

Epidemiologic study of insect allergy in children. II. Effect of accidental stings in allergic children

One hundred eighty-one children with non-life-threatening reactions to insect stings and positive venom skin tests were randomized to treatment (53) or no-treatment (128) groups and followed up clinically and immunologically for at least two years to assess the results of accidental stings. Twenty-eight stings in 17 treated patients and 74 stings in 47 untreated children occurred, leading to one mild reaction in a treated patient, and eight in the no-treatment group ($P = NS$). No reaction was more serious than the original. Based on IgE antibody changes and skin test results, 87% of the untreated children were stung by an insect to which they had clinical sensitivity by skin test. Vespid skin test sensitivity decreased 10-fold or more in both treated (72%) and untreated (44%) children. Of those with increased sensitivity, $\approx 70\%$ had been stung. These data indicate that the incidence of severe reactions on resting is low in insect-allergic children, and that the majority show decreased skin test sensitivity over time. (*J PEDIATR* 102:361, 1983)

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INSECT-ALLERGIC INDIVIDUALS frequently experience anaphylactic reactions after a sting; these are frightening, but rarely fatal. The incidence of this sensitivity is not known accurately, but is certainly higher than the 0.4 to 0.8% reported in the literature.^{1,2} We have recently studied an epidemiologically defined population of adults and find that fully 20% of these individuals have evidence of sensitization, either by history of an untoward reaction to a sting or by the presence of venom-specific skin tests.³ Anaphylactic reactions to insect stings can be prevented. We have carried out trials of venom immunotherapy in adults and children and demonstrated an efficacy approaching 97%.^{4,5} As in many clinical situations, however, the appropriate way to use this therapy, and particularly, for whom it is required, have not been established.

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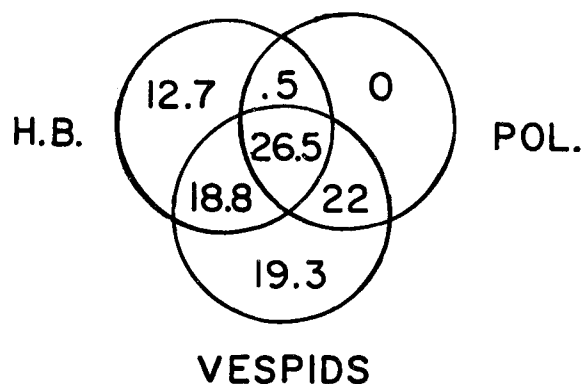


Figure. Distribution of skin test sensitivity in children. *HB*, Honeybee; *Vespid*, yellow jacket, white hornet, and yellow hornet; *Pol*, *Polistes*.

Several years ago we began a prospective study in children to address these questions. Children were chosen because of the possibility of long-term therapy (perhaps lifelong) and because of the extreme rarity of known deaths associated with insect sting reactions in individuals younger than 20 years. The study design focused on children who had a history of systemic reactions with only cutaneous manifestations (e.g., urticaria, angioedema)

Table I. Baseline characteristics of patients

	<i>n</i>	<i>Age (yr)</i> (mean $\pm$ SD)	<i>Percent</i> <i>males</i>	<i>Previous</i> <i>whole-body</i> <i>extract (%)</i>	<i>Skin test</i> <i>score (mean</i> <i>$\pm$ SD)</i>
Random treatment	32	9.40 $\pm$ 2.53	68.7	28	2.75 $\pm$ 0.95
Random no-treatment	42	9.57 $\pm$ 3.14	71.4	26	3.14 $\pm$ 0.75
Nonrandom treatment	21	10.35 $\pm$ 3.02	52.3	33	3.23 $\pm$ 0.78
Nonrandom no-treatment	86	9.22 $\pm$ 3.68	73.2	29	2.88 $\pm$ 1.06
Total	181	9.45 $\pm$ 3.27	69.6	28.8	2.96 $\pm$ 0.95

Table II. Results of accidental stings during the first two years of study

	<i>Treatment</i> <i>group</i> (<i>n</i> = 53)	<i>No-treatment group</i> (<i>n</i> = 128)
Total stings	28	74
Patients stung	17/53 (32%)	47/128 (36%) <i>P</i> = NS*
Systemic reactions	1	8
Systemic reaction/sting	3.6% (1/28)	10.8% (8/74)
Systemic reactors/ patient stung	5.9% (1/17)	17.0% (8/47) <i>P</i> = NS
As serious as original reactions	0/28	1/74

**P* > 0.05, chi-square.

after a sting; this group encompasses approximately 80% of children with anaphylactic reactions. The clinical and immunologic characteristics of the children who were selected have been reported.⁶

The patients were assigned to either immunotherapy or no-treatment groups. The plan was to allow accidental field stings and to assess the incidence and progression of systemic reactions in the two groups, and to see if any clinical or immunologic criteria would predict which children would have a subsequent systemic reaction to a sting.

METHODS

Patients. Children with insect allergy, aged 3 to 16 years, were recruited to the Allergy Clinic at The Good Samaritan Hospital through a public relations campaign and by physician referral. From the total group we selected children with non-life-threatening systemic reactions (i.e., those with only cutaneous symptoms such as erythema, urticaria, and angioedema). Those with more serious cardiovascular or respiratory symptoms (*n* = 97) were treated with venom immunotherapy and excluded from the study. From November 1978 to November 1980, the clinical criteria for entrance into the program were met by 208 children.

The initial evaluation consisted of a thorough medical and allergy history, with emphasis on all prior insect sting reactions, a physical examination, venom skin testing, and venom-specific IgE and IgG antibody measurements.

Venom skin testing. Honeybee, yellow jacket, yellow hornet, white-faced hornet, and *Polistes* (wasp) venoms, supplied by Pharmacia Diagnostics (Piscataway, N.J.), were applied and measured in the standard fashion⁷; a 2+ reaction (wheal size 5 $\times$ 5 mm or greater) was considered positive. Scoring was on a 4-point system described previously.⁶

Antibody measurements. IgE antibodies against yellow jacket venom and phospholipase A, the major allergen of honeybee venom, were measured by radioallergosorbent test (RAST),⁸ and are expressed as arbitrary units based on a standard curve. Most positive skin tests to the other vespids (white hornet, yellow hornet, *Polistes*) represent cross-reactivity with yellow jacket venom, so antibody levels were not determined to those venoms. A rise in RAST titer was defined as a poststing titer at least 50% greater than the presting titer.

IgG antibodies to the same antigens were measured by staphylococcal protein A assay and are expressed in micrograms per milliliter.⁹

Baseline toxicity studies. Complete blood count, sedimentation rate, automated chemistry screen, and urinalysis were obtained initially and yearly on all venom treatment patients.

Statistics. The Fisher exact *t* test or chi-square tests were performed as noted in the tables.

Study design. Patients with non-life-threatening systemic reactions and positive venom skin tests were enrolled in a program in which one group, by random assignment, received venom immunotherapy and the other group did not. The ratio of randomization was 1.0:1.5, treatment to no-treatment. More children were placed in the no-treatment group to allow us to gather more information on the natural history of insect allergy and to allow for an anticipated higher dropout rate. The patients who chose not to be randomized were allowed to select their own group. Venom therapy was administered according to an established regimen.¹⁰

Table III. Characteristics of "systemic" vs "local" reactors

	Systemic reactors (n = 8)	Local reactors (n = 39)	
Age (yr) (mean $\pm$ SE)	9.12 $\pm$ 3.2	9.34 $\pm$ 3.8	P = NS*
Percent males	75	76.9	P = NS
Original skin test score (mean $\pm$ SE)	3.12 $\pm$ 0.96	3.00 $\pm$ 0.88	P = NS
Presting yellow jacket RAST titer (mean $\pm$ SE)	276 $\pm$ 169	402 $\pm$ 643	P = NS
RAST rise with sting	6/8 (75%)	23/39 (58.9%)	P = NS
Presting yellow jacket IgG > 4.00 μ g/ml	2/8 (25%)	10/39 (25.6%)	P = NS

*P > 0.05, Fisher exact t test.

Table IV. Changes in vespid skin test sensitivity after one year

Skin test sensitivity	Treatment group		No-treatment group		Total	
Increased	2 (7%)	1/2 (50%)	13 (21%)	9/13 (69%)	15 (16%)	10/15 (67%)
Same	6 (21%)	3/6 (50%)	18 (35%)	3/18 (17%)	24 (26%)	6/24 (25%)
Decreased	21 (72%)	5/21 (24%)	32 (44%)	14/32 (44%)	53 (58%)	19/53 (36%)
Total	29 patients	9 stung	63 patients	26 stung	92 patients	35 stung

Both groups were carefully instructed in the emergency use of epinephrine, and emergency self-treatment kits (Epi-Pen, kindly provided by Center Laboratories, Port Washington, N.Y.) were given to each patient.

Follow-up in both groups consisted of quarterly blood samples for antibody titers, yearly skin tests and toxicity studies, and skin tests and antibody measurements after accidental stings when possible. Detailed accounts of the results of accidental stings were recorded promptly after the stings.

RESULTS

Of the 415 children who came to the Allergy Clinic, 208 met the clinical criteria of non-life-threatening reactions. Of the 207 remaining patients, 97 had life-threatening systemic reactions, 89 had large local reactions, and 21 had other types of reactions.

Of the 208 patients with non-life-threatening reactions, 181 (87%) had positive venom skin tests and were entered in the program. Seventy-four (approximately 40%) were randomized; the remaining 107 selected their own group, with the majority choosing no treatment. In all, there were 53 patients in the treatment group and 128 in the no-treatment group. There were small intergroup differences in baseline characteristics, which do not appear to be clinically important (Table I). Many children had skin test sensitivity to multiple venoms (Figure).

The immunotherapy for the treated group was effective, causing an increase in IgG antibody against venom antigens in all patients: (4.66 $\pm$ 7.19 to 16.8 $\pm$ 8.9 μ g/ml, n = 37). Both treated and untreated groups started with approximately the same level of IgG antibody (which is a function of time since stung), and the titer decreased over

time in the untreated group (7.68 $\pm$ 15.9 to 2.1 $\pm$ 4.14 μ g/ml, n = 107).

During the first two years of this program, the study patients were stung accidentally 102 times: 28 times in 17 treated patients and 74 times in 47 observation patients (Table II). Approximately one third of each group was stung, and among those stung, an average of 1.6 stings occurred per patient. The systemic reaction rates per sting and per patient stung were low in both groups, and the difference was not statistically significant. No reactions were more serious than the original, and only one of the eight systemic reactions in the no-treatment group was as serious as the original. Seven of the nine systemic reactions resolved without epinephrine therapy.

A major problem with accidental field stings is the uncertainty that patients were stung by insects to which they were sensitive. Of the 64 patients accidentally stung, 54.6% (35 of 64) had prior skin test sensitivity to both honeybee and vespid venoms; for these patients, any accidental sting would have been relevant. Five of the 64 patients were sensitive only to honeybees, and 24 (37.5%) were skin test positive only to the vespids. Changes in venom-specific RAST titers, usually assessed at three months before and three months after an accidental sting, were evaluated as an aid in identifying the stinging insect. Presting and poststing data from 47 stings in individual untreated patients were available for analysis. In 61.7% (29 of 47) of the stings, increases in either honeybee, yellow jacket, or both venom-specific RASTs could be demonstrated. In four of six of the patients showing increased titers to both venoms, multiple stings had occurred. No measurable rise in either the honeybee or yellow jacket RAST titer occurred in 18 patients. The

magnitude of the RAST rise varied considerably from the minimum of 50% to over sevenfold, and contrasted strikingly with the spontaneous decline (to approximately half the original titer) seen in 28 randomly selected, untreated, unstung patients. In addition, for the 18 stings that did not result in increased RAST titers, 12 of the patients stung had prior skin test sensitivity to both venoms and would have been sensitive to any insect. Therefore, combining both RAST and skin test sensitivity, we found that in 41 of 47 (87%) untreated patients, accidental stings were inflicted by insects to which the patients were clinically sensitive.

The eight untreated patients who had systemic reactions after entering the study were characterized by age, sex, original skin test scores, pretesting yellow jacket RAST titer, percent demonstrating "RAST rise" with sting, and percent with elevated pretesting yellow jacket IgG antibody titers ($> 4 \mu\text{g/ml}$) (Table III). When they were compared with the 39 untreated patients who subsequently had local reactions only, no statistically or clinically significant differences could be found.

Finally, the effects of accidental stings on venom skin test sensitivity were assessed by comparing initial venom skin tests with repeat tests obtained one year after entering the program. A "change" in skin test sensitivity is defined as at least a 10-fold difference in the lowest venom concentration required to elicit a positive (2+) skin test reaction. Separate comparisons for honeybee and vespid venoms were made for each patient, with the vespid score obtained by following the most positive of the yellow jacket, hornet, or wasp venoms. Data are available for 102 patients (33 treated, 69 untreated). The results were similar for honeybee and vespid venoms. Of the 92 patients who had initial, positive vespid skin tests, approximately half in both the combined treatment and combined no-treatment groups had decreased skin test sensitivity with time (Table IV). The proportion that increased or maintained skin test reactivity was also similar in both groups. If the data from both groups are combined, patients who were stung were more likely to have increased vespid skin test sensitivity than those who were not stung (10/35 vs 5/57, $P < 0.05$).

DISCUSSION

This study is an interim report on our prospective study of insect-allergic children, and provides information that should aid the clinician in deciding whether to treat children with systemic, cutaneous manifestations after an insect sting. Although our conclusion must remain tentative, the data provided indicate that most children with skin manifestations will not have another reaction after resting, even without therapy.

The greatest difficulty in a study such as this, which allows reactions to occur in the field, is knowing whether the child was stung by an appropriate insect (i.e., one to which he or she is sensitive). For this purpose, there are only two types of insects, honeybees and vespids (yellow jacket, yellow hornet, white hornet, and *Polistes*), because there is extensive cross-reactivity among vespid venom allergens. Our studies have shown that over 95% of patients have skin test sensitivity to vespids other than yellow jacket by virtue of this cross-reactivity.¹¹ In children the question of a relevant sting is somewhat simplified, because more than 50% are sensitive to both types of insects; in adults this figure is less than 20%. We were able to improve the accuracy of our estimation of relevancy by assessing whether the rise in IgE antibody level as a result of the sting was specific for honeybee or vespid antigens. It is curious that the sting is such a potent immunologic event. The yellow jacket, for example, injects $< 10 \mu\text{g}$ venom during a sting, but the subsequent immune response, in terms of both IgE and IgG antibody, is considerably greater than that induced by the therapeutic injection of $100 \mu\text{g}$ venom. Indeed, an increase in IgE antivenom antibodies is seen in some treated children who are stung while receiving regular maintenance injections of $100 \mu\text{g}$ venom. The reason for this phenomenon is not clear, but in the present context it is useful. Measurement of the poststing IgE antibody level has allowed us to conclude that almost 90% of the stings experienced by untreated children in this trial were relevant in terms of the child's sensitivity.

There are multiple and striking differences between insect sensitivity in adults and children. In children there is a significant decrease in skin test sensitivity to venom antigens over time, even during immunotherapy. More than half the patients had a 10-fold or greater increase in the concentration of venom necessary to cause a 2+ skin test, whereas after two years of therapy this was observed in only a small percentage of adults.¹² Only a few children showed an increased skin test sensitivity, which appeared to be largely attributable to the fact that they were stung in the interim. It is not readily apparent why there should be such a difference in the change in skin test sensitivity over time, but children are more likely to lose their sensitivity than adults are.

One of the aims of this study was to assess a variety of historical and immunologic factors, with the hope that we would be able to ascertain which children would have subsequent systemic reactions. Unfortunately, thus far we have been completely unsuccessful. Neither age, sex, skin test sensitivity nor pretesting IgE antibody level is a useful discriminator. Furthermore, although there is evidence that IgG antibody is protective, the data derived thus far

indicate that this variable will also not be useful. Our preliminary assessment of changes in IgE antibody levels (i.e., the rate of fall over time) also indicates that this value will not be useful.

Our most striking observation is how few reactions occurred after restings. In adults we found that approximately 60% of individuals with a positive history and positive venom skin tests had a systemic reaction on deliberate, in-hospital challenge sting.⁴ In children this percentage is about 10%. Although in this study the stings were accidental, the low rate of reaction was unanticipated, and we are unable to speculate effectively on this difference between children and adults. Furthermore, the progression from cutaneous to life-threatening reactions did not occur.

Further work is necessary, but these data should allow the physician to provide patients with an assessment of the risk of withholding therapy and perhaps allow temporizing until the data are more definitive.

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