VIT, venom immunotherapy.

^aPatients with positive sIgE test results represent the denominator values listed in this row.

compares the ED use of epinephrine in children vs adults with stinging insect reactions. With our data revealing concerning discrepancies, further studies are needed.

We noted a suboptimal rate of epinephrine administration of 37% in patients who met the clinical criteria for anaphylaxis. This finding is in line, however, with the findings of Clark et al.⁹ who found a rate of epinephrine administration of 34% from 1999 to 2001 with an increased rate of 49% from 2013 to 2015 in stinging insect reactions in patients presenting to the ED. Although epinephrine administration rates were concerning, our study provided some limited reassurance that patients with more severe reactions were not only more likely to present to the ED but also more likely to receive epinephrine. In our cohort, patients with any level of reaction were equally likely to receive an antihistamine and were also equally likely to receive steroids. Steroid use is not indicated as first-line treatment for venom hypersensitivity reactions, including anaphylaxis.^{21,28} Despite this knowledge, our study indicates that steroids continue to be used independent of severity. Clearly, a multifactorial approach is necessary to tackle the underuse of epinephrine in the treatment of anaphylaxis.²⁹

Regarding follow-up evaluation, this study found that 73% of all patients seeking care in an allergy clinic after having a hymenoptera reaction had positive sIgE test results, and 85% of those with positive sIgE test results initiated lifesaving VIT. Significantly higher rates of positive test results were seen in those with history of IFA reactions compared with the FH group. This finding may be attributable to the generally high sensitization rates in IFA endemic regions.^{10,14–16} Of those patients who tested positive (positive for sIgE on skin or serologic tests), those with reactions to FH, IFA, or both were all equally likely to initiate VIT.

There are several limitations of the study. One limitation is recall bias; much of the initial reaction data were based on subjective history when ED records were not available. A further limitation is the single site in an IFA endemic region that prevents comparison to other regions of the country. Lastly, our study was performed in a military clinic with patients who relocate frequently. Although speculative, this reality may affect their decision to pursue VIT. Future studies are needed to explore the rationale for barriers to initiating VIT.

Patients with IFA and FH reactions have many similarities in their baseline characteristics, initial reactions and ED treatments. The severity of HVA reactions correlated with ED visits and the use of epinephrine independent of age. Asthma was noted to occur 2.6 times more frequently in patients with reactions to stinging insects than in the general US population. Epinephrine use in the ED for patients presenting with anaphylaxis to a stinging insect are suboptimal at 37%. Children have initial reactions and are treated in the ED similarly to adults, with a notable (although not statistically significant) decreased use of epinephrine. In addition, most patients (73%) seen in the ED and subsequently followed up in an allergy clinic had their venom allergy confirmed and went on to initiate life-saving immunotherapy.

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