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Stinging insect allergy: Natural history and modification with venom immunotherapy

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The natural history of stinging insect allergy and its modification by venom immunotherapy was investigated by follow-up observations of patients with histories of venom anaphylaxis and detectable venom-specific IgE. The patients were divided into three categories: (1) receiving venom immunotherapy, (2) declined venom immunotherapy, and (3) terminated venom immunotherapy. One hundred twenty-seven patients were evaluated after 6 mo to 9 yr of venom immunotherapy. Most received top venom doses of 50 µg of yellow jacket and/or honeybee venoms every 4 wk. There were 87 restings in 48 patients resulting in two systemic reactions, only one of which could be considered a treatment failure (1%). Fifty-six patients never received venom immunotherapy. In this group there were 40 restings in 28 patients with 14 systemic reactions (35%). In 88 patients who stopped venom immunotherapy, 61 restings in 41 patients led to 11 systemic reactions (17%). Patients with cardiovascular/or respiratory symptoms with initial sting anaphylaxis were at risk for subsequent reactions. With one exception, patients with hives and edema only as the initial reaction either had a similar or no reaction when they were restung. These results confirm the efficacy of venom immunotherapy but also suggest that there are factors other than the presence of venom-specific IgE modulating the occurrence of clinical anaphylaxis. (J ALLERGY CLIN IMMUNOL 76:735-40, 1985.)

Purified venoms have been commercially available for the past 5 yr for the diagnosis and treatment of stinging insect allergy. These venom preparations, used in appropriate concentrations for skin tests or RAST, reliably detect specific IgE antibodies.^{1,2} Immunotherapy with venoms has proved effective in preventing subsequent sting anaphylaxis.³

However, observations of patients with stinging-insect allergy have uncovered an inconsistency between immunologic reactivity and clinical sensitivity.^{3,4} Numerous patients have been observed who have had typical sting anaphylaxis, have positive venom skin tests, and yet, when they are restung, fail to have allergic reactions. The therapeutic benefit ascribed to whole body-insect extracts, now recognized as impotent extracts,⁵ was probably related to this inconsistency in reactions to subsequent venom exposure.

In an attempt to obtain further insight into the natural history of insect-sting anaphylaxis and its modification by venom immunotherapy, we have studied insect-allergic patients who have (1) declined venom immunotherapy, (2) terminated venom immunotherapy without physicians' advice, and (3) received

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TABLE I. Venom immunotherapy: Summary of patient data

No. patients	127
Duration of therapy	6 mo to 9 yr
Mean	34 mo
Age (yr)	7 to 79
Mean	27
≥ 16 yr	93
< 16 yr	34
M/F	90/37
Initial anaphylactic symptoms	
Urticaria/edema only	47
Respiratory	54
Cardiovascular	25
Gastrointestinal	10
Venom immunotherapy	No. patients (%)
Honeybee	39 (31)
Yellow jacket	51 (40)
Honeybee plus yellow jacket	26 (20)
Multiple vespid	7 (5)
Honeybee plus multiple vespid	2 (2)
Hornet	1 (1)
Wasp	1 (1)

venom immunotherapy. These results confirm the efficacy of venom immunotherapy but also suggest that there are factors other than the presence of venom-specific IgE modulating the occurrence of clinical anaphylaxis.

MATERIAL AND METHODS

Patients

All patients referred for evaluation of stinging-insect sensitivity from 1976 through 1983 and who had a history of sting anaphylaxis and detectable venom-specific IgE were included in this study. Systemic anaphylaxis was defined as the occurrence of typical allergic symptoms, such as generalized hives, angioneurotic edema, generalized pruritus, nausea, vomiting, diarrhea, hypotension, shock, asthma, and upper airway edema within several minutes to several hours after an insect sting. Venom-specific IgE was detected by skin tests with serial dilutions of honeybee, yellow jacket, bald-faced hornet and *Polistes* venoms. The honeybee, yellow jacket, and hornet venoms were collected locally by electrical stimulation.⁶ Previous studies have demonstrated the potency of these venoms to be equal to that of the commercial venom sac extracts.⁷ *Polistes* venom was obtained commercially. Skin tests were considered positive if reactions were found at venom concentrations of 0.01 μ g/ml or less.⁸ The presence of venom-specific IgE was confirmed by RAST, although these results are not pertinent to this presentation.

Venom immunotherapy was recommended for all patients meeting these qualifications, the history of sting anaphylaxis,

TABLE II. Venom immunotherapy: Resting data

No. patients	48
No. restings	87
Insect positively identified as same causing initial reaction	41
Reactions	2
Honeybee sting in patient on honeybee venom therapy	
Yellow jacket sting in patient on honeybee venom therapy	

laxis, and the presence of venom-specific IgE. All patients were instructed in the appropriate use of emergency medication and received epinephrine in preloaded syringes.

In 1983 all patients who had been evaluated for the previous 7 yr were contacted for reevaluation. These patients were categorized into three groups: (1) receiving venom immunotherapy, (2) never received immunotherapy, and (3) received immunotherapy and stopped without physician advice. Follow-up information included a history of any further stings and subsequent reactions and, when it was possible, measurement of venom-specific IgE by skin test and RAST.

RESULTS

One hundred twenty-seven patients, ranging in age from 7 to 77 yr, received venom immunotherapy (Table I). There were 90 male and 37 female patients; 93 patients were 16 yr of age or older, and 34 were less than 16 yr. Continuous venom immunotherapy had been administered for 6 mo to 9 yr.

Initial symptoms of anaphylaxis were as follows: urticaria and edema only, 47 patients; respiratory symptoms, 54 patients; cardiovascular symptoms, 25 patients; and gastrointestinal symptoms, 10 patients. There was no relationship between the symptom complex and age.

Venom immunotherapy was administered primarily with honeybee and/or yellow jacket venoms. Of the 127 patients, 39 (31%) received honeybee venom, 51 (40%) received yellow jacket venom, 26 (20%) received honeybee and yellow jacket venoms, seven (5%) received multiple vespid venoms, two received multiple vespid and honeybee venoms, one patient received hornet venom, and one patient received *Polistes* venom. The decision for the use of individual venoms was based on patient history and skin test results.

Venom immunotherapy was usually initiated with doses of 0.001 μ g/ml to 0.1 μ g/ml. Weekly increments were administered according to either a traditional or rush dose schedule until a maximum of 50 μ g was achieved, usually in about 6 to 8 wk. Maintenance doses were administered every 4 to 6 wk.⁹

There were 87 restings in 48 patients (Table II). In at least 41 episodes the insect could be identified as the same as that causing the initial reaction. In the other resting episodes the offending insect could not be identified with certainty. There were only two systemic reactions in two patients. In one individual, a 79-yr-old dentist on honeybee venom therapy for 5 yr, a honeybee sting led to generalized hives, pruritus, angioneurotic edema, and wheezing. Serum analysis 1 yr before the sting indicated elevated levels of bee venom-specific IgG and modest elevations of bee venom-specific IgE. After this sting there was an increase in both antibody titers. Subsequently, the venom dose was increased to 100 µg every 4 wk.

The second reaction occurred in a 35-yr-old man receiving honeybee-venom therapy. Within 15 min of a yellow jacket sting, he developed swelling of the lips and shortness of breath. Before this sting he did have mildly elevated titers of yellow jacket venom-specific IgE in his serum. Subsequently, yellow jacket venom was added to his therapy.

No venom immunotherapy

There were 56 patients who had had typical generalized anaphylaxis after insect stings and had positive venom skin tests (Table III). No patient in this group had prolonged hypotension and shock. Venom immunotherapy was recommended to all but for various reasons was declined.

The ages of the patients ranged from 4½ to 83 yr with a mean of 24 yr. There were 36 male and 20 female patients. The initial sting reaction was generalized hives and edema only in 27 patients and cardiovascular and/or respiratory symptoms in 29. Two of the patients had nausea, vomiting, and diarrhea. All patients were provided with emergency medication and with advice regarding insect avoidance.

The follow-up intervals after the initial anaphylactic reaction ranged from 5 mo to 12 yr. There were 40 resting episodes in 28 patients (Table IV), resulting in 14 systemic reactions. The interval between the initial sting anaphylaxis and the subsequent sting ranged from 2 mo to 12 yr.

The resting data are further analyzed in Table V. There were 18 patients with hives and edema only after their initial reaction. When these patients were restung, six again had hives and angioneurotic edema only, and 12 had no reaction. There were 10 patients who had cardiovascular and/or respiratory symptoms with the initial sting anaphylaxis. After resting six had similar cardiovascular and respiratory symptoms, two had hives and angioneurotic edema, and two had no reaction. These data suggest that patients who develop cardiovascular and/or respiratory symptoms with sting

TABLE III. No venom immunotherapy:

Patient data

No. patients	56
Age (yr)	4½ to 83
Mean	24
M/F	36/20
Initial reaction	
Hives/edema only	27
Cardiovascular/respiratory symptoms	29
Duration of follow-up	5 mo to 12 yr
Mean	56 mo

TABLE IV. No venom immunotherapy:

Resting data

No. patients	28
No. restings	40
No reactions	14
Interval from previous sting	2 mo to 12 yr

TABLE V. No venom immunotherapy:

Resting details related to clinical symptoms

Initial sting reaction		Resting reaction	
Hives/edema only	18	Hives/edema only	6
		No reaction	12
Cardiovascular/respiratory symptoms	10	Cardiovascular/respiratory symptoms	6
		Hives/edema only	2
		No reaction	2

TABLE VI. No venom immunotherapy:

Resting details related to age

Age	No. patients	No. restings	Systemic reactions
>16	15	21	6
≥16	13	19	8

anaphylaxis are more likely to have subsequent reactions when they are restung.

In patients less than 16 yr of age, there were 21 restings in 15 patients resulting in six systemic reactions (Table VI). In patients older than 16 yr, there were 19 restings in 13 patients with eight systemic reactions. These data suggest that age, per se, does not appear to be a major factor in predicting systemic resting reactions.

Venom immunotherapy stopped

Eighty-eight patients stopped venom therapy without physicians' recommendation. They ranged in age from 10 to 76 yr (Table VII). Thirty-two patients had

TABLE VII. Venom immunotherapy stopped:
Patient data

No. patients	88
Age (yr)	10 to 76
Mean	33
M/F	67/21
Initial reaction	
Hives/edema only	32
Cardiovascular/respiratory/ other	56
Duration of venom therapy	1 mo to 6½ yr

TABLE VIII. Venom immunotherapy
stopped: Resting data

No. patients	41
No. restings	61
No. reactions	11
Interval from last venom im- munotherapy and resting	1 mo to 6 yr

TABLE IX. Venom immunotherapy stopped:
Resting details related to clinical symptoms

Initial sting reaction		Resting reaction	
Hives/edema only	14	Hives/edema only	2
		Cardiovascular/respira- tory symptoms	1
		No reaction	11
Cardiovascular/respira- tory symptoms	27	Hives/edema only	2
		Cardiovascular/respira- tory symptoms	6
		No reaction	19

urticaria and angioneurotic edema only as their initial anaphylactic response. Fifty-six individuals had cardiovascular and/or respiratory symptoms. Venom immunotherapy had been administered from 1 mo to 6½ yr.

There were 61 resting episodes in 41 patients (Table VIII). Almost all the patients had received maintenance doses of venom immunotherapy of 50 µg every 4 wk. These restings occurred at intervals of 1 mo to 6 yr after venom immunotherapy was stopped and resulted in 11 systemic reactions. Serum venom-specific IgG levels were not known just before the restings.

The resting details were further analyzed according to the type of initial reaction (Table IX). Fourteen patients had hives and edema as the sole manifestation of their initial sting anaphylaxis. When these patients

were resting, two had hives and edema only, one had cardiovascular and respiratory symptoms, and the other 11 patients had no reaction. There were 27 individuals who had cardiovascular and/or respiratory symptoms with their initial anaphylactic reaction. When the individuals were resting, six had cardiovascular and respiratory symptoms, two had hives and edema only, and 19 had no reaction.

Nine restings occurred in eight patients less than age 16 yr, leading to one systemic reaction. Fifty-two restings occurred in 33 patients more than age 16 yr, resulting in 10 systemic reactions.

The resting experience in the three groups of patients is summarized in Table X. Venom immunotherapy was almost completely protective in preventing subsequent anaphylaxis. Without venom therapy the resting reaction rate was about 35%. In patients who stopped therapy, the incidence was 17%. Again, it should be emphasized that as the identification of the resting insect was not always possible, these reaction rates may be higher.

DISCUSSION

The results of these studies confirm that venom immunotherapy is effective in preventing subsequent anaphylaxis in allergic patients and emphasize the inconsistency between immunologic reactivity and clinical sensitivity.

Insect-venom immunotherapy was initially demonstrated to be effective in studies comparing the response to intentional restings in patients treated with venom, placebo, and whole body-insect extract.³ Since that time, numerous patients have been treated with almost 100% protection achieved, defined by the lack of response to subsequent insect stings. Our own experience confirms these results. Only two systemic reactions occurred after restings in treated patients. One reaction occurred in an individual who was being treated with honeybee venom and was stung by a yellow jacket. As these insects are in different families, these reactions may be mediated by a separate antibody.¹⁰ The second reaction occurred in an individual receiving honeybee venom who was stung by a honeybee. This might be considered the only treatment failure in this group.

Our regimen of treatment differs somewhat from that generally recommended. When vespid venom was required, most patients received only yellow jacket venom. The yellow jacket is the most frequent cause of insect stings in our area. Most patients do have some skin test reactivity with other vespid venoms. Prior studies have indicated fairly extensive cross-reaction, particularly between the yellow jacket

TABLE X. Summary of resting experience

Treatment group	No. restings	No. patients	No. systemic reactions	Reaction rate	
				per patient (%)	per sting (%)
Venom immunotherapy	87	48	1*	2	1
No venom immunotherapy	40	28	14	50	35
Venom immunotherapy stopped	61	41	11	27	17

*One other patient treated with honeybee venom had a reaction to a yellow jacket sting and is not considered a treatment failure.

and hornet venoms.^{11, 12} The yellow jacket and hornet venoms are collected locally by electrical stimulation. Their potency is equivalent to those collected by venom sac dissection and currently used commercially.⁷ Fifty micrograms, equivalent to one sting, has been used as a top dose. This does stimulate IgG antibody response.¹³

Golden et al.¹⁴ compared the effectiveness of 50 μ g and 100 μ g doses by in-hospital sting challenges after 20 wk of venom therapy. The higher dose provided 97% protection, and in the 50 μ g dose group, four of 19 challenged patients had mild systemic reactions resolving without treatment. Therefore, these investigators recommended the 100 μ g dose for maintenance therapy.

The most important results of our studies are the continued observation of the unexplained inconsistency of the immunologic reactivity that is indicated by the presence of specific IgE antibodies and the clinical response to restings. In the untreated group of patients, only 50% had systemic reactions when they were restung. When it is recognized that the identity of the resting insect was not always specified, the reaction rate might be somewhat higher. Nevertheless, a large proportion of the patients presumed sensitive, based on prior sting anaphylaxis and the presence of venom-specific IgE, did not react when they were restung. Thus, it is clear that a large number of patients being treated with venom immunotherapy do not require such treatment.

This inconsistency in clinical response has been noted previously. In the initial study at Johns Hopkins with insect venoms, approximately 40% of the patients in the placebo and whole body-insect extract groups did not respond to sting rechallenge.³ Parker et al.¹⁵ used deliberate sting challenges in patients with prior anaphylaxis and detectable venom-specific IgE and concluded that "no in vitro or in vivo test predicted with certainty the clinical immune status of a sting-sensitive person." We studied one individual very extensively who, after generalized urticaria after

a yellow jacket sting, was stung on multiple occasions by other insects over a 2-year period with no reaction. This individual had high titers of specific IgE antibodies reacting with several insect venoms and no serum IgG antibody.⁴

Schuberth et al.¹⁶ concluded that children who have urticaria alone as the sole manifestation of sting anaphylaxis do not require venom immunotherapy. Most of these children did not react when they were restung; those who reacted had mild reactions readily controlled with symptomatic medication. Analysis of our own data confirm these results and extend these conclusions to adults. Eighteen patients who had hives and urticaria only in their initial reaction, were restung. Six had similar symptoms, 12 had no reaction, and none were worse. In this group there were 12 patients under 16 yr, and six were more than 16 yr. In contrast, of 10 patients who had had cardiovascular or respiratory symptoms with their initial sting, six had similar reactions with a resting. Within this group, five were more than 16 yr, and five were less than 16 yr. These data in total suggest that patients with urticaria and angioneurotic edema alone, regardless of age, may not require venom immunotherapy. Only in the patients who stopped therapy without physicians' advice was there one individual with hives and edema initially who had a more severe reaction after a resting.

In patients who stopped venom therapy, the resting reaction rate was approximately 17%, confirming the results in the untreated patients. The relationship of the initial clinical reaction to subsequent sting anaphylaxis was also similar. Of 14 patients who had hives and edema only, restings led to similar reactions in two, a more severe reaction in one, and no reaction in 11. In contrast, of 27 patients with cardiovascular and/or respiratory symptoms, restings caused similar reactions in six, hives and edema only in two, and no reaction in 19. Restings occurred at a wide interval after cessation of therapy. Titers of venom-specific IgG, that antibody presumed to mediate protection from insect stings, were not available just before the

resting experience. Golden et al.¹⁷ found very similar results in patients who stopped venom immunotherapy; 29 restings resulted in six systemic reactions, a reaction rate of 21%.

The quality and quantity of antigenic exposure might influence the allergic response. The amount of venom delivered with each sting could vary. The composition of venom does not appear to change over the summer months.¹⁸ It is possible that some changes in venom may occur with aging of the insect.^{19, 20}

The lack of a clinical reaction in individuals with specific IgE antibody and a prior history of immediate allergic reaction may not be restricted only to those patients with insect-sting sensitivity. Limited data in other models have suggested that similar patterns exist. Bock et al.²¹ studied infants and children who had histories of adverse reactions to foods. Approximately half of the children who had a history of an allergic reaction after food ingestion and positive puncture skin tests did not react when they were intentionally rechallenged with the specific food. In studies of penicillin hypersensitivity,²² nine patients with positive skin tests to penicillin or its major metabolite, penicilloyl polylysine, were challenged with penicillin. Six reacted, and three did not react.

Insect-venom immunotherapy is effective prophylaxis in preventing subsequent reactions in allergic individuals. Clearly, other factors appear to mediate the clinical allergic response other than venom-specific IgE. The experiences in venom allergy may not reflect a unique model but rather may be common to other types of hypersensitivity reactions. Further delineation of the factors modulating clinical anaphylaxis is most important, both in the basic understanding of the reaction and in its application to the appropriate selection of those patients requiring immunotherapy.

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