

Clinical and entomological factors influence the outcome of sting challenge studies

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Background: The reported frequency of systemic reactions to challenge sting varies greatly.

Objective: To evaluate the interaction of clinical and entomological factors that determine the outcome of a challenge sting.

Methods: Patients allergic to yellow jacket were stung and monitored for systemic reaction. The frequency and severity of sting reactions were analyzed in relation to the species of insect used and patient characteristics.

Results: Objective systemic reactions occurred in 21 of 69 patients (30%) stung with *Vespula maculifrons* and in 8 of 71 patients (11%) with *Vespula germanica* ($P = .005$). Systemic reactions were more frequent in patients with a severe history (9/30; 30%) than in those with a mild or moderate history (21/145; 14%; $P = .04$). In only 1 of 111 patients (0.9%) was the reaction to sting challenge more severe than previous reactions. The reaction rate was higher when venom skin tests were positive at $<1.0 \mu\text{g/mL}$ (17/75 = 23%) than when sensitivity was milder (9/100 = 9%; $P = .012$). We compared sting outcome and venom-induced histamine release in relation to insects collected in July or in October, and found no difference. **Conclusion:** Allergic reactions to sting challenge are determined by the species of yellow jacket used, the severity of previous sting reactions, and the degree of skin test sensitivity, but not by the time of year. These factors are important to clinicians when they evaluate the chance of reaction to a future sting and to researchers when they design and report sting challenge studies. (J Allergy Clin Immunol 2006;117:670-5.)

Key words: Sting challenge, Hymenoptera, insect sting, anaphylaxis, insect venom

Hymenoptera venom immunotherapy (VIT) is recommended to patients who have had a systemic reaction to a sting, but the relative need for VIT depends on the chance, and severity, of a systemic reaction to subsequent stings in untreated patients. Deliberate challenge of patients with insect allergy with live insect stings has been the gold standard used to evaluate the risk of systemic reaction to stings before, during, and after VIT, and is assumed to avoid the variability in reactions that can occur with stings in the field. However, our early studies found the outcome of sting challenge to be unpredictable, and susceptible individuals do not always react as expected to a sting.¹ In untreated patients with a history of systemic sting reactions and positive venom skin tests, the risk of a repeat systemic reaction ranges from 30% to 65%, with an average of 46%.¹⁻⁹ The 2 largest and most recent studies from Europe both showed a relatively low risk for a repeat systemic reaction,^{3,9} which was different from the earlier experience of our group and others.^{1-3,10} We have reopened a program of investigation into the mechanisms of insect sting allergy to address this difference.

Clinicians are sometimes confounded in predicting the risk of future reactions in their patients by the variability of systemic reactions observed in sting-allergic individuals, some of whom are known to have reactions to some stings and not others. Many studies have found no clinical or laboratory test that accurately predicts the outcome of a sting in an individual patient.^{1,7-9,11,12} Published sting challenge studies may differ in several ways, including the characteristics of the patients selected for study, the methods and materials used for diagnostic testing, and the insects and techniques used for sting challenge. Many of our patients have suspected that systemic reactions occur more commonly with particular yellow jacket species and with stings later in the season.

The aim of this study is to identify and evaluate the entomological factors that determine the outcome of a challenge sting, and how they interact with clinical factors. Recognition of these variables should lead to a more standardized approach to sting challenges as an investigative tool and may elucidate the factors that most accurately predict the outcome of future stings, and therefore serve as

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Abbreviations used

BP: Blood pressure

VIT: Venom immunotherapy

a guide for the clinician in determining the treatment of affected individuals.

METHODS

We recruited healthy ambulatory volunteers, age 18 years and older, from physician referrals, mailings, public announcements, and newspaper advertisements. Sting challenge with live yellow jackets was performed on 111 patients with their informed consent. Some patients had a repeat sting challenge performed on 1 or more occasions, either 4 to 6 weeks or 1 to 3 years after the first sting, to determine whether the outcome would be different. The observer and the patient were blind to the yellow jacket species used for the sting. All patients gave informed consent for all aspects of the investigation in accordance with the Institutional Review Board of The Johns Hopkins Bayview Medical Center. Ethical considerations were reviewed, but sting challenge was considered to be justified in patients who refused VIT with the exception of patients with a history of near-fatal reactions.

Venom skin tests were performed and graded as previously described.¹³ Intradermal injection was performed with 0.02 to 0.03 mL (to raise a 3-mm bleb) using commercial *Hymenoptera* venom extracts (ALK Laboratories, Round Rock, Tex) at concentrations ranging between 0.001 and 1.0 $\mu\text{g/mL}$, to find the lowest concentration of venom that produced a positive skin test reaction. Commercial venom extracts contain a mixture of venoms, in defined proportions, from several yellow jacket species, including *Vespula germanica* and *Vespula maculifrons*.

Sting challenges were performed between the first week of July and the second week of October, when yellow jackets are reliably available in our area. The species used for sting challenge, *V maculifrons* and *V germanica*, are 2 of the most common yellow jackets in the eastern United States and are similar (or the same in the case of *V germanica*) to the common yellow jacket species in the western United States and in Europe. Insects were captured nontraumatically while foraging to minimize aggressive behavior, and were chilled for 24 to 48 hours before use to eliminate escape behavior or desiccation. Within 60 seconds of rewarming, they become fully active for sting challenge.

The sting challenges were performed in the National Institutes of Health supported general clinical research centers at Johns Hopkins Bayview Medical Center and Penn State Hershey Medical Center, with medical monitoring and supervision. After establishing baseline vital signs and an intravenous infusion, the insect sting was applied with a device developed by us and used in our previous studies of the past 20 years. Once stinging occurred, the insect was held in that position for 10 seconds and then removed. We monitored patients for subjective symptoms, objective signs (flushing, urticaria, angioedema), and changes in vital signs (blood pressure [BP], pulse, respiration rate, peak expiratory flow rate, oxygen saturation by pulse oximetry). The species of each specimen used for sting challenge was subsequently confirmed by examination.

The severity of systemic reactions was classified on the basis of the observed (challenge) or historical (field) symptoms after a sting. Subjective reactions were those believed by the patient to be a potentially dangerous generalized reaction, but presenting no objective sign of anaphylaxis during observation by a physician (during challenge stings). Subjective symptoms included varying

degrees of malaise, lightheadedness, and discomfort in the throat or chest. Mild systemic reactions include scattered hives distant from the sting, moderate dizziness (but still able to walk without assistance), or mild shortness of breath. Objective signs of a mild systemic reaction include generalized hives and/or a drop in peak flow of 15% to 20%, but the systolic BP remained >90 mm. Moderate systemic reactions include severe generalized hives, and/or angioedema of the tongue or throat, and/or positional dizziness with a need to lie down, or moderate dyspnea. Objective signs include a peak flow drop of 20% to 30%, or systolic BP of 70 to 90 mm. Severe reactions involve marked dyspnea or documented hypotension with syncope, but the patient becomes conscious when laid supine. Observed signs were a peak flow drop $>30\%$, or systolic BP of 50 to 70 mm. Near-fatal reactions involve prolonged unconsciousness and extreme hypotension, and/or severe respiratory distress or intubation.

For comparison of yellow jacket venom potency in July and October, we identified 3 yellow jacket (*V maculifrons*) nests in July. A sample of the insects was collected from each nest in July and again from the same nests in October. The venoms from each batch of insects were prepared by Vespa Laboratories, Inc (Spring Mills, Pa) and compared for their potency in causing histamine release from leukocytes of patients with insect allergy using the method previously described.¹⁴

Statistical comparisons were made by using the Pearson χ^2 test in Crosstabs (SPSS v10; SPSS Inc, Chicago, Ill).

RESULTS

In the first 3 years of the study, 962 respondents were screened by telephone interviews, and 264 described systemic reactions, of whom 190 had positive yellow jacket venom skin tests, but 55 declined sting challenge, and we excluded the 24 patients with a history of extremely severe reactions (near-fatal).

Sting challenge with live yellow jackets was performed on 111 patients with their informed consent. The mean age ($\pm$ SD) of the 111 patients (63 male subjects, 48 female subjects) stung was 45 ($\pm$ 11) years, with a range of 19 to 67 years. The yellow jacket venom skin test was positive at 0.01 $\mu\text{g/mL}$ in 13 patients, at 0.1 $\mu\text{g/mL}$ in 34 patients, and at 1.0 $\mu\text{g/mL}$ in 39 patients, and 25 patients had negative skin tests but positive venom RAST. The clinical history was classified as mild in 30 cases, moderate in 58, and severe in 23.

In total, 175 yellow jacket sting challenges were performed in 111 patients over a 3-year period (Table I). Each patient received an initial sting challenge, and the challenge was repeated at a later date in 43 patients. No systemic reaction occurred in 126 of the stings (72%) in 67 patients (60%). Objective systemic reactions occurred in 27 of 111 patients (24%) and in 30 of 175 stings (17%). Among the 30 objective systemic reactions, 21 (19 patients) were mild, 6 (5 patients) were moderate, and 3 (3 patients) were severe. An additional 19 sting challenges (11%) in 17 patients (15%) caused subjective systemic reactions, strongly believed by the patient to be a systemic reaction, but with no detectable objective signs of reaction. Only objective reactions were included in the analysis of systemic reactions.

Yellow jacket sting challenge was repeated in 37 patients, of whom 4 (11%) developed a systemic reaction

TABLE I. Outcome of sting challenges

	Patients	Stings
Sting challenge	111	175
No systemic symptoms	67 (60%)	126 (72%)
SR-subjective	17 (15%)	19 (11%)
SR-objective	27 (24%)	30 (17%)
Mild	19	21
Moderate	5	6
Severe	3	3

SR, Systemic reaction.

TABLE II. Outcome of sting challenges with 2 yellow jacket species, *V maculifrons* and *V germanica*

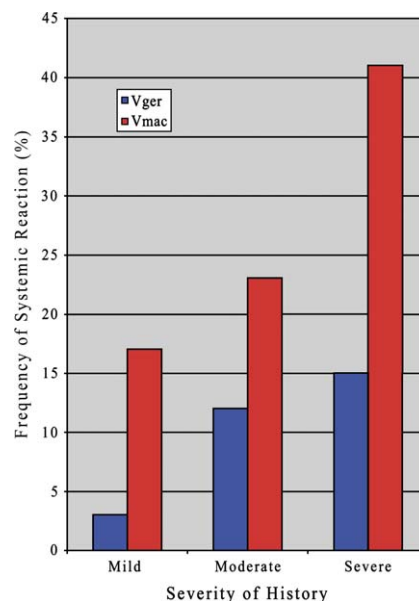
	<i>V maculifrons</i>	<i>V germanica</i>
Patients stung	69	71
Systemic reactions (%)	21 (30%)	8 (11%) ($P = .005$)
Total stings	84	91
Systemic reactions (%)	21 (25%)	9 (10%) ($P = .008$)

(3 mild and 1 severe). There were 52 repeat stings: 27 were performed the same summer and 25 in a subsequent summer. The repeat stings caused 4 systemic reactions, all of which occurred when the sting was performed the same summer (16%), and none when the sting was performed the next summer. It is noteworthy that the most severe reaction occurred in a patient who had no reaction to the first sting challenge.

We analyzed the frequency of systemic reaction in relation to the yellow jacket species used for the sting (Table II). Objective systemic reactions occurred in 21 of 69 patients (30%) stung with *V maculifrons* and in 8 of 71 patients (11%) with *V germanica* ($P = .005$). Of the 84 stings with *V maculifrons*, 21 (25%) caused objective systemic reactions, compared with 9 of 91 stings (10%) by *V germanica* ($P = .008$).

In the 29 patients who were stung (on separate occasions) by *V maculifrons* and *V germanica*, 7 (24%) had a systemic reaction to a *V maculifrons* sting, and 2 (7%) reacted to a *V germanica* sting. Reactions occurred to only the *V maculifrons* sting in 5 patients, and to both species in 2 patients, and none reacted only to the *V germanica* sting. Of the 27 patients who had no reaction to the *V germanica* sting, 5 (19%) reacted to the *V maculifrons* sting. Of the 22 patients who had no reaction to the *V maculifrons* sting, none reacted to the *V germanica* sting.

We analyzed the reaction rate to challenge stings in relation to the severity of previous (historical) sting reactions. The reaction rate was 10% (5/52) in the patients with a history of mild reactions to previous stings, and 17% (16/93) in those with moderate previous reactions. In patients with a history of severe reactions to stings, the reaction rate of 30% (9/30) was significantly higher than the 14% reaction rate in the mild and moderate reactors (21/145; $P = .04$). We analyzed the effect of the yellow jacket species on the reaction rate (Fig 1). The correlation

**FIG 1.** Frequency of systemic reactions to sting challenge is related to the severity of the history and to the species of insect. *Vger*, *V germanica*; *Vmac*, *V maculifrons*.

of the challenge sting reaction rate with the severity of previous sting reactions was more pronounced with the *V maculifrons* stings than with the *V germanica* stings. In patients with a history of mild systemic reactions, the challenge stings caused reactions in 3% (1/29) for *V germanica* and 17% (4/23) for *V maculifrons*. In patients with a moderate history, the reaction rate was 12% (6/49) for *V germanica* and 23% (10/44) for *V maculifrons*. In patients with a severe history, the reaction rate was 15% (2/13) with *V germanica* and 41% (7/17) with *V maculifrons*. These apparent trends were analyzed for possible statistical interaction by logistic regression and linear regression, but the difference detected was not significant for this sample size.

The severity of the challenge sting reaction was compared with the severity of previous reactions by history. In only 1 of the 175 stings (0.6%; 1 of the 111 patients, 0.9%) was the reaction to a sting challenge more severe than previous (historical) reactions. The patients with a history of a mild systemic reaction had the same (mild) reaction (4/30) or no reaction (25/30) on sting challenge, but 1 patient (1/30) developed a moderate reaction. Those with a moderate history had mild (9/58), moderate (3/58), or no reaction (46/58) to challenge sting. Those with a severe history had mild (6/23), moderate (1/23), severe (3/23), or no reaction (13/23) to the challenge sting. Severe reactions responded well to epinephrine treatment and/or rapid intravenous infusion of fluids.

The severity of the challenge sting reaction was also compared with the degree of venom skin test sensitivity. Of the 175 total stings, 17 (10%) were in patients with positive venom skin tests at 0.01 $\mu\text{g/mL}$ concentration, 58 (33%) were in patients with venom skin tests positive at 0.1 $\mu\text{g/mL}$, 65 (37%) were in patients with venom skin

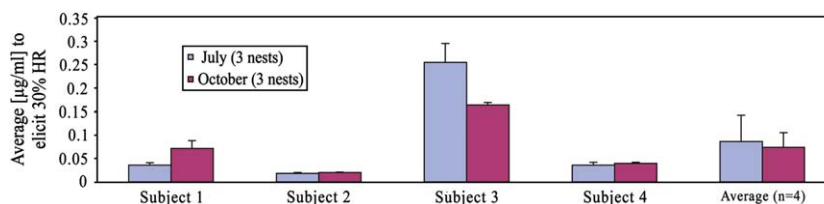


FIG 2. Histamine release response of human basophils to *V maculifrons* yellow jacket venoms from 3 nests collected in July and October, showing no consistent intranest or internest differences.

tests positive at 1.0 µg/mL, and 35 (20%) had negative skin tests but positive RAST. Systemic reactions occurred in 4 of 17 stings (24%) in patients with skin tests positive at 0.01 µg/mL, in 13 of 58 stings (22%) in patients with skin tests positive at 0.1 µg/mL, in 5 of 65 stings (8%) in patients with skin tests positive at 1.0 µg/mL, and in 4 of 35 stings (11%) in patients with negative skin tests but positive RAST. The reaction rate was significantly higher when the venom skin tests were positive at <1.0 µg/mL (17/75 = 23%) than when they were positive at 1.0 µg/mL or negative with positive RAST (9/100 = 9%; $P = .012$). As with the severity of the history, the correlation of the skin test sensitivity with the frequency of reaction to challenge sting was more pronounced with the *V maculifrons* stings than with the *V germanica* stings (data not shown).

To address whether allergic reactions to stings are more common in the fall than in early summer, we analyzed our sting challenge data, and also evaluated the potency of the venom obtained from insects collected in early and late season. There was no difference in the reaction rate between stings performed in the first half of the season (July 5 to August 14; 15/90 = 17%) and the second half of the season (August 15 to October 6; 15/87 = 17%). It is possible that in nature, more stings in the fall might occur with *V maculifrons* than with *V germanica*. In this study, the insects collected for sting challenge were 40% *V maculifrons* in the first half of the season, and 54% in the second half of the season ($P = \text{NS}$). Fig 2 shows the results of leukocyte histamine release experiments in 4 different patients, comparing 6 venom extracts: 3 collected from 3 separate nests in July, and 3 collected from the same nests in October. We found no significant directional difference in the histamine release dose-response curve between the early season and late season venoms. These histamine release experiments were preliminary in nature and were not powered for statistical significance. Nevertheless, the results are consistent with our other observations on the lack of any difference in reaction rate in the late season.

DISCUSSION

Selection of patients for VIT is based on observations of the risk of reaction to future stings without treatment. Published reports show an average risk for a systemic reaction of almost 50% in untreated patients, but reaction rates ranged from less than 30% to more than 60%.¹⁻⁹ Many variables, in the patients and the insects, could

contribute to a lower risk of reaction in some patients studied. For instance, the frequency and severity of subsequent sting reactions is lower in children than in adults,^{10,13-17} and in patients with a less severe history of reaction to stings.^{9,10,13,18,19} The incidence of systemic reactions is lower after more than 10 years from the last systemic reaction,^{2,15,18,20-22} and is very low (5-10%) in patients who have had large local reactions.^{2,15,18,20,22-24} Differences in results reported in various studies may be related to the inclusion in some studies of some of the lower-risk patients described. In addition, stings in the field may result in a higher frequency of reported reactions because of the inclusion of subjective symptoms, whereas challenge sting reactions usually include only objective findings. It is important to recognize the reasons for variability in the outcome of insect stings so that peer-reviewed studies can be more accurately interpreted and compared, and so that future studies can be designed with these factors in mind. This variability is equally important to the clinician who must provide guidance and recommendations to patients about the risk of future reactions on the basis of the occurrence (or not) of reactions to previous stings. The clinician must be able to interpret not only the patient's history of reactions but also the significance of published sting challenge studies.

Differences between studies may include not only differences in the patient population but also differences in the insect population. Our results confirm that both of these factors affect the outcome of sting challenges. The differences between the 2 yellow jacket species used in our study are important for the interpretation of our results. *V maculifrons* is one of the most common yellow jackets in the eastern United States, and there are comparable *Vesputa* species in other regions of the world. *V germanica* is one of the most widely distributed yellow jackets in the world. Defensive behavior by both species is mediated by an alarm pheromone, although in our field experience, *V maculifrons* colonies have a lower threshold for attack.²⁵ Individual *V germanica* workers differ substantially from *V maculifrons* in their stinging behavior, the latter often firmly locking themselves in place with clenched mandibles and legs while inserting their stings. Unlike *V germanica*, the sting lancets of *V maculifrons* frequently hold fast in human skin and are often torn from the insects' bodies when they are brushed off by the victims.²⁶ These differences may facilitate locating and collecting insects from *V germanica* nests than *V maculifrons* nests for use in sting challenges.

Both the frequency and severity of systemic reactions were increased with stings by *V maculifrons* compared with *V germanica*. This difference was also observed in individual patients who were stung with the 2 yellow jacket species on separate occasions. In 29 such patients, 5 patients had a systemic reaction to *V maculifrons* but not *V germanica*, and 2 patients had a reaction to both species, but no patient reacted to *V germanica* and not *V maculifrons*. This clearly demonstrates that patients with yellow jacket allergy are more likely to have a systemic reaction to a sting by *V maculifrons* than to *V germanica*. Studies that enroll a greater proportion of patients with mild history, as in our current sting challenge trial, would show a dramatically lower reaction rate if stung with predominantly *V germanica* (3%) compared with studies that included patients with more severe reactions, especially if stung with *V maculifrons* (41%; Fig 1).

The severity of historical systemic reactions has been suggested as being predictive of the risk of future reactions in untreated and posttreatment patients.^{9,10,18,27,28} Those same reports suggest that patients only infrequently have progressively more severe reactions. The current study confirms both of these observations. The frequency of a reaction was significantly higher in patients who had a history of severe reactions than in those with mild or moderate reactions. The severity of reactions to challenge stings was also clearly related to historical severity in that only a single patient thus far in the study has had a reaction more severe than previously. We demonstrate here that the yellow jacket species is a significant cofactor in determining the frequency and severity of systemic reaction. This correlation was more marked with *V maculifrons* stings than with *V germanica* stings (Fig 1), but the difference in the trends was not statistically significant for this sample size. The study was not designed to study the interaction of these variables and therefore has insufficient power for this analysis.

Positive venom skin tests demonstrate the presence of allergen-specific IgE antibodies but have not been a reliable indicator of the risk of a reaction. In the patients reported here, there was a higher frequency of systemic reactions in patients with higher levels of skin test sensitivity, but the degree of skin test sensitivity did not correlate reliably with the severity of reaction, as described in the past.^{7,9,11,18} We observed that severe reactions can still happen in patients with lower levels of skin test sensitivity, and conversely, mild reactions can occur even when skin test sensitivity is very strong. Our data also show that the reaction rate to sting challenge in the patients with the strongest skin tests sensitivity was 44% (4/9) for *V maculifrons* stings and 0 (0/8) for *V germanica* stings. If we analyze only the *V maculifrons* stings, there is a clear correlation of the frequency of systemic reactions with stronger skin test sensitivity: 44% (4/9) for those with skin tests positive at 0.01 $\mu\text{g/mL}$, 31% for those with skin tests positive at 0.1 $\mu\text{g/mL}$, 11% (3/28) when skin tests were positive at 1.0 $\mu\text{g/mL}$, and 5.5% (1/18) for patients with negative skin test and positive RAST. It would be impossible to compare sting challenge

studies for the effect of skin test sensitivity if the species used were unknown. The clinician must be aware that even in a highly sensitized patient, there can be no reaction to a *V germanica* sting, but a severe reaction may occur to a *V maculifrons* sting.

We believe the overall sting rate to be higher in the fall because of the larger size of nests and the greater number of insects, and this may account for the suspected higher frequency of reactions in the fall. However, allergic reactions to stings have been reported to be evenly distributed through the summer.^{29,30} We found no difference between early summer and late summer in the reaction rate to stings of either species. We also found no interest, or intranest differences in histamine release using venom collected in July or October. Our results confirm the previous report that there was no difference in allergenic activity of hornet venoms collected in early and late summer.³¹

It is not clear why there should be a difference in the reaction rate to different yellow jacket species. We found no difference in histamine releasing activity from IgE-sensitized cells between *V maculifrons* and *V germanica* venoms, suggesting that there is no difference in potency between the venoms of these species (data not shown). Although the venoms of the 2 yellow jacket species have been reported to show extensive cross-reactivity, the molecular differences between them make it possible that some individual patients could have different sensitivity to the 2 species.³²⁻³⁴ It has been postulated that the quantity of small molecular weight substances, such as vasoactive amines, present in the venom can affect the likelihood of an allergic reaction.¹ Such a difference might also exist between species. It has been reported that there is considerable variation in the volume of venom injected during individual stings.³⁵ However, it is not known whether there is any difference between different species. It is possible that *V maculifrons* may deliver a higher dose of venom than *V germanica* when the sting becomes detached and there is continued contraction of the attached venom sac. However, we normalized for this variable during sting challenge by holding the insect in contact with the skin for 10 seconds while stinging occurred. There are no comparative data available on the clinical response to stings of yellow jackets of other species, or between vespid genera.

Although our overall systemic reaction rate is at the lower end of that described in other published reports, our population is selected and should not be compared with others. We do not include subjective systemic reactions regardless of apparent severity (as described by the patient). If included, as they would have been in a study of field stings (and some studies of challenge stings), our total reaction rate would have been 39%. Our population was also self-selected in that severely affected patients usually chose VIT rather than the sting challenge study, and the study protocol excluded those with a history of unconsciousness or near-fatal reactions. We believe the more severely affected patients would have been most likely to react to challenge sting. This also explains the preponderance of mild systemic reactions to the challenge stings.

We conclude that the outcome of sting challenge is affected by the species of yellow jacket used, but not by the time of the season. We confirm that the severity of the previous sting history and the magnitude of the skin test sensitivity each correlate with the chance of a systemic reaction to a challenge sting, but our data show that in both cases, the effect is more pronounced with *V maculifrons* stings than with *V germanica* stings. Thus, the clinician cannot conclude that an intervening sting that caused no reaction implies no reaction to a future yellow jacket sting. It is important for research studies using insect sting challenge to report the exact composition of their patient population (age, severity of previous sting reactions, skin test and RAST results) and to describe the species of insect used for challenge.

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