
Subsequent insect stings in children with hypersensitivity to Hymenoptera

Pia Hauk, MD, Katrin Friedl, Klaus Kaufmehl, MD, Radvan Urbanek, MD, and Johannes Forster, MD

From University Children's Hospitals, Freiburg, Germany, and Vienna, Austria

To investigate the risk of life-threatening reactions to future stings, we sequentially challenged 113 children (aged 2 to 17 years) allergic to insect stings with a sting by the relevant insect. The time interval between the challenges varied from 2 to 6 weeks. The history of the index stings was a large local reaction (LR) in 16% and a systemic reaction (SR) in 84% of the test subjects. On the first challenge, 76% had a normal LR, 11% a large LR, and 13% an SR. On the second challenge, 78% of the children had a normal LR, 5% a large LR, and 17% an SR. Thirty-nine of the untreated children were exposed to a field sting during the subsequent 3-year follow-up period. In comparison with other diagnostic evaluations such as skin-prick tests, determinations of specific IgE and IgG antibodies, and single-sting exposure, the dual sting challenge scheme appears to be the best predictor of reactions to subsequent stings. It also appears to be helpful in selecting patients with an uncertain sensitization status for venom immunotherapy. (J PEDIATR 1995;126:185-90)

In childhood, allergy to Hymenoptera venom is mainly caused by stings of honeybees and wasps. In Europe, yellow jackets are known as "wasps," whereas in the United States, *Polistes* wasps are known as "wasps."¹ Between 0.4% and 4% of the population have systemic allergic reactions to insect stings.²⁻⁴ The incidence of systemic reactions to subsequent stings is lower in children and adolescents than in adults.⁵⁻⁸ Prospective observations of the natural course of insect allergy show that adults have a risk of 27% to 57%^{3, 9-11} of having repeated systemic allergic reactions, in comparison with a risk of 10% to 20% in children.^{4-6, 8} Therefore venom immunotherapy should be indicated less frequently in children.⁸ In vitro assays and risk scores provide only limited help in identifying those patients at risk of having further life-threatening allergic reactions. Numerous studies¹²⁻¹⁵ have been unsuccessful in showing a correlation between the standard diagnostic methods—mainly skin-prick tests and measurements of specific IgE and IgG

antibodies—and the reactions to subsequent insect stings. Treatment recommendations based only on those criteria typically lead to an overestimation of the number of children who require venom immunotherapy.^{6, 8, 16}

Although single diagnostic sting challenges give additional information, there is increasing concern about the possible booster effect. From the natural history of bee venom allergy, we know that one sting followed by another

See commentary, p. 257.

AU	Arbitrary unit(s)
LR	Local reaction
SR	Systemic reaction

2 to 4 weeks later will result in the highest incidence of systemic reactions. We tried to mimic this naturally occurring event by subjecting test subjects to sequential sting challenges to detect the group of patients at highest risk. Those who did not react and therefore were not assigned to receive venom immunotherapy were followed for up to 3 years for life-threatening events after natural stings.

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Reprint requests: Johannes Forster, MD, University Children's Hospital, Mathildenstr. 1, D-79106 Freiburg, Germany.

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Table I. Score estimating the risk of subsequent sting reactions used for recommendation of venom immunotherapy¹⁷

	Risk points	
	1	2
Reaction to index sting	Large LR, moderate SR	Severe SR
Skin-prick test (100 µg/ml venom)	Wheal diameter <3 mm	Wheal diameter ≥3 mm
Specific IgE (RAST)	Class 1	Classes 2-4

Recommendation for venom immunotherapy: ≥5 points.
RAST, Radioallergosorbent test.

METHODS

From 1988 to 1991, a total of 71 boys and 42 girls aged 2 to 17 years (median, 9 years) with "insect allergy" were recruited from the outpatient clinic to undergo sequential sting challenges. Only children with large local reactions and systemic but not life-threatening reactions were included in this study. The initial evaluation consisted of a medical and allergic history with emphasis on prior insect sting reactions, a physical examination, venom skin testing, and venom-specific IgE and IgG antibody measurements. Furthermore, the patients were graded according to their risk score¹⁷ (Table I), on which recommendations for venom immunotherapy are based in Germany.¹⁸

Venom skin testing. Skin-prick testing was performed with purified bee and wasp venom (ALK-prick SQ; ALK/Scherax, Hamburg, Germany) on the flexor surface of the forearm at concentrations of 0.1, 1, 10, and 100 µg/ml. Negative (diluent) and positive (histamine, 10 mg/ml) controls were also applied. The diameter of the wheal present 20 minutes after administration was measured. At a venom concentration of 100 µg/ml, a wheal diameter of <3 mm was considered a positive result and ≥3 mm a strongly positive result.

Antibody measurements. IgE antibodies to whole bee and wasp venom were measured by the radioallergosorbent test (Pharmacia AB, Uppsala, Sweden) and were expressed as classes 1 to 4. IgG antibodies were measured with enzyme-linked immunosorbent assay.¹⁹ Results were expressed as low (bee venom <400 AU; wasp venom <25 AU) or high (bee venom ≥400 AU; wasp venom ≥25 AU). Blood samples for the determination of IgE and IgG antibodies were taken from each patient on the days on which the first and second challenge stings were performed.

Classification of hypersensitivity reaction. Depending on the clinical history, sensitized patients (positive skin-prick test result or specific IgE antibodies to bee or wasp venom)

Table II. Baseline characteristics of patients

Index sting reaction	n	Age (yr): median; range	Male/female	Risk score ≥5 points
Large LR	18	9; 2-17	12/6	4
Moderate SR	57	8; 3-16	33/24	12
Severe SR	38	9; 3-15	26/12	21
TOTAL	113			37*

*Scored (37/91) as "at higher risk" of having a life-threatening reaction at first visit.

were placed into one of the following categories: large LR: an LR with redness and swelling >10 cm in diameter and lasting longer than 24 hours; moderate SRs: skin symptoms (general urticaria, redness, itching), angioedema, and gastrointestinal symptoms; and severe SRs: respiratory symptoms (wheezing, shortness of breath) and mainly cardiovascular symptoms (hypotension, collapse, cardiac arrhythmias).

Sequential sting challenges. The sting challenges were carried out by placing live insects on the flexor side of the forearm during intensive medical observation and with an intravenous line already in place. The second challenge was performed 2 to 6 weeks after the first challenge. A second challenge was omitted and venom immunotherapy was started if the patient had a severe SR on the first challenge and his or her parents agreed with the recommendation for treatment.

The procedure was approved by the medical ethics committee of the university, and informed consent was obtained from the parents, in particular with respect to the possible booster effect.

Follow-up. During the summer of 1992, all the patients and their parents underwent a structured telephone interview regarding reactions to subsequent field stings. Patients of both groups and their family doctors were instructed to send a serum sample for the determination of specific IgE and IgG antibodies 4 weeks after a subsequent insect sting. Only eight patients not undergoing immunotherapy sent serum samples irregularly, between 1 month and 3 years after the sequential challenge, when they were restung. All 11 patients undergoing venom immunotherapy treatment sent serum samples every 3 to 6 months.

Statistical analysis. We carried out statistical analysis with the SPSS-PC program (chi-square test of Pearson, Kruskal-Wallis test, one-way analysis of variance, logistic regression analysis) (SPSS Inc., Chicago, Ill.). The data obtained were compared to establish statistically significant differences ($p < 0.05$) between groups of patients showing different types of reactions.

Table III. Severity and number of clinical reactions to sting challenges in comparison with the index sting

Clinical reaction	Index sting reported	Bee and wasp sting challenges	
		First challenge	Second challenge
Normal LR	—	95	98
Severe LR	18	14	6
Moderate SR	57	14	10
Severe SR	38	2	11
TOTAL	113	125	125

RESULTS

Baseline characteristics of patients are shown in Table II. Patients who had shown different types of index sting reactions had no significant differences in the results of skin-prick tests and measurements of specific IgE and IgG antibody levels (data not shown). Of 113 subjects, the tests of 91 could be scored according to the described risk score (Table I): 41% (37/91) were classified as at risk, with a score of ≥ 5 points. Thirty percent (34/113) had been sensitized to bee venom, 5% (6/113) to wasp venom, and 65% (73/113) to both. Sixteen percent of the children (18/113) had reported large LRs and 84% (95/113) SRs to the index sting.

Sting challenges. Monosensitized patients were sequentially challenged with the relevant insect only. In 61 of 73 doubly sensitized children, the sequential challenge was performed with the insect of clinical relevance on the basis of the history, the more prominent reaction to the skin-prick test, or a higher specific IgE concentration. Of the 73 patients, 12 were sequentially challenged by a bee and a wasp on 2 consecutive days.

First challenge. The time interval between the index sting and the first challenge varied from 2 weeks to 73½ months. This interval was not correlated with the reaction to the challenge.

One hundred thirteen patients were challenged with 125 stings (Table III). Of the bee venom-allergic patients, 69.2% (63/91) had a normal LR, 13.2% (12/91) a large LR, and 17.6% (16/91) an SR. The wasp challenges resulted in local reactions only. None of the children with large LRs or moderate SRs, or both, received venom immunotherapy after the first challenge, and therefore all of them were included in the second-challenge study group. In two children who had a severe SR, venom immunotherapy was advised but the recommendation was not accepted. At their parents' request, both were stung a second time.

Second challenge. The second challenge was performed 2 to 6 weeks after the first challenge. The time interval

Table IV. Severity and number of clinical reactions to subsequent field stings in children without immunotherapy 2 weeks to 35 months (median, 14½ months) after the sequential challenges in comparison with the index sting

Grade of clinical reaction	Index sting reported	Field sting reactions*
Normal LR	—	35
Severe LR	18	2
Moderate SR	57	1
Severe SR	38	1†
TOTAL	113	39

*According to the standardized interview.

†Mild respiratory symptoms.

between the first and the second challenge did not influence the reaction to the second challenge.

One hundred thirteen patients again were challenged with 125 stings (Table III). After the second challenge sting, 72.5% (66/91) of the bee venom-allergic patients had a normal LR and 6.6% (6/91) a large LR. In 20.9% (19/91) a systemic reaction occurred, which in 10 cases (11%) was severe. Only two SRs (6%) occurred among the wasp venom-allergic children, one of which was severe (3%). Those 11 children with a severe SR to the second challenge underwent subsequent venom immunotherapy. Of these 11 patients, 8 had a history of severe SRs and repeated severe SRs in the second challenge. Both children who had a severe SR to the first challenge had a local reaction to the second challenge. Once again, their parents refused venom immunotherapy.

Children not recommended for venom immunotherapy were carefully instructed in the use of emergency self-treatment kits containing clemastine tablets or syrup and an epinephrine inhaler.

We found no correlation between the grade of the reactions to sting challenges and the results of the initial skin-prick test, the initial IgE and IgG antibody concentrations, and the levels of specific antibodies during the challenges (data not shown).

Field stings. Between 2 weeks and 35 months after the challenge procedure, 45 (40%) of the 113 challenged children were stung in the field by the relevant insect. Of the patients who received venom immunotherapy, one had a moderate SR with only urticaria, which was treated with orally administered clemastine. The other five had LRs only. One of these used clemastine locally, and one orally for an extended swelling. Of the 39 patients not assigned to receive venom immunotherapy, only two had SRs (Table IV). One girl who had a history of severe SRs before the sequential challenge was restung on the foot 16 months after the second challenge. She was treated by a physician with

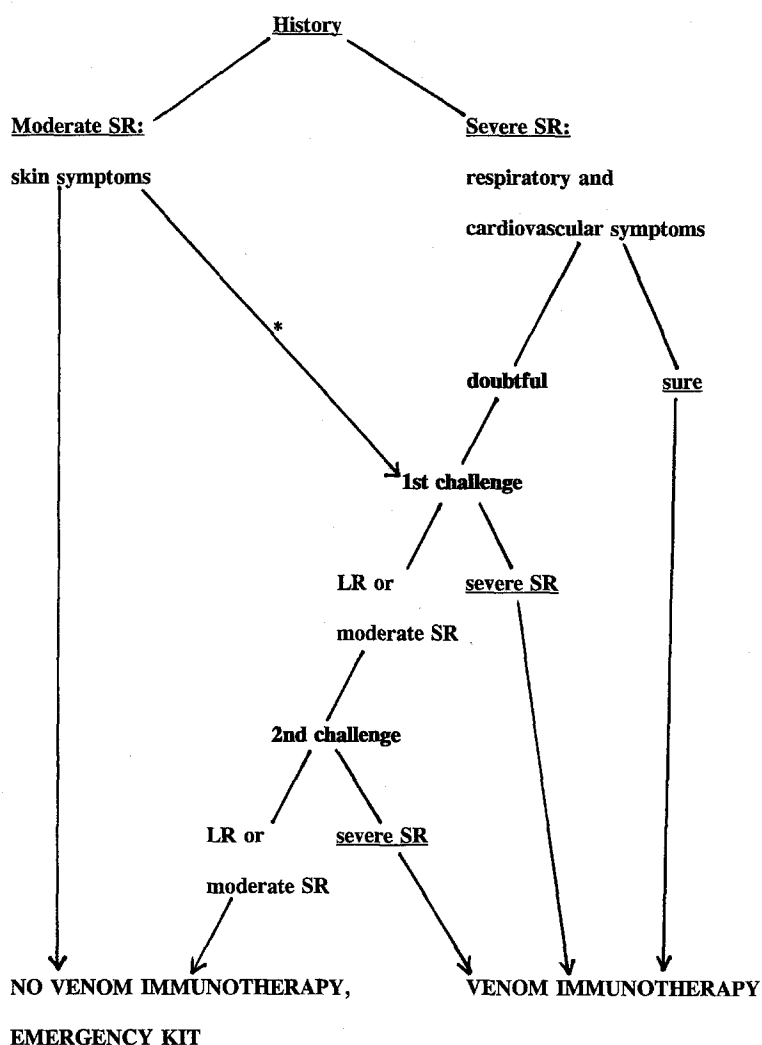


Figure. Diagnostic and therapeutic procedure in sensitized insect sting-allergic children and adolescents (positive skin-prick test result and/or specific IgE) with previous SRs. Asterisk indicates patient's request.

orally administered clemastine for urticaria 30 minutes after the sting. The other child had a history of moderate SRs and was restung on the forearm 14 months after the second provocation. This child was treated after 10 minutes with orally administered clemastine and subcutaneously administered terbutaline, because urticaria and mild respiratory symptoms developed. Venom immunotherapy was commenced subsequently.

The reaction to the first challenge was not predictive of the reaction either to the second challenge or to field stings. On the basis of the reaction to the second challenge, one of 39 patients had been misclassified as belonging to the group not recommended for venom immunotherapy. Thus the prediction that a severe systemic reaction would not occur was correct in 38 children (97.4% = negative predictive value; 95% confidence interval, 86.5 to 99.9).²⁰

Doubly sensitized children were not more likely to have severe reactions to subsequent field stings. Whether those individuals were sensitized to multiple insects or had a cross-reactivity among venom proteins was not investigated.

Follow-up of sensitization markers. Patients receiving venom immunotherapy had a typical course of specific IgE and IgG antibodies²¹ during the treatment. Patients who received no immunotherapy had changes in specific IgE and IgG antibodies dependent on subsequent stings that were not correlated with the sting reaction (data not shown).

DISCUSSION

In childhood, the benign natural history of allergy to Hymenoptera stings and the lack of correlation between the index sting and standard diagnostic methods leave the treating physician without precise criteria in determining

whether an individual child should receive venom immunotherapy. We tried to separate the endangered insect venom-allergic children from those with a mild or transient hypersensitivity by subjecting them to sequential insect sting challenges within a period of 2 to 6 weeks. This particular period was chosen to include a possible booster effect of the first sting in the evaluation of individual reactivity. Mueller et al.²² have shown that the highest grade of sensitization in terms of specific IgE levels is to be expected 2 to 4 weeks after a sting event. Therefore an additional sting at this time is the most dangerous situation that can arise for an insect venom-allergic person. Our patients faced such situations under ideal medical surveillance; consequently, none of them had any acute or permanent sequelae. Sequential challenge stings are generally not recommended in adults because they pose a higher risk of severe SRs in older patients.^{10, 14}

In agreement with others who have investigated the natural course of insect allergy by prospective observations⁵⁻⁸ or single-challenge tests,^{11, 12} we demonstrated a lower frequency of subsequent SRs than expected on the basis of history or predicted by *in vitro* sensitization markers, or both. Valentine et al.⁸ found that children whose allergic SRs had been only cutaneous have a risk of about 10% of having SRs to future stings, which was comparable to our data.

After the index sting, 16% of our bee and wasp venom-allergic children had a large LR and 84% an SR. In the sequential challenge, reversed percentages were obtained, and this result was confirmed with the second bee sting challenge. In the first challenge, all wasp sting-allergic children had LRs only; on the second provocation, SRs occurred in 6%. Thus wasp sting-allergic children were less likely to have repeated SRs. The latter finding might be at least partly explained by the different amount of venom applied by one wasp sting. This difference seems to be more pronounced in wasp stings than in bee stings,²³ because wasps are able to sting several times. Although there were more severe reactions in the group of children who required immunotherapy according to our assessment, no significant correlation could be detected between the reactions to the index sting and to the challenge stings, or between the reactions to the index sting and to the field sting.

We also confirmed the results of other studies,¹²⁻¹⁵ which revealed the disappointing correlation between standard diagnostic methods—mainly skin-prick tests and measurement of specific IgE and IgG antibodies—and the reactions of an allergic individual to further insect stings. Because the level of specific IgE and IgG antibodies did not correlate with the concomitant sting reaction at any time during the study or the follow-up period, we have not shown these data in detail. Neither was it possible to use these tests to deter-

mine whether one or more subsequent stings could have induced immunity in the subjects. There is no *in vitro* test to examine the possibility of stimulating a protective state by administering sequential sting challenges; thus clinical immunity can be demonstrated only by the clinical reactions to subsequent field stings by patients not receiving venom immunotherapy.

Methods of treating insect-sting allergy recommended by the committee on insects of the European Academy of Allergy and Clinical Immunology²⁴ are based on standard diagnostic methods. Venom immunotherapy is recommended for those sensitized patients who have had a systemic allergic reaction more severe than skin symptoms only. This criterion corresponds to the result of the risk score mentioned above. Considering the previous reaction to the index sting and the results of skin-prick tests and venom-specific IgE measurements as criteria for the recommendation of venom immunotherapy, 41% of the scored bee venom- and wasp venom-allergic children would have been assigned to this treatment, but only 9% received venom immunotherapy as a result of the clinical reaction to the second challenge. Although this procedure may appear very invasive, children eventually benefit because the risk and inconvenience of 3 to 5 years of immunotherapy can be avoided in four of five current candidates for venom immunotherapy. The reliability of the sequential challenge procedure was evaluated by assessment of the reactions to subsequent stings in children who were not assigned to venom immunotherapy (large LR and moderate SR to second challenge). In our patients, this test had a negative predictive value of 97.4% (confidence interval, 86.5 to 99.9) for subsequent life-threatening reactions. Although this is not a 100% safety record, we believe that the sequential insect sting challenge performed in the hospital represents the safest and most informative method of eliminating unnecessary venom immunotherapy in children having mild to moderate SRs to an index sting. However, the procedure should be performed only by well-trained staff with intensive care facilities at hand.

On the basis of the data presented, we suggest the following diagnostic and therapeutic procedures for children up to 16 years of age: Sensitized patients, identified by a positive skin-prick test result or specific IgE finding, who had only a large LR to the index sting, need neither a challenge sting nor venom immunotherapy. However, if parents insist on treatment, the challenge can be used in an effort to convince them that venom immunotherapy is not necessary. In sensitized patients with a previous moderate SR with generalized skin symptoms, sting challenges and venom immunotherapy are not indicated, but these patients should carry an emergency kit.^{6, 8} All sensitized patients who have life-threatening SRs should undergo venom im-

munotherapy without previous challenges. However, the challenge procedure can be offered to estimate the patient's individual risk to demonstrate the necessity of venom immunotherapy (Figure). Patients who are not sensitized to any insect venom according to standard tests but who have had a systemic allergic reaction to an insect sting should in any case be challenged to reveal their risk of having life-threatening reactions to the insect in question.

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