Risk assessment of Hymenoptera re-sting frequency: implications for decision-making in venom immunotherapy

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Abstract: BACKGROUND: Venom immunotherapy is highly efficacious in preventing anaphylactic sting reactions. However, there is an ongoing discussion regarding patient selection and whether and how to apply a cost-benefit analysis of venom immunotherapy. In order to help decision-making, we investigated the re-sting frequency of hymenoptera-venom-allergic patients to single out those at high risk. METHODS: In this retrospective study, re-sting data of 96 bee-venom-allergic patients and 95 vespid-venom-allergic patients living mainly in a rural area of Switzerland were analyzed. Hymenoptera venom allergy status was rated according to the classification system of H.L. Mueller [J Asthma Res 1966;3:331-333]. Different risk-groups were defined according to sting exposure and their median sting-free interval was calculated. RESULTS: The risk factors for a wasp or bee re-sting were outdoor occupation, beekeeping and habitation close to a bee-house. Half of all vespid-venom-allergic outdoor workers were re-stung within 3.75 years compared to 7.5 years for indoor workers. Similarly, 50% of the bee-venom-allergic beekeepers or subjects with a bee-house in the vicinity suffered a bee re-sting within 5.25 years compared to 10.75 years for individuals who were not beekeepers. CONCLUSIONS: The high degree of exposure of vespid-venom-allergic outdoor workers and bee-venom-allergic beekeepers and subjects living close to bee-houses underlines the high benefit of venom immunotherapy for these patients even if they suffered a non-life-threatening grade II reaction. Yet, bee-venom-allergic individuals with no proximity to bee-houses and with an indoor occupation face a very low exposure risk, which justifies epinephrine rescue treatment for these patients especially if they have suffered from grade II sting reactions.

DOI: https://doi.org/10.1159/000338942

Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2013;160:86–92
DOI: 10.1159/000338942

Received: October 31, 2011
Accepted after revision: April 18, 2012
Published online: September 1, 2012

Risk Assessment of Hymenoptera Re-Sting Frequency: Implications for Decision-Making in Venom Immunotherapy

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Key Words
Hymenoptera sting frequency · Hymenoptera venom allergy · Venom immunotherapy

Abstract
Background: Venom immunotherapy is highly efficacious in preventing anaphylactic sting reactions. However, there is an ongoing discussion regarding patient selection and whether and how to apply a cost-benefit analysis of venom immunotherapy. In order to help decision-making, we investigated the re-sting frequency of hymenoptera-venom-allergic patients to single out those at high risk. ***Methods:*** In this retrospective study, re-sting data of 96 bee-venom-allergic patients and 95 vespid-venom-allergic patients living mainly in a rural area of Switzerland were analyzed. Hymenoptera venom allergy status was rated according to the classification system of H.L. Mueller [J Asthma Res 1966;3:331–333]. Different risk-groups were defined according to sting exposure and their median sting-free interval was calculated. ***Results:*** The risk factors for a wasp or bee re-sting were outdoor occupation, beekeeping and habitation close to a bee-house. Half of all vespid-venom-allergic outdoor workers were re-stung within 3.75 years compared to 7.5 years for indoor workers. Similarly, 50% of the bee-venom-allergic beekeepers or subjects with a bee-house in the vicinity suffered a bee re-sting within 5.25 years compared to 10.75 years for individuals who were not beekeepers. ***Conclusions:*** The high degree of exposure of vespid-venom-allergic outdoor workers and bee-venom-allergic beekeepers and subjects living close to bee-houses underlines the high benefit of venom immunotherapy for these patients even if they suffered a non-life-threatening grade II reaction. Yet, bee-venom-allergic individuals with no proximity to bee-houses and with an indoor occupation face a very low exposure risk, which justifies epinephrine rescue treatment for these patients especially if they have suffered from grade II sting reactions.

Introduction

Hymenoptera venom allergy is a potentially life-threatening condition. The reported prevalence of systemic allergic reactions is 0.3–7.5% in Europe [1]. The emergency treatment comprises the administration of antihistamines, oral corticosteroids and, in the case of moderate to severe anaphylactic reactions, intramuscular injection of epinephrine [2–4]. The only disease-modify-

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ing treatment option is venom immunotherapy (VIT) with an established efficacy of 95% in vespid-venom-allergic and 75–85% in bee-venom-allergic patients [2, 3, 5, 6]. VIT has also been shown to improve the health-related quality of life of the patients [7–8]. Although highly efficacious, VIT requires injections every 4–8 weeks over 3–5 years [2, 3, 9], and is associated with a risk of treatment-associated allergic side effects in up to 20% of all patients [10] which impedes treatment compliance [11, 12]. Furthermore, prediction of the future course of hymenoptera venom allergy (i.e. prediction of the reaction to a re-sting) is difficult, keeping the discussion about patient selection for VIT ongoing [13, 14].

There are indeed regional differences in the recommendations to initiate VIT. In the USA, VIT is recommended for all adult patients who have experienced a systemic reaction [2]. European guidelines recommend VIT for patients with a history of severe life-threatening grade-III or grade IV systemic allergic sting reactions according to H.L. Mueller (table 1) [15, 16], including respiratory or cardiovascular symptoms [3]. Such recommendation is based on the observation that patients with an initial grade III or grade IV reaction face a 30–60% risk of suffering a life-threatening systemic reaction upon a re-sting, if untreated [17, 18]. However, there is a grey zone concerning patients with a grade I or grade II systemic reaction. For such patients, who have suffered a non-life-threatening grade I or grade II reaction, (i) other factors associated with a high risk of suffering a severe reaction upon a re-sting (table 2), (ii) high sting exposure or (iii) highly impaired quality of life also justify initiation of VIT [3]. While the former issue has been extensively investigated, data regarding exposure risk is poor. Occupation, leisure activity, residence, age and sex have been described as influencing the exposure risk [9, 18–22]. Furthermore, a personal history of an anaphylactic sting reaction also affects exposure risk as the fear of a future allergic reaction induces behavioral changes associated with avoidance measures [8]. Moreover, patient education including preventive measures has the potential to minimize the re-sting risk [3]. Yet, the actual sting frequency in allergic patients has never been quantified so far. However, this parameter might help to evaluate the benefit for individual patients of undergoing VIT.

This study therefore investigated and quantified the sting frequency in hymenoptera-venom-allergic patients in order to define high and low sting-exposure groups and to help decision-making with regard to VIT initiation, particularly in grey-zone situations concerning patients with grade I and grade II allergic reactions.

Table 1. Classification of allergic reactions modified according to H.L. Mueller [15]

Large local reaction	swelling at site of sting with diameter >10 cm, lasting >24 h
Systemic reaction grade I	generalized urticaria, itching, malaise and anxiety
Systemic reaction grade II	any of the above, plus 2 or more of the following: angioedema, constriction in the chest, nausea, vomiting, diarrhea, abdominal pain and dizziness
Systemic reaction grade III	any of the above, plus 2 or more of the following: dyspnoea, wheezing, stridor, dysphagia, dysarthria, hoarseness, weakness, confusion and fear of death
Systemic reaction grade IV	any of the above plus 2 or more of the following: a drop in blood pressure, collapse, loss of consciousness, incontinence (urine or stools), cyanosis

Table 2. Risk factors for a severe reaction to a hymenoptera sting [18, 19, 22, 25, 26]

History of a prior severe sting reaction (with respiratory or cardiovascular symptoms)
Vespid venom allergy (for field stings)
Time interval between stings (<5 years)
Elevated serum tryptase, mastocytosis
Preexisting diseases (e.g. cardiovascular or asthma)
Drugs (e.g. beta-blocker and angiotensin-converting enzyme inhibitors)
Older age
Male sex

Material and Methods

Study Design and Patient Selection

This study was designed as a retrospective observational study. Patients were recruited from an allergologist's practice in a Swiss town, Lucerne (76,000 inhabitants), with a large rural agglomeration (274,000 inhabitants). Patients with a severe systemic allergic sting reaction or a high level of fear due to the allergic sting reaction were treated with VIT. Hence, hymenoptera venom allergy status was rated between Mueller grade III and grade IV in 95% of the patients. Patients who started ultrarush VIT between the years 1996 and 2003 were included and followed up until the end of 2008 in order to obtain data regarding hymenoptera stings. With the exception of beekeepers who were instructed to wear protective clothing with nets and gloves, patients did not get specific recommendations on how to prevent future hymenoptera stings. Patients who were lost to follow-up were not in-

Table 3. Baseline characteristics of study population

Characteristics	Study population	
	bee-venom-allergic (n = 96)	vespid-venom-allergic (n = 95)
Re-stung	45 (46.9%)	50 (52.6%)
Mean age ± SD, years	30.6 ± 17.3	36.1 ± 17.3
Male	63 (65.6%)	53 (55.8%)
Female	33 (34.4%)	42 (44.2%)
Residency		
Rural area	79 (82.3%)	63 (66.3%)
Town/agglomeration	17 (17.7%)	32 (33.7%)
Occupation		
Indoor work	46 (47.9%)	55 (57.9%)
Outdoor work	25 (26.0%)	27 (28.4%)
Children	25 (26.0%)	13 (13.7%)
Beekeeping		not applicable
Beekeeper	4 (4.2%)	
Bee-house in the vicinity	35 (36.5%)	
No relation to beekeeping	57 (59.4%)	
Leisure activity		
Outdoor hobby	65 (67.7%)	53 (55.8%)
No outdoor hobby	31 (32.3%)	42 (44.2%)

cluded in the respective analyses. A total of 106 bee-venom-allergic patients and 108 vespid-venom-allergic patients undergoing VIT were enrolled, and the re-sting data of 96 bee-venom-allergic patients and 95 vespid-venom-allergic patients could be analyzed. The median follow-up period was 6.6 years.

The study was performed with the approval of the local ethics review committee.

Re-Sting Data Collection

The demographic data, data on the patients' medical history and the results of any hymenoptera-specific diagnostic tests were collected from the medical records. Details on hymenoptera stings during therapy were obtained at follow-up visits 3 or 5 years after the start of VIT. Patients were sent a questionnaire to assess the sting frequency after therapy discontinuation. Patients who did not return the questionnaire were contacted by phone.

Statistical Analysis

The evaluation of the risk of suffering a sting was calculated with a multivariate logistic regression analysis. The final model included variables from table 3, if $p < 0.1$ as well as the factor 'time of observation', for which the outcome variable was controlled. Unfortunately, with only 4 beekeepers in our sample, we could not run a logistic regression analysis with beekeeping as a risk factor, instead merging them with the group of patients living close to a bee-house.

For calculation of the time interval from the start of VIT to the first re-sting, a Kaplan-Meier survival analysis was performed with a log-rank test.

Results

A total of 96 bee-venom-allergic patients and 95 vespid-venom-allergic patients with re-sting data could be analyzed. Male sex was overrepresented in both groups. Three quarters of the patients were living in a rural environment. The mean age at the start of VIT was 30.6 years for bee-venom-allergic patients and 36.1 years for vespid-venom-allergic patients, respectively (table 3).

Risk Factors for Re-Sting

The logistic regression analysis revealed that working outdoors, being a child or having a bee-house in the vicinity represented a 2–3 times higher risk for bee-venom-allergic patients to be re-stung (table 4). In the multivariate regression analysis, the significance level of 0.05, however, could not always be met (table 5). It must be noted that the group of beekeepers was merged with patients living near a bee-house. It is obvious that beekeepers face a much higher risk of being re-stung; all 4 reported to have received more than 30 stings.

Vespid-venom-allergic patients with an outdoor occupation were found to have a 5 times higher risk of suffering a re-sting than those with an indoor occupation (tables 6, 7). Sex, age, residency and leisure activity were not associated with a higher sting risk (tables 4, 6).

Sting-Free Time

A Kaplan-Meier analysis revealed a median sting-free interval of 7.75 years (93 months, 95% CI 58.34–127.67) for the patients with bee-venom-allergy and a median sting-free interval of 5.52 years (65 months, 95% CI 55.91–74.09) for patients with vespid-venom-allergy. Sting-free time was significantly different according to occupation for vespid-venom-allergic patients ($p < 0.001$) and according to the presence of a bee-house in the vicinity for bee-venom-allergic patients ($p = 0.019$) (fig. 1, 2). A log-rank test was not calculated to investigate the association between occupation and sting-free time for bee-sting-allergic patients as the proportional hazards assumption was not met.

Stratifying the data according to the factor bee-house in the vicinity for bee-venom-allergy resulted in median sting-free intervals of 5.25 years (63 months, 95% CI 54.9–71.1) for people with a bee-house in the vicinity and 10.75 years (129 months, 95% CI 85.8–172.2) for people not living near one. Stratification for occupation revealed a median re-sting-free interval of 6.66 (116 months) years for outdoor workers and 9.66 years (80 months, 95% CI 62.5–97.5) for indoor workers (table 8).

Table 4. Univariate logistic regression analysis for risk of a bee re-sting

Variable	Total (%)	Crude OR	95% CI	p value
Age	96 (100)	0.988	0.965–1.011	0.303
Sex				
Male	63 (65.6)	0.625	0.268–1.459	0.277
Female	33 (34.4)	1		
Residency				
Town/agglomeration	17 (17.7)	0.406	0.131–1.261	0.119
Rural area	79 (82.3)	1		
Leisure activity				
No outdoor hobby	31 (32.3)	1.324	0.562–3.121	0.521
Outdoor hobby	65 (67.7)	1		
Occupation				
Outdoor work	25 (26.0)	2.386	0.882–6.460	0.087
Children	25 (26.0)	2.812	1.030–7.677	0.044
Indoor work	46 (47.9)	1		
Beekeeping				
Beekeeper/bee-house nearby	39 (40.6)	2.287	0.996–5.253	0.051
No relation to a bee-house	57 (59.4)	1		
Time of observation	93 (100)	1.294	0.996–1.680	0.053

Table 5. Multivariate logistic regression analysis for risk of a bee re-sting

Variable	Total (%)	Adjusted OR	95% CI	p value
Occupation				
Outdoor work	24 (25.8)	2.431	0.833–7.095	0.104
Children	25 (26.9)	2.992	1.032–8.675	0.044
Indoor work	44 (47.3)	1		
Beekeeping				
Beekeeper/bee-house nearby	38 (40.9)	2.147	0.878–5.247	0.094
No relation to a bee-house	55 (59.1)	1		
Time of observation	93 (100)	1.288	0.975–1.702	0.075

Table 6. Univariate logistic regression analysis for risk of a wasp re-sting

Variable	Total (%)	Crude OR	95% CI	p value
Age	95 (100)	0.992	0.969–1.015	0.495
Sex				
Male	53 (55.8)	1.208	0.537–2.720	0.648
Female	42 (44.2)	1		
Residency				
Town/agglomeration	32 (33.7)	1.030	0.439–2.416	0.945
Rural area	63 (66.3)	1		
Leisure activity				
No outdoor hobby	42 (44.2)	1.166	0.518–2.625	0.711
Outdoor hobby	53 (55.8)	1		
Occupation				
Outdoor work	27 (28.4)	5.250	1.827–15.086	0.002
Children	13 (13.7)	1.750	0.518–5.907	0.367
Indoor work	55 (57.9)	1		
Time of observation	94 (100)	0.908	0.654–1.260	0.564

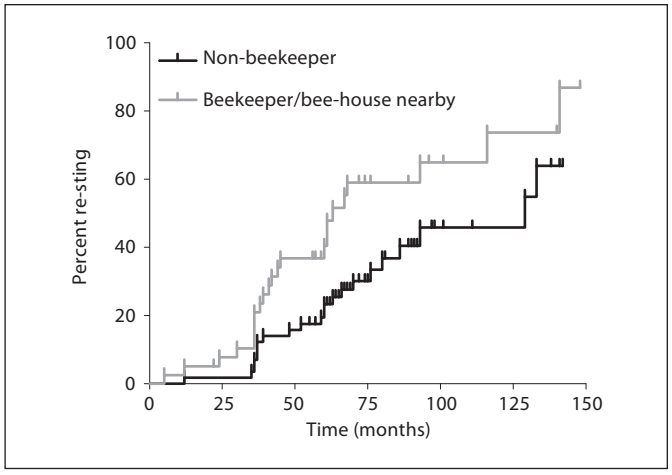

Fig. 1. Kaplan-Meier analysis for bee-venom-allergic patients showing the cumulative percentage of re-stings for beekeepers/subjects in the vicinity of a bee-house compared to subjects who were not beekeepers (p = 0.019).

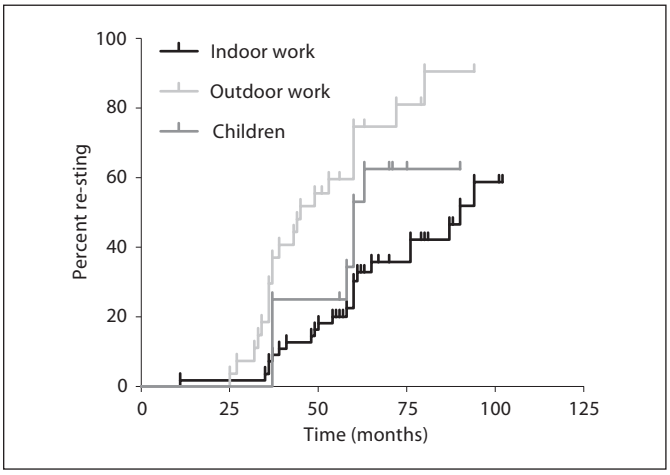

Fig. 2. Kaplan-Meier analysis for vespid-venom-allergic patients showing the cumulative percentage of re-stings for indoor workers compared to outdoor workers and children ($p < 0.001$).

Table 7. Multivariate logistic regression analysis for risk of a wasp re-sting

Variable	Total (%)	Adjusted OR	95% CI	p value
Occupation				
Outdoor work	27 (28.7)	5.187	1.798–14.961	0.002
Children	12 (12.8)	1.501	0.428–5.261	0.526
Indoor work	55 (58.5)	1		
Time of observation	94 (100)	0.956	0.677–1.352	0.800

Table 8. Median sting-free time for bee-venom-allergic and vespid-venom-allergic subjects according to whether or not they have a bee-house in their vicinity and their occupation

	Estimate months	Lower 95% CI	Upper 95% CI
Bee venom			
Bee-house in vicinity			
Yes	63.0	54.9	71.1
No	129.0	85.8	172.2
Occupation			
Outdoor work	80.0	62.5	97.5
Children	70.0	31.8	108.2
Indoor work	116.0	–	–
Wasp venom			
Occupation			
Outdoor work	45.0	34.8	55.2
Children	60.0	54.8	65.2
Indoor work	90.0	70.8	109.2

For vespid-venom-allergy, stratification according to occupation revealed median re-sting-free intervals of 3.75 years (45 months, 95% CI 34.8–55.2) for outdoor workers and 7.5 years (90 months, 95% CI 70.8–109.2) for indoor workers (table 8).

Discussion

Venom immunotherapy is the only disease modifying treatment option for hymenoptera venom allergy showing a high success rate. However, a long treatment duration requiring injections every 4–8 weeks over 3–5 years associated with high treatment costs, and the risk of treatment-associated allergic side effects keeps the discussion on whom to select for VIT ongoing. We focused on the determination of the sting frequency of different hymenoptera-venom-allergic patients in order to help decision-making, especially with regard to patients suffering from mild systemic sting reactions.

Analyzing data from Swiss hymenoptera-venom-allergic patients living to a large extent in a rural environment, we found outdoor occupation to be the only risk factor for a wasp re-sting whereas outdoor occupation, beekeeping or living in the vicinity of a bee-house are all risk factors for a bee re-sting. Being a child also seemed to be associated with a higher risk of a bee re-sting, but not for a wasp re-sting.There was, however, no difference in the risk of re-stings between children living in the vi-

cinity of a bee-house and children living nowhere near one. While this result is difficult to explain, we do not want to overstate its importance, particularly as its statistical significance is only moderate. Beyond that, our study shows that 50% of the patients belonging to a high-risk group were re-stung within 3.75 to 5.25 years on average. In contrast, 50% of vespid-venom-allergic indoor workers and bee-venom-allergic subjects other than the beekeepers working indoors experienced periods of 7.5 and 10.75 years respectively without suffering a wasp or bee re-sting, respectively. These figures have to be interpreted cautiously, however, as we cannot be completely sure that patients recalled correctly when they had been re-stung.

For a long time, beekeepers and their family members have been identified as a high-risk group of hymenoptera-venom-allergic patients, and management options for this population have already been adapted, recommending VIT not only to beekeepers suffering from mild grade I and grade II systemic allergic reactions, but even to those suffering from repeated large local reactions [23]. However, the majority (63%) of bee-venom-allergic patients do not belong to this high-risk group and only face a small risk of being re-stung. For the bee-venom-allergic patients – other than the beekeepers, with no vicinity to a bee-house and with an indoor occupation – who only suffered a non-life-threatening grade I or grade II sting reaction in the absence of other risk factors (see table 2), the benefit of a time-consuming and risk-associated VIT is small and prescription of autoinjectable epinephrine as a rescue treatment is justified. Indeed, young patients especially have been shown to prefer this to VIT [24].

With regard to vespid-venom-allergic patients, the impact of our study mainly concerns vespid-venom-allergic outdoor workers with mild systemic reactions, who suffer a high degree of exposure. It has been demonstrated that hymenoptera re-stings within a time interval of 2 weeks to 5 years comprise a 40–77% risk of inducing a more severe reaction [18]. Combined with our data, these observations allow the conclusion that vespid-venom-allergic outdoor workers with a grade II systemic reaction face a considerable risk of suffering a future grade III reaction when re-stung. Prescription of VIT is therefore highly recommended after grade II systemic reactions for these individuals. Contrarily, re-sting risk for vespid-venom-allergic indoor workers is small, reducing benefit of VIT after mild systemic sting reaction for this patient group.

Even though hymenoptera venom allergy has been studied extensively, the actual sting frequency has never been thoroughly investigated. It has been described that climate, temperature and certain occupations and activities (such as beekeeping) influence the risk of being re-stung [19], but this risk has never been quantified. Based on the analysis of a Swiss population living mainly in a rural environment, we substantiated the high sting frequency not only of beekeepers and their family members, but also of vespid-venom-allergic outdoor workers. On the other hand, both bee-venom-allergic patients in no proximity to a bee-house and with an indoor occupation as well as vespid-venom-allergic subjects who work indoors face a very low sting exposure risk. This information may affect the decision-making process in VIT situations concerning patients with grade I and grade II systemic allergic reactions where the cost benefits of VIT come into question.

Acknowledgements

This study was supported by a grant from the Allergie-Stiftung Ulrich Müller-Gierok. We thank Professor Ulrich R. Müller for helpful discussions.

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