

Age-dependent sting recurrence and outcome in immunotherapy-treated children with anaphylaxis to Hymenoptera venom

A. I. Stritzke¹ and P. A. Eng²

¹Department of Paediatrics, Kantonsspital Aarau, Switzerland and ²Allergy Unit, Children's Hospital, Kantonsspital Aarau and Lucerne, Switzerland

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Summary

Background Data on outcome of insect venom immunotherapy in children are rare.

Objective We investigated the rate of sting recurrence and outcome of Hymenoptera venom anaphylaxis in children of different age groups treated with immunotherapy.

Methods Data from children consecutively referred for anaphylaxis to Hymenoptera venom were collected using a standardized questionnaire.

Results During mean follow-up of 7.7 years after commencement of immunotherapy, 45 of 83 children (56%) were re-stung 108 times by the insect they were allergic to. This corresponds to a rate of 0.23 stings per child and year of follow-up. The younger the subject, the higher was the prevalence of re-stings, with rates of 0.41 in children < 6 years, 0.21 at school age and 0.15 in adolescents ($P = 0.001$). In contrast, prevalence of systemic allergic reactions to field stings was significantly lower in pre-school (3.4%) and school-age children (4.3%) compared with adolescents (15.6%; $P < 0.05$). Overall, prevalence of systemic allergic reactions at re-sting was 15.6% in the honey bee venom and 5.9% in the *Vespula* venom allergic group ($P = \text{ns}$). Younger boys with anaphylaxis to honey bee venom predominated in our cohort ($P = 0.019$).

Conclusion and Clinical Relevance A majority of children with anaphylaxis to Hymenoptera venom (56%) in our cohort were re-stung, equally by honey bees or *Vespula* species. Younger children were more likely to be re-stung, but less likely to have a systemic reaction. Venom immunotherapy induces long-term protection in most children: 84.4% of subjects with anaphylaxis to honey bee and 94.1% of those to *Vespula* venom were completely protected at re-stings.

Keywords children, honeybee venom, hymenoptera venom allergy, long-term protection, re-stings, venom immunotherapy, vespula venom

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Correspondence:

Peter Andreas Eng, Allergy Unit, Children's Hospital, 6000 Lucerne, Switzerland.

E-mail: peter.eng@ksl.ch

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Introduction

Many children affected by anaphylaxis to Hymenoptera venom do not outgrow their allergies to insect stings [1, 2]. The risk for future allergic reactions is greatest in those children with initially more severe systemic allergic reaction (SAR), particularly those involving the respiratory tract and/or the cardiovascular system [1–3]. Recurrence rates of SAR to Hymenoptera stings in untreated subjects with moderate-to-severe SAR are reported as high as 32–58% in children [1, 3] compared to even higher rates of 65–77% in adults [4]. Insect venom immunotherapy (VIT) has been shown to protect individuals with IgE-mediated SAR from new SARs to

insect re-stings [1, 5]. According to current guidelines, VIT is indicated in children, as well as in adults, with a history of severe SAR including respiratory and/or cardiovascular symptoms and documented IgE-mediated sensitization to the respective insect [5–8].

Anaphylaxis affecting the respiratory tract and/or cardiovascular system is the most severe and potentially life-threatening reaction to an allergen, with insect venom as the second most prevalent cause of anaphylaxis in children after food allergy [9, 10]. In these children, VIT is an effective causal treatment. There is little knowledge available, however, about the long-term protective effect of VIT in young individuals [2, 3]. Children are naturally more threatened by re-stings, as

they are less aware of their environment and generally spend a large proportion of time outside their homes. Thus, they might be more susceptible for subsequent sting recurrence and at risk for another allergic reaction to insect venom.

The aim of this study is to describe the rate of sting recurrence and outcome in children with a history of anaphylaxis to Hymenoptera venom who were treated with VIT. Furthermore, we evaluated for a possible age dependency on the rate and severity of subsequent SAR.

Materials and methods

Patients

This was a retrospective cohort study. All paediatric patients consecutively referred from October 1990 to June 2007 for assessment of anaphylaxis to Hymenoptera venom to the allergy units of two participating referral children's hospitals in Aarau and Lucerne, Switzerland, were eligible to participate. The area served by these two medical centres is rural and urban mixed. Inclusion criteria were a diagnosis of Hymenoptera venom allergy with anaphylaxis, followed by commencement of specific VIT. Diagnosis of anaphylaxis to Hymenoptera venom was made based on three parts that all had to be positive:

- History of a Hymenoptera sting followed by a grade III or IV SAR affecting the respiratory and/or cardiovascular tract in addition to cutaneous symptoms according to the classification of Mueller [11].
- Positive intracutaneous skin test with European honey bee (BV) and/or *Vespula* venom (VV) in one of the following concentrations: 0.02 mL containing 10^{-3} – 10^{-8} g/L insect venom.
- Documented increase in specific IgE antibodies (> 0.7 kU/L) to BV and/or VV (Immuno-CAP, Pharmacia and Upjohn Diagnostics, Uppsala, Sweden).

All patients were handed out Emergency Rescue Medication (ERM), including an adrenaline auto-injector with appropriate instruction and written guidelines. Laboratory challenge stings were not performed.

Venom immunotherapy

Venom immunotherapy was commenced in the hospital with Pharmedgen (ALK, Denmark) European honey bee, *Vespula* spp. or both types of venom. Different protocols were used for introduction phase: conventional (16 weekly sc injections), rush (build-up phase in hospital within 5 days) and ultra-rush (6 sc injections on a single day in increasing doses and 30–60 min intervals up to cumulative 111 µg insect venom). Maintenance doses of 100 µg depot preparation (Alutard SQ, ALK Denmark) were given subcutaneously at the paediatrician's office

every 4 weeks during the first year and every 5–6 weeks during subsequent years. All patients were re-evaluated regularly at 18–24 months intervals until stopping VIT after 3–5 years duration.

Follow-up

Information about patients with a diagnosis of anaphylaxis to Hymenoptera was extracted from their medical records. All identified potential study participants were contacted by telephone and/or at their regular visits in the outpatient clinic. Efforts were made to contact the family or the patient via the last known telephone number or email. If ineffective, telephone number databases were employed or the patient's general health care provider was contacted. Primary research tool was a standardized questionnaire administered by a non-blinded single investigator. To ensure the right patient identity, individuals were asked to confirm the details of their treatment before being invited to participate in the trial. Study subjects or their parents gave verbal voluntary consent to participate.

The questionnaire included a list of questions about any accidental stings after commencement of VIT, either during or after discontinuation of VIT. Questions targeted information about tentative species of culprit insect, occurrence setting, severity and time course of any reactions after the sting as well as exact details of any symptoms. Subsequent allergic reactions at time of re-sting were graded according to the classification of Mueller [11]. Data of re-sting occurrence, offending insect and outcome obtained by questionnaire were compared with description in the medical records, where available. If unclear, patients were contacted a second time to match data of questionnaire to those described in medical records.

To examine the impact of age on incidence and severity of SARs, three age groups were pre-defined at the time of diagnosis of Hymenoptera allergy:

- Group 1: 'pre-school', included infants < 6 years.
- Group 2: 'school age' children 6–10 years of age.
- Group 3: 'adolescents', > 10 –16 years of age.

This follow-up study on rate and outcome of re-sting occurrence in children of different age groups was approved by the institutional review boards of the Children's Hospitals Aarau and Lucerne, Switzerland.

Statistics

Pearson Chi-square test and Fisher's exact test were used to compare the number and rate of re-stings as well as percentage of SAR between BV- and VV-allergic patients and between individuals of different age groups. Age dependency in prevalence of sting

recurrence was determined by Poisson regression analysis. Age-dependent gender analysis for BV- and VV-allergic individuals and age-dependant prevalence of SAR upon re-stings were performed using logistic regression analysis.

Results

There were 87 patients identified who fulfilled study inclusion criteria. A total of 83 of them (95%) were successfully contacted and agreed to participate, 4 children were lost to follow-up. Forty-nine (59%) of included subjects were treated with BV, 29 (35%) with VV. Five patients (6%) were treated with both insect venoms. Average duration of VIT was 3.6 years. Average follow-up time from beginning of VIT was 7.7 years (range 0.4–15.9 years), encompassing a total of 639 patient years. Comparative patient characteristics of BV- and VV-allergic groups are shown in Table 1.

More than half of the children (56%) had been re-stung by the respective insect they were allergic to. The cumulative number of re-stings was 108 which corresponded to an average of 1.2 stings per person for the whole cohort, or 2.2 stings per re-stung patient (range 1–8). The rate of re-stings was 0.23 per patient per year of follow-up with no significant difference between honey bee and *Vespula* stings (Table 2).

Younger children were re-stung more often than older patients: in group 1 the rate was 0.41 per patient year, compared to 0.21 in group 2 ($P = 0.005$), and 0.15 in group 3 ($P = 0.001$, Fig. 1). Regression analysis confirmed re-sting occurrence to be age dependent ($P = 0.001$).

A total of 32 children with anaphylaxis to BV were re-stung, 5 thereof (15.6%) reported SARs to 6 re-stings. Of 17 patients allergic to VV and sting

Table 2. Number and rate of re-stings

	BV N	VV N
Number of re-stings	68	40
Number of patients re-stung (%)	32 (59)	17 (50)
Mean number of re-stings/patient (range)	2.2 (1–8)	2.35 (1–8)
Rate of re-stings per patient and year of follow-up	0.24	0.19

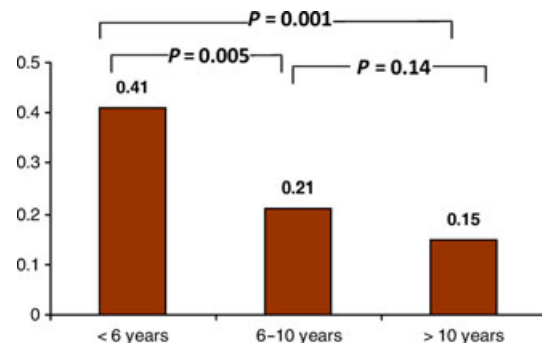


Fig. 1. Rate of re-stings per patient and year of follow-up according to age at diagnosis and commencement of venom immunotherapy (VIT).

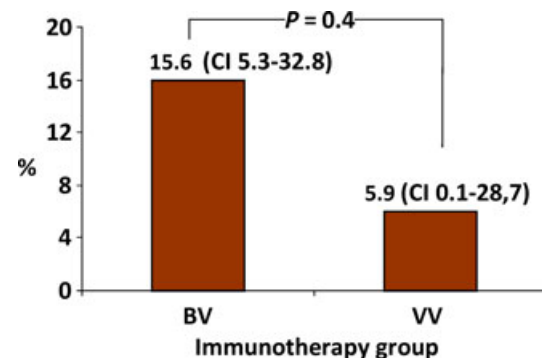


Fig. 2. Percentage of patients with systemic allergic reaction (SAR) to sting recurrence according to venom species used for immunotherapy.

Table 1. Patient and venom immunotherapy (VIT) characteristics

	BV N (%)	VV N (%)
Number of patients	54 (61)	34 (39)
Group 1 (< 6 years)	14	3
Group 2 (6–10 years)	24	15
Group 3 (10–16 years)	16	16
Male gender	33 (67)	23 (67)
Mean age at diagnosis (years, range)	8.6 (3.7–15.4)	10.1 (4.7–15.5)
Introduction protocol of VIT		
Conventional	9 (16.7%)	4 (11.8)
Rush	2 (3.7)	2 (5.8)
Ultra-Rush	43 (79.6%)	28 (82.4)
Mean duration of VIT (years, range)	3.6 (0.4–5.6)	3.5 (0.9–5.1)
Mean observation period (years, range)	6 (0.4–15.9)	10.4 (1.7–12.4)
Active VIT at time of survey	25 (46)	19 (56)

recurrence, 1 patient (5.9%) reported SARs after two different re-stings by *Vespula* spp. (Fig. 2). Sixty-three per cent of all SARs occurred upon the first sting after commencement of VIT, 25% after the second and 12% after the third re-sting. The majority of recorded re-stings (81%) occurred during VIT, 11% after completion of VIT, the timing of the remaining re-stings was unclear. Seven of the 8 SARs occurred before completion of the VIT. We were not able to establish an increased rate of SARs with shorter duration of VIT or time elapsed since discontinuation of treatment. This study was not powered to answer those questions. The majority of the SARs associated with re-stings were mild and confined to dermal symptoms. Two of the re-sting associated SARs were severe. One of these

severe SARs occurred in a patient allergic to BV, the other in a subject with allergy to VV. They both developed marked respiratory distress at re-exposure to insect venom (grade III reaction), which was in the same degree as their initial SAR, but no cardiovascular compromise. Taken together, 94.1% of patients with VV and 84.4% of patients with BV allergy were completely protected against SARs with at least having commenced VIT.

SARs upon re-sting occurred in an age-dependant fashion: 3.4% in youngest group 1 reacted, 4.3% in group 2 and 15.6% in group 3 (Fig. 3). Overall, there was a trend for higher incidence of SARs upon re-sting with increasing age that did not reach statistical significance ($P = 0.079$).

Boys were generally overrepresented, the younger the more pronounced: Group 1 consisted of 82% boys, group 2 of 69% and group 3 of 56% (Fig. 4). Particularly in BV-allergic individuals, there was an age-dependent predominance of boys ($P = 0.019$), which was not seen in VV-allergic patients. Furthermore, the younger, the more likely the patient was allergic to BV: 82% in group 1, 61% in group 2 and half in group 3 (Fig. 4).

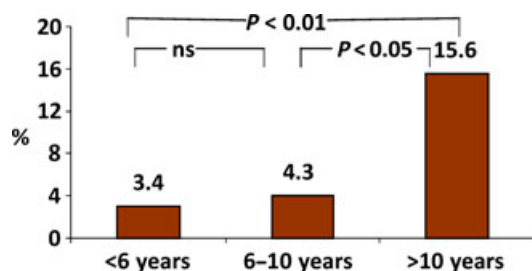


Fig. 3. Percentage of systemic allergic reaction (SAR) upon re-stings in relation to age at diagnosis.

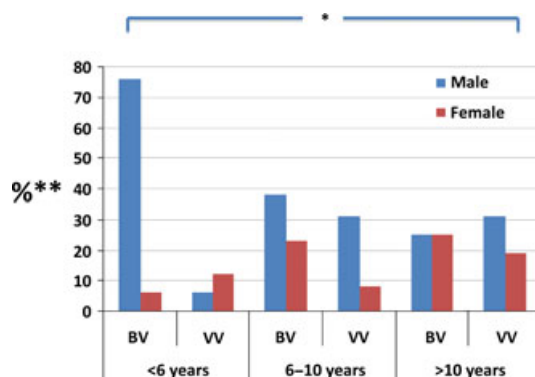


Fig. 4. Age and gender distribution of BV- and VV-allergic children treated with venom immunotherapy (VIT). * All three age groups: gender distribution skewed towards male gender for BV ($p = 0.039$), but not for VV ($p = 0.24$). Overall there is a trend of decrease in male predominance with increasing age ($p = 0.063$). ** Percentage of patients with BV and VV allergy in an individual age group.

Discussion

In this long-term outcome study of 88 cases with IgE-mediated anaphylactic reaction to Hymenoptera venom, we were able to demonstrate that VIT induces long-term protection in 84.4% of BV- and 94.1% of VV-allergic individuals at a total of 108 re-stings, thus supporting the evidence for this causal treatment also in children.

Re-sting occurrence is a major concern, as we could show that the majority of children (56%) with severe Hymenoptera venom allergy were re-stung by the respective insect. Younger children were more likely to be re-stung, but less likely to have a systemic reaction than older children and adolescents. Incidence of re-sting occurrence in our population was not different between BV- and VV-allergic individuals.

A similar high rate of re-stings has been reported for Swiss adults with 62% in a 3–7 years post-treatment observation study [12]. In contrast, Golden reported a lower rate of only 43% in Boston children over a period of 18 years [1]. This may be explained by a more outdoor lifestyle of Swiss children compared with their US counterparts. Furthermore, we also included a relatively high number of very young subjects with 17 patients below the age of 6 years at diagnosis who are less aware of their environment and therefore may be more prone to re-stings [1, 13, 14].

In our cohort there was a strong male predominance. The younger the patients, the more likely they were male and allergic to BV. Overall, 67% of our population were male, but in our youngest age group as many as 82% were boys (Fig. 4). Similar to adults, boys are known to be not only more allergic to Hymenoptera venoms but also more likely allergic to BV compared with girls [3, 15]. Also, honey bees tend to attack the smallest of patients more often because they tend to be hidden in grass and disturbed by walking outside bare-foot. *Vespula* spp. on the other hand tend to live in nests on the ground or under roofs and are less likely to be reached by the smallest children.

Data about the natural course of disease of severe Hymenoptera venom allergies without treatment are rare due to ethical limitations [16]. In a group of untreated paediatric patients with moderate-to-severe SARs to Hymenoptera venom, Reisman showed a rate of SAR following re-stings of 40%, with the SARs being the more severe if the initial reaction had been severe [4, 17]. Golden et al. studied children with Hymenoptera venom allergies of mixed severity and showed a reduction in SARs from 17% without to 3% with VIT. The subgroup of children with moderate-to-severe allergy to insect venom had greatest benefit from VIT with reduction from 32% without to 5% with VIT [1]. This failure rate of 5% despite VIT compares with our

subgroup of VV-allergic individuals failing VIT in 5.9%, probably reflecting the higher rate of VV allergies in the US population.

In a Swiss study of adult patients, VIT proved effective in reducing SAR rate upon re-stings to 15.8% in BV-allergic and 7.5% in VV-allergic individuals [12], numbers which have been quoted from 7 to 17% in a number of other studies in other settings [14, 16, 18–21]. In this study, we report a failure rate of VIT in children with anaphylaxis to BV of 15.6% and 5.9% in young individuals with anaphylaxis to VV. This demonstrates that comparable results are obtainable with VIT treatment in children as in adults.

The youngest of our included patients were 4 children < 4 years of age who all tolerated VIT well. According to international guidelines, however, introduction of VIT is only recommended in patients > 5 years of age [7]. We believe this age limit is rather arbitrary. Our data support that young individuals are at higher risk of re-stings and may benefit from VIT. Venom immunotherapy may need consideration in specific cases of very young children with anaphylaxis to insect venom and high exposure to stinging insects where continuous surveillance by parents and the application of the adrenaline auto-injector by the patients themselves are not possible.

To determine efficacy and failure rates of VIT, it would be best to compare outcome of anaphylactic patients with and without treatment. A drawback of our study is the absence of a control group of children without VIT. However, we believe that it is ethically not

justified to withhold children with life-threatening SARs to insect venom from a treatment, which has been demonstrated to be highly effective in patients with severe SARs to insect venom [5]. Furthermore, as in any retrospective study we do rely on patients' recall. Potential underlying recall bias may have caused us to overestimate the dramatic and underestimate the minor events.

In summary, a majority of children with anaphylactic reactions to BV and VV are re-stung by the insect they are allergic to without a difference in re-sting rates between honey bees and *Vespula* species. The younger the children, the more often they are re-stung, however, the higher is also their tolerance. Venom immunotherapy with Hymenoptera venoms is an efficient treatment including the youngest children with diagnosis of severe Hymenoptera venom allergy affecting the respiratory tract and/or cardiovascular system. Under therapeutic intervention with VIT 94.1% of children with severe allergic reactions to VV and 84.4% to BV are completely protected from SAR at sting recurrence.

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Conflicts of interest

None of the authors have any conflict of interest to declare.

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