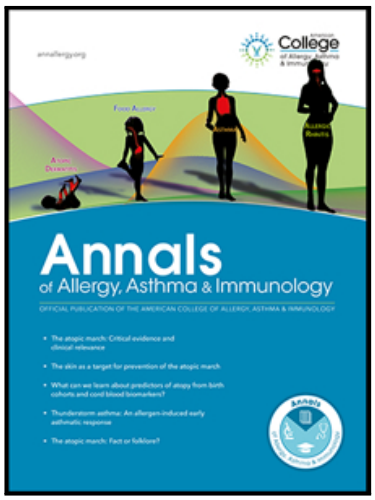

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A Twenty-two-year Experience with Hymenoptera Venom Immunotherapy in a US Pediatric Tertiary Care Center: 1996-2018

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Keywords

Venom immunotherapy; Hymenoptera stings; Insect Stings; Pediatric; Children; Tryptase; Systemic Reactions; Safety ; Honey Bee; Vespinae; Wasp;

Abbreviations: BCH, Boston Children's Hospital; CCD, Cross-reactive Carbohydrate Determinant; HB, Honey Bee; IDT, Intradermal Test; SPT, Skin Prick Test; SR, Systemic Reaction; SPT, skin-prick test; VIT, Venom Immunotherapy; WH, White-faced hornet; YH, Yellow Hornet; YJ, Yellow Jacket

Introduction

The severity of allergic reactions to insect stings ranges from mild, local reactions to systemic, life-threatening anaphylaxis.[1, 2] Systemic reactions (SRs) to Hymenoptera stings can occur in 0.5-3.3% of adults in the US and 0.3-7.5% of adults in Europe.[3, 4] In pediatric patients, the prevalence of SRs is lower, from 0.15-0.8%.[5-8] In addition, in children, the majority of SRs from sting consist of exclusively cutaneous symptoms.[9] Venom immunotherapy (VIT) is very effective in decreasing the SR risk after

subsequent sting and is generally indicated in subjects with histories of SRs to Hymenoptera stings with extra-cutaneous symptoms.[10]

While most patients tolerate VIT well, some may experience SRs during therapy. In a 3-year, European, multicenter prospective study of 840 VIT patients age 5-77 years, 20% of patients had SRs to VIT, the vast majority of which were mild with only 6 patients requiring epinephrine.[11] In comparison, the United States Hymenoptera venom Study III reported SRs in 12% of 1,410 VIT patients treated from 1979-1982.[12] However, the incidence of SR and rate of reactions per injection-visit to VIT in pediatric patients has not been well evaluated.[13, 14] In addition, studies evaluating concomitant sensitivity to different venoms by skin prick/intradermal and/or serum specific IgE testing in children have been limited.[13, 15] In this retrospective chart review, we report on our 22-year experience at Boston Children's Hospital (BCH), with pediatric patients receiving Hymenoptera VIT. We discuss patient presentation, demographic information, safety of VIT and concomitant sensitivity to Vespinae (Yellow Jacket, Yellow Hornet and White-Faced Hornet), Polistes (Wasp) and Honey Bee (HB).**Methods:**

Chart review

We performed a chart review for patients age 3-18 years who were initiated on VIT in the Allergy Program at BCH's main and 4 satellite locations (all within a 20-mile radius from Boston, MA) between January 1996 – January 2018. For patients treated from 2007-2018, the number of injection-visits was calculated by electronically retrieving VIT visits billed under CPT codes 95115 and 95117. For patients treated before 2007, the number of injection-visits for each patient receiving VIT was retrieved from the electronic medical record on EPIC. We excluded patients who received aeroallergen

subcutaneous immunotherapy or Omalizumab. The BCH Institutional Review Board approved this protocol. Information related to age, gender, atopic conditions, severity of reactions to field insect sting, tryptase level, venom testing as well as SRs from VIT was retrieved.

Evaluation of patients with insect field sting reactions

Allergic reactions to insect stings were classified as local if only localized reaction at the site of the sting was reported, or systemic if other sites were involved. SRs were graded as mild, moderate, or severe, similar to the classification of Golden, *et al*.[2] Mild (cutaneous) SRs included skin reactions including urticaria, angioedema or both, distant from the sting site without involvement of other organs. Moderate sting SRs included cutaneous symptoms combined with respiratory symptoms, such as chest or throat discomfort, symptoms of airway obstruction, lightheadedness and/or mild dizziness. Severe sting SR included symptoms of shock, hypotension or unconsciousness. Severity of field sting reactions was evaluated prior to and after VIT initiation.

Evaluation of venom sensitization:

All patients who received VIT underwent skin prick/intradermal testing and/or serum venom-specific IgE testing to define venom sensitivities and to guide selection of VIT extracts for individual patients. VIT was generally administered to pediatric patients with clinical history of moderate-to-severe SR and positive venom-specific skin-prick/intradermal testing and/or venom-specific IgE testing. A few patients received VIT for mild cutaneous or large local reactions (≥5 cm) to sting, primarily because of parental anxiety. Patients received VIT for all Hymenoptera species for which they had positive testing. Skin prick test (SPT), intradermal testing (IDT) and venom-specific IgE

testing were performed to: honey bee (HB), wasp, and *vespinae* venoms including yellow jacket (YJ), yellow hornet (YH) and white-faced hornet (WH). SPT was performed on the flexor surface of the forearm by using extracts with a concentration of 1 mcg/ml. Venom-specific SPT was considered positive if produced a wheal ≥3mm larger than saline control. If SPT was negative, IDT was performed, starting at a concentration of 0.001 ug/mL for patients with a history of severe reaction and 0.01 ug/ml for all other patients. A volume of 0.02-0.03 ml sufficient to raise a 3-4 mm bleb in the skin was administered for each IDT. If initial IDT was negative at the initial step, additional IDT was performed at a concentration of 0.1 ug/ml, followed, if negative, by a final intradermal test at 1 ug/ml. SPT and intradermal extracts were obtained from Hollister-Stier (WA, USA). Venom-specific IgE testing was measured by ImmunoCAP; common extracts were obtained from Phadia (MI, USA). Values >0.35 KU/L were considered positive. Serum tryptase levels were measured at ARUP or VCU laboratories using the UniCAP method. Values greater than 11.4 ng/mL were considered elevated.[16]

VIT protocol

VIT consisted of a weekly build-up period of 8-10 weeks starting at a venom dose of 0.1 mcg until the maintenance dose of 100 mcg was reached (Table 1), after which doses were administered every 4-6 weeks. VIT bulk extracts were obtained from Hollister-Stier (WA, USA). Patients were examined by a nurse or a physician prior to dose administration and observed for at least 30 minutes before discharge from clinic. Doses were withheld if patients reported or demonstrated signs of infection or asthma exacerbation.

Grading of VIT SRs

Venom immunotherapy SRs were discussed at monthly meetings attended by BCH Allergy faculty and clinical fellows-in-training. For patients who reacted, we reviewed meeting minutes and medical records to collect reaction signs and symptoms, timing of the reactions after VIT administration, extract(s) administered, dose injected and rescue therapy administered. The authors used the World Allergy Organization (WAO) 5-level grading system (Table 2) to assess the severity of SRs to VIT.[17] SRs were classified as either immediate (occurring within 30 minutes) or delayed (occurring more than 30 minutes after VIT administration). SRs were treated with rescue medications based on reaction severity, at the discretion of the supervising allergy physician.

Statistical analysis

Descriptive statistics (means and standard deviations) were calculated using SPSS Statistics version 23 (IBM). For categorical variables, comparisons between groups were performed using Fisher's exact test. $p \leq 0.05$ was considered significant.

Results

VIT patient characteristics

Seventy-eight pediatric patients received VIT at 3,564 injection-visits. Sixty patients were male (77%), and 18 (23%) were female. The mean age at the time of the allergic reaction to insect sting was 8 ± 3.8 years. Mean age at the time of VIT initiation was 9 ± 3.6 years. Fifty percent of patients had atopic disease, with asthma present in 28%, allergic rhinitis in 29%, food allergies in 14% and atopic dermatitis in 8% of subjects (Table 3).

Only 11 patients (14%) had evaluation of serum tryptase levels. Tryptase was normal in all but one subject (9%). This patient initially had a total serum tryptase at the upper limit

of normal (11.2 ng/mL, normal range 0-11.4 ng/mL). Her total serum tryptase level increased further to 15 ng/mL after 5 years of VIT, while mature tryptase remained normal. She had a moderate SR to insect sting prior VIT and did not have any subsequent SR from therapy or from stings. Notably, one patient with cutaneous mastocytosis had a normal tryptase level.

Characteristics of insect field sting reactions pre-VIT

Nine patients (11.6%) of the 78 patients on VIT experienced severe SRs after Hymenoptera field stings, 56 (72.7%) had moderate SRs and 8 (10.4%) had only mild cutaneous SRs. Only 4 patients (5.3%) had large local reactions. Overall, 84.3% of patients who received VIT had either moderate or severe reactions to Hymenoptera stings prior to therapy. Epinephrine was used by first responders and/or emergency physicians to treat all severe SRs, 60 % of moderate SRs and 50% of mild SRs. Interestingly, of the 9 patients with severe SR's, only one patient (11%) had positive testing to HB (in addition to *vespinae)*. The remaining 8 (89%) were positive to vespinae, wasp or both but negative for HB.

Time from sting to onset of SRs was reported in the medical record for 73% of patients in this cohort. In these patients, the majority of SRs (84%) were reported to occur within 10 minutes of the sting. These immediate reactions were predominantly moderate-to-severe SRs (87%).

Risk factors for moderate to severe reactions to Hymenoptera field stings pre-VIT

We evaluated patient gender as a potential risk factor for SR severity to insect field sting. In males, most insect field sting SR's were moderate or severe SRs (93%); the remainder were mild SRs (5%) or large local reactions (2%). In contrast, in females,

50% of reactions to stings were moderate-to-severe SRs, compared to 27.7% mild SRs and 16.7% large local reactions. Male gender was a significant risk factor for moderate-to-severe SR (p=0.008).

Venom testing

We evaluated the frequency of positive venom testing by SPT/IDT, serum venom-specific IgE and both skin and blood tests combined. In this analysis, vespinae were all included as one group, considering their significant cross-reactivity.[18]

SPT and intradermal testing to HB, wasp, and vespinae venoms were performed in 71 patients. SPT was negative in the vast majority of these patients (91.5%). Among the 6 patients who had positive SPT, 2 were positive to HB extract and 3 to at least one of the vespinae. Only one subject had positive SPT to all venom extracts. In contrast to SPT, IDT was positive in the majority of patients (94%). Serum venom-specific IgE testing was performed in 49 patients. Of these, 37 (75.5%) had positive venom-specific IgE.

The results of concomitant sensitivity between the 2 modalities (skin and venom-specific IgE testing) were very similar (Figure 1A and 1B). When including patients positive on either or both tests, the vast majority of patients (98.7%) were positive to vespinae, two-thirds were positive to wasp and only 41.5% were positive to HB (Figure 1C). In addition, 31.1% were positive to all 3 groups. Three-quarters of patients were sensitive to a combination of vespinae, wasp and/or HB. Almost a fourth of patients (23.2%) were sensitive only to vespinae. Only 1 patient (1.3%) was positive exclusively to wasp, and none were exclusively positive to HB.

As we did not perform sting challenges to evaluate clinical reactivity to a specific venom, we compared the differential sensitivity of patients to YJ and HB venoms by intradermal

and serum-venom specific IgE testing. Sixty-eight percent of patients were positive on intradermal testing to YJ at a concentration at least 10-fold lower than HB, while 13% were positive to HB at a concentration at least 10–fold lower than YJ. Similarly, almost half the patients (46%) had YJ-specific IgE level at least a 3.16 fold or half-log higher than HB-specific IgE, while only 4.8% of patients had HB-specific IgE level at least half log higher than YJ-specific IgE.

Vespinae concomitant sensitivity by SPT/IDT and/or serum IgE testing

To further evaluate the concomitant sensitivity between WH, YJ and YH in children, we considered patients who had positive testing to vespinae by SPT/IDT (Figure 2A), venom-specific IgE (Figure 2B) and both tests combined (Figure 2C). YJ-specific IgE was positive in 94.4% of vespinae allergic patients compared to 85.3% by SPT/IDT. This might suggest greater sensitivity of venom-specific IgE testing than skin testing, however, this difference was not statistically significant (p=0.318). When combining both tests, YJ was positive in 90.3% of patients, WH in 73.7% and YH in 83.8 % of patients. More than two-thirds of patients were sensitive to all three vespinae species (67%), and 16.8% were positive to 2 vespinae. YJ was exclusively positive in 11.8% of subjects. Only 1.4% of patients were exclusively positive to WH and none to YH.

Systemic reactions to venom immunotherapy

A total of 7 SRs occurred in 7 patients secondary to VIT (9% of total patients, Table 4 and eTable 1). The rate of SR was 0.2% of injection-visits (7 of 3,564 injection-visits). Five SRs were grade 1 (71.4%), and 2 were grade 2 (28.6%). There were no grade 3, 4 or grade 5 SRs. The majority of SRs (85.7%) occurred within 30 minutes of receiving VIT; one SR (14.3%) was delayed (grade 1). Two SRs (28.6%) did not require treatment

as symptoms subsided quickly, 4 were treated with antihistamines and 1 with albuterol. No SR required treatment with epinephrine. Furthermore, four SRs (57.1%) occurred in the build-up phase of the protocol and 3 (42.9%) occurred during the maintenance phase. None of the 7 patients who reacted to VIT had a history of severe reaction to insect stings; 6 had moderate sting reactions and 1 patient had a mild reaction. No statistically significant increase in risk of SR from VIT was associated with comorbid atopic conditions (p= 1.000), male gender (p=1.000), asthma (p=0.094), or age (≤11 years old versus 12-18 years; p= 0.643).

Subsequent Insect Field Stings after VIT initiation

Twenty-one patients (27%) were subsequently stung while on VIT. At time of re-sting, one patient was on build-up VIT; all others were on maintenance. Most of these patients (12 or 57%) had a local reaction upon being re-stung; 8 (38%) had no reaction at all. Only one patient (5%), an 8-year old male, had an insect sting SR while in the first year of maintenance VIT, which consisted of a very mild cough and few hives. This reaction was milder than his anaphylactic reaction from the first sting prior to VIT initiation, during which he had extensive swelling at the sting site with purple skin discoloration, diffuse rash and significant abdominal pain.

Venom Re-testing

Thirty patients (38.5%) underwent re-testing by SPT/IDT and/or serum IgE testing within 3-5 years after starting VIT (Figure 3). Of these, 18 (60%) had negative testing and VIT was subsequently discontinued. However, in 9 patients (30%), IDT was either unchanged or became positive at higher concentration compared to baseline. Of these, 6 (20%) were continued on VIT per treating physician's discretion and/or patient's

preference and 3 (10%) discontinued therapy. Furthermore, only 3 patients (10%) had a new sensitivity to venoms, including one with positive IDT at lower concentrations compared to baseline. Two of these patients were continued on VIT and one was discontinued.

Discussion

To our knowledge, this is the largest US-based pediatric study specifically evaluating the rate of SRs to VIT and the concomitant sensitivity of patients to different Hymenoptera venoms. We found that SRs to VIT occurred in 9% of subjects, at a rate of 0.2% of injection-visits. SRs were mild, and none required epinephrine therapy. No specific demographic variable could be identified as significant risk factor for VIT-associated SR. The vast majority of SRs from VIT were immediate, while 14% were delayed. This is very similar to what we and others have observed in patients treated with subcutaneous aeroallergen immunotherapy.[19, 20]

In our study, 75.3% of patients were treated with combination of extracts rather than an exclusive therapy to a class of venom. In addition, no patient was exclusively sensitive to HB, and 41.5% of patients received HB combined with other extracts. HB therapy in our patients was not associated with a higher rate of SRs to VIT. Mixed vespinae and wasp were given to 100% of patients who developed SRs, while HB combined with mixed vespinae and wasp venom were given to 71% of them. Interestingly, of the 9 patients with severe SRs prior to VIT, only one (11%) was positive on testing to HB and vespinae. The remaining 8 (89%) were positive to vespinae, wasp or both. As in other studies, the severity of the initial, pre-VIT insect field sting reactions in our patients did not correlate with the occurrence of SRs from VIT.[12]

The rate of SRs observed in our cohort is similar to that reported by Chipps, *et al*. in 1980,[13] who found 6% of 44 children seen in the in the mid-Atlantic USA developed SRs, at a rate of 0.3% of injection-visits, and to a recent Turkish study in which 6.3% of 101 VIT-treated children developed SRs, with a SR rate of 0.17% of injection-visits.[14] However, in the latter study, the severity of SRs from insect field stings prior to VIT were not reported and weekly build-up injections up to a maintenance dose of 100 mcg lasted for 6 months, while in our study, up-dosing took only 8-10 weeks. In addition, the vast majority of the patients in Turkey received only *Vespula* (75.7%) and 23% only *Apis mellifera* (European Honey Bee) immunotherapy. Interestingly, 19% of patients receiving *Apis* IT developed SRs, compared to 3.7% of *Vespula* treated patients.[14] In a recent pediatric study from Israel comparing rush immunotherapy over 3 days to conventional build-up over 17 weeks up until a maintenance of 100 mcg was reached, 83.3% of patients were treated exclusively with HB immunotherapy. Around 20% of subjects developed SRs from VIT and epinephrine was given to 6.29% of subjects.[21] Lockey, *et al*. also reported in their large adult and pediatric study that subjects who had SRs from VIT received HB more than any other venom.[12] Unlike studies where patients may be treated based on patient recognition of the insect or on the type of terrain where the sting occurred,[14, 22] in our center, patients generally receive VIT for all venoms to which they are sensitized, based on SPT/IDT and/or venom-specific IgE level. As we do not routinely perform sting challenges prior to VIT, our study has limited ability to address the definite venom allergenicity in our patients at the time of initiation to VIT. However, on testing, more than 2/3rd of our patients demonstrated IDT positivity to YJ at least 10-fold lower concentration than to HB, and almost half had a YJ-specific IgE level

at least a half-log higher than HB-specific IgE. Hence, our results suggests that HB allergy in the New England pediatric population may not be as significant as in children living in the Mediterranean area or in Europe.

When combining the results of both SPT/IDT and venom-specific IgE testing, we found that all patients except one (98.7%) were sensitive to at least one vespinae. In addition, 84% were sensitive to more than one vespinae and 90% were positive to YJ. This rate of vespinae-sensitivity is higher than other US pediatric studies, where the rate was found to be 73.2-88.6%.[9, 13, 15] In addition, these studies found an exclusive HB sensitivity of 11.3-22.1% of subjects. Only 1.3% of our patient population was exclusively sensitive to wasp, comparable to previous reports (3.7-3.9%).[9, 13, 23]

In our study, skin testing appeared more sensitive than venom-specific IgE, but the results of these 2 modalities were not completely identical, suggesting that combining both testing may be valuable prior to VIT initiation. However, a significant limitation in our data is that we did not evaluate cross-reactive carbohydrate determinant (CCD) free component-specific IgE testing, which is not routinely performed in our center. Double-positivity to YJ and HB has been reported in up to 60% of venom allergic patients and is more commonly noted on venom-specific IgE testing than skin testing. This phenomenon is attributed to IgE antibodies directed against clinically irrelevant CCDs, rather than true double positivity.[24-27] Interestingly, in our study, concomitant sensitivity to vespinae and HB was slightly more frequent with skin testing (32.8%) than with serum venom-specific IgE (27.1%, Figure 1A and B). However, the rate of true double-positivity could not be evaluated.

Prior studies have suggested that insect sting reactions are more common in males than in females. [7, 9, 23] In our cohort, 77% of VIT-treated patients were males. A similar rate was reported by 2 recent pediatric VIT studies.[14, 21] We also found that male gender, compared to female, was a significant risk factor for moderate-to-severe SRs after insect field sting (p=0.008). Interestingly, male gender was also found to be a risk factor for more severe reactions in adults.[28] It remains unclear why gender plays a role in insect sting reaction frequency or severity.

Elevated basal tryptase serum levels have been reported to be associated with severe SRs to Hymenoptera stings.[28-31] Of 11 patients in our cohort tested for serum total tryptase, only one female subject (9% of patients tested) had an elevated level. This is similar to rates reported by previous studies (7.3-11.6%).[29, 30] Interestingly, this patient had only a moderate reaction to Hymenoptera sting prior to VIT and tolerated her VIT with no SRs. The rate of elevated tryptase level and its significance in children with Hymenoptera allergy requires further evaluation.

We found that atopic diseases were present in 50% of patients on VIT. Our findings are similar to those reported in Spanish children, where atopy was found in 44% of 175 patients who reacted to insect sting with either local reactions (83.9%) or SR (16.4%).[32] In the Hymenoptera Venom Study I,[23] a history of atopic diseases was present in only 32% of patients who reacted to Hymenoptera insects. It was beyond the scope of this study to evaluate the demographics of all patients who presented at BCH with insect sting reactions, as we focused on patients who were ultimately treated with VIT.

VIT has been shown to be very effective in reducing the risk of subsequent insect sting SR to as low as 5%.[33, 34] In our cohort, 5% of patients had a SR after being re-stung

while on VIT. This is lower than the rate reported in Turkish patients who were exclusively treated with a single VIT extract, as 13-20% of those who were re-stung developed SRs.[14] It was beyond the scope of this study to evaluate the rate of SRs from insect sting following cessation of VIT.

We found that the rate of SRs to VIT in our pediatric patients was low, at 0.2% of injection-visits, and SR to VIT occurred in only 9% of patients. Most SRs from VIT were very mild (grade 1) and no severe reactions occurred. Overall, VIT appears to be safe in children, even in those with a history of severe SRs to insect sting. No specific venom was associated with higher risk of SR from VIT. However, it is possible that our results were affected by a decreased prevalence of HB allergy in our patient population. Male gender appears to be a risk factor for moderate-to-severe reactions to insect sting in children. Larger, multi-center studies are needed to evaluate further the safety of VIT in pediatric patients and the effect of risk factors including geographic variation, gender, atopic diseases, and elevated serum basal tryptase level on the severity of reactions to Hymenoptera stings.

Conflict of Interest

The authors state no conflict of interest

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None

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Figure 1. Distribution of positive Honey Bee, Wasp and Vespinae venom-specific testing. (A) Skin-prick/intradermal venom-specific testing. (B) Serum venom-specific IgE testing. (C) Combined skin-prick/intradermal and/or serum venom-specific IgE positive testing.

Figure 2. Distribution of positive Vespinae venom-specific testing. (A) Skin-prick/intradermal testing. (B) Serum venom-specific IgE test. (C) Combined skin-prick/intradermal and/or serum venom-specific IgE.

Figure 3. Flow diagram detailing outcome of patients who underwent repeat venom testing after venom immunotherapy initiation.

Table 1. Conventional weekly venom immunotherapy build-up protocol

Week	*Concentration (mcg/ml)*	*Volume (ml)*
1*	1	0.1
2*	10	0.1
3	10	0.5
4	100	0.1
5	100	0.2
6	100	0.4
7	100	0.5
8	100	0.6
9	100	0.8
10	100	1

*In some patients, the first 4 doses were administered twice a week for 2 weeks.

Table 2. World Allergy Organization (WAO) grading of systemic reaction severity.

Grade 1	Symptom(s)/signs of 1 organ system present: generalized urticaria with/without angioedema (NOT laryngeal, tongue, or uvular) or nausea or upper respiratory
Grade 2	Asthma responding to an inhaled bronchodilator and/or gastrointestinal symptoms, including abdominal cramps, vomiting, or diarrhea, or uterine
Grade 3	Severe asthma not responding to a bronchodilator or laryngeal, uvular, or tongue edema, with or without stridor.
Grade 4	Respiratory failure or hypotension with or without loss of consciousness.
Grade 5	Fatal reaction

Table 3. Demographic data.

Patients, n	**78**
Age at initial insect sting SR , years (mean ± SD)	8 ± 3.8
Age at initiation of VIT, years (mean ± SD)	9 ± 3.6
Initial Sting Reactions, n (%)	
Mild Cutaneous Systemic	8 (10.4)
Moderate Systemic	56 (72.70)
Severe Systemic	9 (11.60)
Large Local reactions	4 (5.30)

Gender (M), n (%)	60 (77)
Allergic rhinitis, n (%)	23 (29)
Asthma, n (%)	22 (28)
Food allergy, n (%)	11 (14)
Atopic dermatitis, n (%)	6 (8)
Cutaneous mastocytosis, n (%)	1 (1.3)

Table 4. Characteristic of patients with systemic reactions to VIT

Patient no	*Sex*	*Age (y)*	*Field Sting Systemic Reaction (grade)*	*Venom IT*	*VIT systemic reaction (grade/symptoms)*	*Treatment*	*Timing of SR (minutes)*	*VIT SR phase*	*VIT SR dose*
1	F	13	Moderate	Mixed vespids, wasp	1/ Throat itching	Antihistamine	< 30	Up-dosing	5 mcg
2	M	11	Moderate	Mixed vespids, HB, wasp	1/ Erythematous conjunctiva	Antihistamines	< 30	Maintenance	100 mcg
3	M	7	Moderate	Mixed vespids, Wasp	1/ Hives	Antihistamine	< 30	Up-dosing	60 mcg
4	M	8	Mild	Mixed vespids, HB, wasp	2/ Cough	Albuterol	< 30	Maintenance	100 mcg
5	M	9	Moderate	Mixed vespids, HB, wasp	2/ Vomiting and throat discomfort	None	< 30	Maintenance	100 mcg
6	M	14	Moderate	Mixed vespids, HB, wasp	1/ Throat itching	None	>60	Up-dosing	0.1 mcg
7	M	7	Moderate	Mixed vespids, HB, Wasp	1/ Hives	Antihistamine	< 30	Up-dosing	50 mcg