

Bee-venom allergy in children: Long-term predictive value of standardized challenge tests

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Venom immunotherapy (VIT) is able to protect insect venom-allergic patients against life-threatening sting reactions. Standardized sting challenges can be used as a diagnostic tool to check whether VIT is required. No data are available on the long-term predictive value of sting challenge tests. The purpose of this study was to investigate the long-term predictive value of sequential bee-sting challenges with respect to the ability to predict future sting reactions in bee-venom (BV) allergic children. Between 1988 and 1992, 92 BV-allergic children had been challenged with sequential bee stings at intervals of 2–6 weeks to determine the necessity of VIT. In 1996, all 92 families were followed-up using standardized telephone interviews. Until the follow-up, 61 children (66.3%) had experienced at least one natural bee sting. Based on the results of the initial challenge tests, 13 of the 61 patients had been started on VIT. Two of these 13 (15.4%) developed systemic reactions 1 year after VIT of 5 years, of which one was mild and one was severe. Among the 48 re-stung patients who were not treated with VIT, three children (6.3%) experienced mild systemic reactions, whereas 45 children reported no more than a local reaction. The long-term predictive value of sequential bee-sting challenge tests for systemic reactions in children not treated with VIT remained at a level of 93.8% (95% confidence interval: 82.8–98.7%) even over a period of more than 6 years. Based on this data, we conclude that sequential bee-sting challenges are a powerful tool to determine the necessity for VIT in BV-allergic children.

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In insect venom-allergic patients it is difficult to predict the severity and frequency of future sting reactions. Systemic allergic reactions to insect stings occur with a frequency of 0.4–4% in the general population (1–3). In adults, 27–57% who had shown a systemic allergic reaction to a bee sting reacted systemically to a subsequent sting (3–5). However, the risk of a repeated systemic reaction is generally lower in children, when compared with adults. Only 10–20% of children with a history of systemic reaction to bee stings reacted systemically again, and the reactions were usually less severe (3,6–9). Unfortunately neither medical history nor the diagnostic tests that are

available to assess the level of sensitization to bee venom (BV) help to define these 10–20% of patients potentially at risk for future systemic reactions. Therefore, until present, venom immunotherapy (VIT) with BV is still performed in more children than required (9–11). However, recent data indicates that standardized single sting challenges (11–13), and especially sequential sting challenges (7), may help to improve the indication for VIT. To date no information is available on the long-term predictive value of sting challenges in children. Therefore, the objective of this study was to examine the long-term predictive value of standardized sequential sting challenges in BV-

allergic children who had not been assigned to VIT after the initial challenge tests (7).

Materials and methods

Between 1988 and 1992, sequential bee-sting challenges were prospectively performed in 28 girls and 64 boys (median age 9 years; range 2–17 years) (7). Parents had reported potential signs ($n=14$) of a systemic reaction (immediate cutaneous reaction and changes in behavior of the child) or clear signs; $n=78$) of a systemic reaction (recurrent urticaria and/or high exposure owing to a residence close to a bee hive; $n=33$), or non-cutaneous signs of systemic reaction, with or without accompanying urticaria ($n=45$), to an insect sting. Patients with a reported life-threatening systemic reaction (severe signs of bronchoconstriction and/or hypotension) were not included in the study, which itself had been approved by the Medical Ethics Committee of the University. Informed consent had been obtained from the parents, particularly with respect to possible booster effects.

Specific sensitization at the time of sting challenges had been proved by skin-prick test (SPT) and/or radioallergosorbent test (Pharmacia AB, Uppsala, Sweden). Titrated SPTs were performed on the volar surface of the forearm using purified and immunochemically characterized bee venom (ALK Scherax, Hamburg, Germany) at concentrations of 100, 10, 1, and 0.1 $\mu\text{g/ml}$. The wheal reaction was evaluated 15 min after application. BV-specific immunoglobulin G (IgG) antibodies were quantified by enzyme-linked immunosorbent assay (ELISA) (14).

Bee-sting challenges were carried out with an intravenous line in place and under intensive medical observation by placing a living bee on the flexor side of the forearm. The insects were kindly supplied by bee keepers in the vicinity of the hospital. The second challenge was performed 2–6 weeks after the first. A second challenge was omitted if the patient had a severe systemic reaction following the first challenge.

Groups of patients who had shown different types of index sting reactions had no significant differences in the results of SPT and measurements of specific IgE and IgG antibody levels (data not shown). If no systemic reaction was observed in both challenge tests, an emergency kit (epinephrine-metered dose inhaler and antihistamine tablets for oral use; if there was still the risk of anaphylaxis an epinephrine injection device was added) was recommended and patients and parents were carefully instructed in its usage.

Venom immunotherapy (Reless[®]; ALK Scherax) was started (15) if the patient had had a systemic reaction on the first or second sting challenge that exceeded cutaneous symptoms and if their parents agreed with the recommendation for treatment. VIT was continued in all patients for at least 3 years with a maintenance dose of 100 μg of BV at 4-week intervals. At that time, during and after VIT, an emergency kit was not recommended. In August 1996 a standardized telephone interview was conducted with the parents of all 92 children. Information on field sting reactions and their treatment was obtained. A bee sting was assumed if the parents identified the stinging insect as a honeybee and/or the sting had remained after exposure to an insect.

Results

The response to the two sting challenges varied: 64 of 88 patients showed identical reactions in both tests; however, seven patients showed a local and moderate systemic reaction (urticaria), 13 patients showed a local and in one test severe systemic reaction (respiratory or cardiovascular), and four patients showed a moderate and severe systemic reaction. Thus, 27.3% (24 of 88) of the patients required two tests in order to avoid misclassification. In 10 patients the first test reaction was stronger than the second, and in 14 patients the second reaction was stronger than the first. As Table 1 and Figs 1 and 2 show, neither the SPT reaction nor the concentrations of bee venom-specific IgE and IgG antibodies were able to predict a moderate or severe systemic challenge test reaction.

An average time of 6.3 years (range 3.8–8 years) had elapsed between the sting challenges and the follow-up interview. At least one subsequent bee sting was reported in 61 out of 92 children. Thirty-three children were re-stung only once, and 28 children were stung at least twice (twice: $n=14$; three times: $n=5$; more than three times: $n=9$; median: 2.1).

Patients who had been assigned to VIT based on the sting challenges

Fifteen patients had been treated with VIT after a severe systemic reaction to the sequential sting challenge, and 13 of these 15 patients were stung by a bee in the follow-up period. Two of those 13 (15.4%) reacted systemically 1 year after completion of 5 years of VIT. One patient reacted systemically with diaphoresis, urticaria, and dyspnea $\approx$ 6 months after discontinuation of VIT. The second child required treatment in an

Table 1. Skin prick test (SPT) to bee venom (largest reaction to one of the concentrations applied)

SPT reaction	Local reaction to both sting challenges (n=48)	Moderate systemic reaction to at least one sting challenge (n=9)	Severe systemic reaction to at least one sting challenge (n=13)
No wheal reaction	20.83%	11.11%	0%
Wheal reaction of ≤ 2 mm	45.83%	44.44%	46.15%
Wheal reaction of ≥ 3 mm	33.33%	44.44%	53.85%

$p=0.38$ (chi-square test).

intensive care unit as result of a bee sting 1 year after completion of VIT (Table 2).

Patients who had not been assigned to VIT based on the sting challenges

Based on the results of the sequential bee-sting challenge, 77 of the 92 children were not treated with VIT. Forty-eight were accidentally re-stung by a bee at least once (median 3.7 years) after the challenge test. Three of these children (6.3%) developed a mild systemic reaction. One child responded with urticaria, the others developed mild dyspnea. None of the children needed treatment with beta-adrenergic drugs. The fact that three mild systemic reactions occurred in 48 bee venom-allergic children who had not been treated with VIT revealed a long-term predictive value of 93.8% (95% confidence interval: 82.8–98.7%) for systemic allergic reactions to subsequent bee stings (Table 2).

Discussion

Three of 48 (6%) children with non-life-threatening sting reactions, who had experienced a

negative sequential sting challenge test and had not received VIT, reacted systemically to a subsequent field sting. This result corresponds to frequencies of systemic reactions in BV-allergic patients treated with VIT (15). It shows that the decision (based on two negative sequential sting challenges) not to treat a patient with VIT does not result in a substantially higher risk of severe allergic reactions when compared to a treated patient.

Telephone interviews constitute a feasible and cost-effective procedure for investigating the sequential sting challenge test with regard to subsequent field stings occurring several years later. It cannot be ruled out that some field stings could not be recalled by our patients or their parents, as an average of 6.3 years had elapsed between the sting challenges and the interviews. It can, however, be assumed that systemic reactions were remembered and thus an underestimation of these is unlikely. Misidentifications concerning the type of insect cannot be excluded, but it was probably a bee-sting if the sting itself remained in the skin.

The follow-up period revealed a long-term predictive value of 93.8% (95% confidence inter-

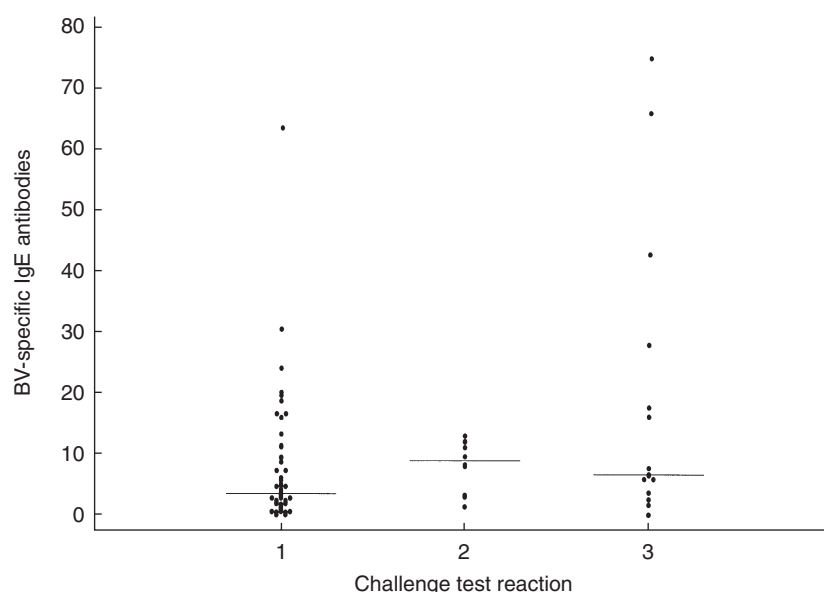
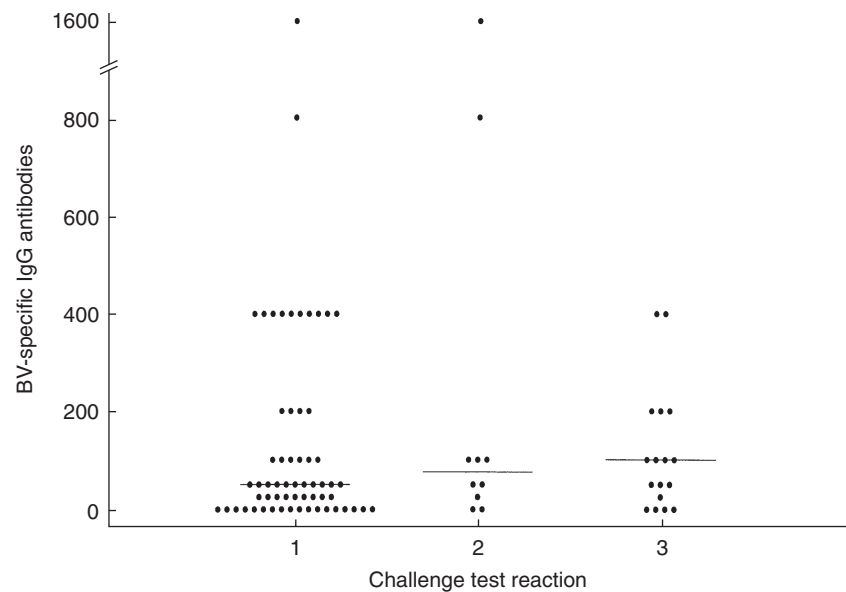


Fig. 1. Concentration of bee-venom (BV)-specific immunoglobulin E (IgE) antibodies (Phadebas RAST units/ml) in relation to the challenge test reactions. 1: Local reaction to both sting challenges (n=57); 2: moderate systemic reaction to at least one sting challenge (n=10); 3: severe systemic reaction to at least one sting challenge (n=16). $p = 0.044$ (Kruskal–Wallis test).

Fig. 2. Concentration of bee-venom (BV)-specific immunoglobulin G (IgG) antibodies (reciprocal titre) in relation to the challenge test reactions. 1: Local reaction to both sting challenges (n=60); 2: moderate systemic reaction to at least one sting challenge (n=10); 3: severe systemic reaction to at least one sting challenge (n=17). $p = 0.34$ (chi-square test).



val: 82.8–98.7%) with respect to future systemic sting reactions in children. As this figure is usually reached only after successful VIT (12,16), the sequential sting challenge test allows the allocation of individuals correctly with regard to the indication for VIT. Moreover, our findings may be relevant as the initial study population appeared to provide a sufficient number of individuals at risk for a severe systemic reaction, as proven by the challenge tests.

This finding highlights the importance of sequential sting challenge as a tool for identifying patients at risk. In our population, severe systemic test reactions were never life-threatening and could always be well controlled. In the 15 respective patients treated with VIT, the background history did not differ substantially from the others. We are convinced that the artificially created situation of an in-hospital sting challenge does not influence the severity of the sting reaction. Moreover, data published previously do not suggest that changes in endogenous catecholamine levels have substantial effects on the validity of this test (17). To ensure that a

sufficient dose of venom was applied, a clear cutaneous reaction – which is a wheal diameter of at least 5 mm (in most cases a wheal diameter of ≥ 10 mm can be seen) – must occur. It should also be borne in mind that a sting challenge can induce or increase sensitivity to BV. It is possible for a single challenge to be followed by a serious systemic reaction to a subsequent field sting (18). Therefore, we suggest performing two sequential sting challenges at 2–4-week intervals. As a result, a situation is created which is optimal for producing a systemic reaction to identify patients at risk (7,11). The use of living bees to challenge the patients has the advantage of monitoring the reaction on the natural venom. The standardized procedure has been described previously (19). Furthermore, a negative test reaction provides a psychological benefit for the patient. The subcutaneous injection of 100 μ g of purified bee venom might be an alternative if no insect is available, but patients' reactions have not yet been evaluated in detail.

One can expect similar results when patients with wasp venom allergy are examined. In

Table 2. Follow-up of sequential bee-sting challenge tests in bee venom (BV)-allergic children

	Sequential bee-sting challenge (n=92)	
	Children without VIT (n=77)	Children with VIT (n=15)
Field sting occurred (bee)	48	13
Reaction		
Not more than local	45	11
Urticaria	1	–
Dyspnea	2 (mild)	1
Emergency	–	1

VIT, venom immunotherapy.

contrast to the procedure with bees, the sting challenge with living wasps is less reliable owing to high variability in the amount of venom applied (19). Therefore, it would be preferable to inject purified wasp venom (our experience suggests: test 1=20 µg, test 2=50 µg) directly. An evaluation of the procedure in children has been reported by Schultze-Werninghaus et al. (20).

In principle, challenge tests bear the risk of systemic allergic reactions, although to date no fatal case has been reported in the literature (13). Nevertheless, the test should be performed only under defined safety conditions (7) and should be employed only if the index sting has not been followed by a life-threatening reaction. Among our total population (n=92) only 14 patients reported an immediate cutaneous reaction and no clear signs of a systemic reaction after the index sting. Nevertheless, one of them showed a systemic reaction (cough, urticaria, cold sweat, tachycardia) after the sting challenge, which suggests that in children the history may underestimate the risk of subsequent systemic reactions. From the clinical history of our initial study population, 78 patients fulfilled the current criteria for VIT (15), but only 13 received it based on our challenge test results. Therefore, 65 untreated patients (83.3%) would have undergone unnecessary therapeutic intervention using current guidelines. However, patients receiving VIT show systemic side-effects in up to 40% of cases (15).

Furthermore, it should be borne in mind that even after 5 years of VIT two of our patients were reported to have had another systemic reaction after an accidental sting. These results, too, are in accordance with the literature on BV allergy in adults (15). Therefore, we advise our patients who are selected as being at high risk (by performing a dual-challenge test) to carry an emergency kit with them after ceasing VIT. Discontinuation of VIT should be considered carefully in cases with very severe BV allergy.

In conclusion, we have demonstrated here an important role for sequential sting challenges among the diagnostic tools in bee-sting allergic children. These challenge tests have been proven to reliably detect children at risk for further systemic reactions over a period of over 5 years and to define the necessity of VIT. However, even in the event of two negative sting challenges, we inform our patients and their parents about limitations of prediction and that carrying an emergency kit can increase their safety.

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