

# Natural history of insect sting allergy: Relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions

Robert E. Reisman, MD *Buffalo, N.Y.*

*To examine the postulate that the nature of the symptoms of initial insect sting anaphylaxis is related to the risk and severity of subsequent sting reactions, the results of field re-stings were analyzed in 220 patients who had had venom anaphylaxis and did not receive venom immunotherapy. The incidence of a reaction after the first re-sting was 56% in the total group, was more frequent in adults (74%) than in children (40%), and was unrelated to the time interval since the initial sting reaction. When re-sting reactions did occur, the nature of the symptoms was similar to the symptoms of the initial sting reaction. Reactions to repeated re-stings tended to be similar. Overall, more severe reactions to re-stings occurred eventually in 24 patients. These observations confirm the frequent self-limiting course of insect sting allergy, especially in children, and the repetitive nature of specific anaphylactic symptoms, and the observations thus suggest that patients with mild to moderate anaphylactic symptoms probably do not require venom immunotherapy. (J ALLERGY CLIN IMMUNOL 1992;90:335-9.)*

**Key words:** *Insect sting anaphylaxis, re-stings, nature of symptoms*

The availability and subsequent commercial distribution of purified insect venoms in 1979 provided reliable allergens for the diagnosis and treatment of patients with insect sting anaphylaxis. Immunotherapy with insect venoms is almost 100% effective prophylaxis, preventing subsequent sting anaphylaxis.<sup>1</sup> An unexplained finding, initially made in the early studies with venom, was the observation that approximately one half of the patients thought to be allergic to insect stings because of a history of venom anaphylaxis and the presence of venom-specific IgE (positive venom skin tests) did not react when re-stung, in the absence of venom immunotherapy.<sup>2</sup> This dichotomy between clinical sensitivity and immunologic reactivity has been extended in studies of the natural history of insect sting allergy.<sup>3</sup> Schuberth et al.<sup>4</sup> have shown that children with dermal reactions as the sole manifestation of sting anaphylaxis have a very benign course. Subsequent re-stings are usually tolerated with no reaction, and when reactions have occurred, the symptoms

remain mild. In contrast, our studies suggest that patients who have had severe anaphylactic symptoms are likely to continue to have similar severe symptoms after subsequent re-stings.<sup>5</sup>

The purpose of this study is to extend these observations of the natural history of insect sting allergy and examine the postulate that the likelihood and severity of re-sting reactions are related to the nature of the symptoms of the initial sting anaphylaxis.<sup>3</sup> Other factors to be considered are the age of the patients and the time interval between repeat stings. The goal is to obtain further insight into the natural history of insect sting allergy and, as a consequence, reassess guidelines for selection of patients requiring venom immunotherapy.

## PATIENTS IN THE STUDY AND METHODS

Records were reviewed of all patients evaluated over the past 10 years because of a history of insect sting anaphylaxis. Patients were included in the study if there was a history of a re-sting after the first episode of sting anaphylaxis in the absence of venom immunotherapy.

Data collected included the age of the patient at the time of the initial sting anaphylaxis, the time interval between the initial sting reaction and subsequent re-sting, the identification of the responsible stinging insects, the nature of the allergic symptoms, and the effects of any sequential re-stings.

To simplify the analysis, the insect sting reactions were graded as follows: I, mild, dermal symptoms (urticaria, angioedema) only; II, moderate, dermal reactions and other non-life-threatening symptoms such as mild asthma or dys-

From the Allergy Division, Departments of Medicine and Pediatrics, State University of New York at Buffalo School of Medicine, Buffalo.

Received for publication Dec. 30, 1991.

Revised April 21, 1992.

Accepted for publication April 28, 1992.

Reprint requests: Robert E. Reisman, MD, Buffalo Medical Group, 295 Essjay Rd., Williamsville, NY 14221.

1/1/38883

**TABLE I.** Summary of relationship of insect sting reaction symptoms to results of subsequent re-sting, in the absence of venom immunotherapy, in the total group of patients

Initial reaction		Re-sting reaction (No. of patients)				
Grade	No. of patients	None	Local*	I Mild	II Moderate	III Severe
I Mild	102	39	14	38	3	8
II Moderate	61	14	6	5	29	7
III Severe	57	17	6	5	3	26
Total	220	70	26	48	35	41

\*A local reaction is defined as swelling extending from the sting site, using peaking in 48 to 72 hours, and lasting 4 to 6 days, in the absence of systemic symptoms.

After re-sting 96 patients (44%) had no reaction and 124 (56%) had repeat reactions.

nea; III, severe, which included symptoms of shock, hypotension, loss of consciousness, upper airway edema, and/or severe respiratory distress.

## RESULTS

Over the past 12 years approximately 1200 patients have been evaluated because of allergic reactions after insect stings. Two hundred twenty patients were identified who met the following criteria for inclusion in this study: the occurrence of a re-sting after an allergic sting reaction, in the absence of venom immunotherapy. One hundred seventy-five of the 220 patients had the initial sting reaction and subsequent re-sting before their consultation and evaluation. Forty-five patients were evaluated after the initial sting reaction and subsequently had a re-sting.

Seventy patients identified the same insect as responsible for the sting reaction and subsequent re-sting. Seventy-two patients identified the insect as being different, and 128 patients could not identify either one or both insects responsible for the paired stings.

The overall results are summarized in Table I. One hundred two patients had initial mild symptoms of sting anaphylaxis. After the next re-sting, 39 had no reaction, 14 had local reactions only, 38 had mild symptoms, 3 had moderate reactions, and 8 patients had severe reactions. Thus 49 (48%) of the patients in this group had a re-sting allergic reaction, 11 of whom had more severe symptoms than the symptoms that occurred with the initial reaction.

Sixty-one patients had initial moderate anaphylactic symptoms. After the subsequent re-sting, 14 had no reaction, 6 had local reactions only, 5 had mild symptoms, 29 had moderate symptoms similar to the initial reaction, and 7 patients had more severe symptoms. To summarize this group, 41 patients (67%) had a re-sting reaction.

Fifty-seven patients had initial severe symptoms. After the re-sting 17 patients had no reaction, 6 had

local reactions only, 5 had mild reactions, 3 had moderate reactions, and 26 had similar severe reactions. In total, 34 (60%) of this group had re-sting reactions, most were similar to the initial reaction.

To summarize, after re-stings 96 patients (44%) had no reaction, and 124 (56%) had repeat reactions. When re-sting reactions did occur, the symptoms tended to be similar to the symptoms of the initial sting reaction. Eighteen of the 163 patients (11%) with initial mild to moderate reactions had more severe re-sting reactions and are discussed in more detail herein.

Seventy patients could identify the same insect as responsible for the initial sting reaction and subsequent re-sting. The overall analysis of this subgroup did not differ significantly from the total group of patients in the study. A similar distribution of patients occurred in the three categories of sting reactions. The incidence and severity of the re-sting reactions were approximately the same as those in the total group (Table II).

The relationship of age at the time of the initial sting reaction to the symptoms of the re-sting reaction in the total group is shown on Table III. Patients under the age of 16 years had less likelihood of re-sting reactions, regardless of the severity of the symptoms of the initial reaction. However, the difference in re-sting reaction rates was only significant ( $p < 0.001$ , chi square) for patients with mild anaphylactic symptoms. Sixty-four of 102 patients with mild sting anaphylaxis were under age 16 years, and 38 were over 16 years old. The re-sting reaction rate was 30% in the children and 79% in the adults. Thirty-one patients were less than 16 years old, and 30 were more than 16 years old in a group of patients with moderate reactions. The re-sting reaction rate was 58% in the children and 77% in adults. Seventeen of the 57 patients with severe anaphylaxis were less than 16 years old, and 40 were over 16 years old. The re-sting reaction rates were 47% and 65%, respectively.

The relationship of the time interval between the

**TABLE II.** Summary of relationship of initial sting reaction symptoms to results of subsequent re-sting in subgroup of patients who identified the same insect as responsible for both stings

Initial reaction		Re-sting reactions				
Grade	No. of patients	None	I Mild	II Moderate	III Severe	Total % reactions
I Mild	24	14	7	—	3	41%
II Moderate	17	4	1	12	—	76%
III Severe	29	7	3	3	16	76%

Total initial reactions 25 (36%); total re-sting reactions 45 (64%).

**TABLE III.** Relationship of age at time of initial sting reaction to result of subsequent re-sting

Initial reaction Grade	Re-sting reaction			
	<16 yr		>16 yr	
	No. of patients	% Reaction	No. of patients	% Reaction
I Mild	64	30%*	38	79%
II Moderate	31	58%	30	77%
III Severe	17	47%	40	65%

\*Difference in re-sting reaction rates between patients under and over 16 years was only significant in groups with mild anaphylactic symptoms ( $p < 0.001$ ).

**TABLE IV.** Relationship of time interval between initial sting reaction and subsequent re-sting to results of re-sting

	Time (yr)			
	0 - 2	2 - 5	5 - 10	>10
No. of re-stings	121	60	23	16
No. of reactions	70 (58%)	30 (50%)	11 (48%)	13 (81%)

initial sting reaction and the subsequent re-sting to the occurrence of re-sting anaphylaxis is shown on Table IV. One hundred twenty-one patients reported a re-sting within 2 years of the initial sting reaction. The re-sting reaction rate was 58%. Sixty patients had re-stings from 2 to 5 years after the initial reaction, with a 50% re-sting reaction rate. Twenty-three patients had re-stings between 5 and 10 years after the initial sting reaction, with a re-sting reaction rate of 48%. Thirteen reactions occurred in 16 patients (81%) who reported re-stings more than 10 years after their initial sting anaphylaxis. Within this latter group, eight patients had initial mild sting reactions. After the re-sting, one patient had no reaction, one patient had a mild reaction, one patient had a moderate reaction, and five patients had severe reactions. Two patients who had initial moderate sting reactions had similar reactions after re-stings. Six patients had initial severe sting reactions, and after re-stings, one patient had no

reaction, one patient had a moderate reaction, and four patients had severe reactions.

As noted in Table I 18 patients had symptoms after a re-sting that were worse than the symptoms that occurred with the initial sting reaction. Eleven patients with initial mild symptoms had worse re-sting reactions. Three patients, one adult and two children had moderate re-sting symptoms, and eight patients, seven adults and one child, had severe symptoms. Seven patients, three adults and four children, had initial moderate symptoms followed by severe re-sting symptoms. Within these groups, three patients under the age of 16 years had initial mild symptoms only and subsequently had moderate or severe re-sting reactions.

After the first re-sting after the anaphylactic reaction, 90 patients had subsequent stings. Sixty patients had reactions from these repeated stings similar to the reaction that occurred after the initial re-sting.

**TABLE V.** Results of repeated re-stings

No of patients with repeated re-stings	90
Similar response	60
No reaction	29
Same reaction	31
Variable response	30
Similar or less intense reaction followed by no reaction	7
No reaction followed by systemic reaction	20
Similar reaction followed by more severe reaction	3

Twenty-nine of these 60 patients had no reaction from the initial re-sting and no reactions after one to nine repeat stings. Fifteen patients in this group had an initial mild sting reaction, 2 patients had a moderate reaction, and 12 patients had had a severe reaction. Thirty-one patients had reactions from 1 to 10 repeat stings that were of the same intensity as the initial sting and first re-sting anaphylaxis. Eight had had mild initial reactions, 14 had moderate reactions, and 9 had had severe reactions.

Thirty patients had a variable response after repeat re-stings. Seven patients had a similar or less intense reaction from the first re-sting and no reaction from subsequent repeat re-stings. Twenty patients had no reaction from one to five re-stings followed by a systemic reaction. Within this group, 3 of the 20 patients had eventual re-sting reactions worse than the original sting reaction. All were adults and had severe re-sting reactions. Two had had initial mild reactions, and one had a moderate reaction.

Three other patients had moderate initial and first re-sting reactions and subsequent severe reactions after further stings. Thus 6 of the 90 patients who had repeated re-stings did eventually have reactions that were more severe than the initial and first re-sting reactions. These data are summarized in Table V.

## DISCUSSION

The results of this study support the postulate that the severity of an insect re-sting reaction is related to the severity of the anaphylactic symptoms that occurred with the initial sting reaction. The likelihood of repeat venom anaphylaxis is not related to the severity of the anaphylactic symptoms that occurred with the initial sting reaction except in children with mild anaphylactic symptoms. These children have a lower incidence of repeat sting anaphylaxis.

The overall incidence of repeat sting anaphylaxis was 56%, interestingly, very close to that reported in

the initial studies that documented the efficacy of venom immunotherapy.<sup>2</sup> The incidence of repeat sting reactions was lower in children (less than 16 years old) regardless of the severity of the initial sting reaction, but was only significant in patients who had mild initial sting reactions. The lower re-sting reaction rate (30%) in children who have had dermal reactions as the only manifestation of sting anaphylaxis is slightly higher than the 18.6% re-sting reaction rate reported in the most recent update of the Johns Hopkins University experience.<sup>6</sup>

In this study the time interval between the initial sting reaction and re-sting was not a factor in predicting subsequent sting reactions, differing from our preliminary report of a small population, which suggested that the longer the interval from the initial sting reaction to the re-sting, the less likelihood exists of a re-sting reaction.<sup>3</sup> It is interesting to note that an extremely high re-sting reaction rate (81%) occurred in those patients who were re-stung more than 10 years after their initial sting reaction. As might be anticipated, only a small number of patients (16) were in this subgroup. The severity of the initial sting reaction symptoms was not a factor. Patients with initial moderate and severe symptoms tended to have similar symptoms after re-stings. Five of the eight patients with initial mild sting reaction symptoms, had severe symptoms after re-stings, differing from the results with the total group. Further experience with more patients is necessary to determine the validity of this seemingly high re-sting reaction rate after the long interval between stings.

One of the critiques of this analysis of field re-stings is the identification of the re-sting insect as being the same as that insect that caused the initial reaction. As noted in the "RESULTS" section, 70 of the 220 patients did identify the same insect as that responsible for both the initial and subsequent sting. The yellow jacket was identified by the majority of patients, 43, and the honeybee was identified by 21. The analysis of the re-sting reactions in these 70 patients was essentially similar to the total group (Tables I and II). The similarity of the results in this subgroup of patients to those found in the total group suggest that the analysis of the total patient group is valid.

Eighteen of 220 patients had symptoms after the first re-sting that were worse than the symptoms from the initial sting. Of particular note were three patients under the age of 16 years with initial mild symptoms only who subsequently had moderate or severe re-sting reactions. Current recommendations are not to treat children who have dermal reactions only with venom immunotherapy. Sixty-four children under the age of 16 years had initial mild sting reactions and

did not receive venom immunotherapy. These three sting reactions of increased intensity represent an incidence of approximately 5% in the group of patients who might not be candidates for immunotherapy. In their recent review Valentine et al.<sup>6</sup> reported 18 systemic reactions after 196 stings in 86 children who had dermal reactions only after initial stings and were not treated with venom immunotherapy. None of the re-sting reactions were worse than the original sting reaction. Thus although the data reported in this study confirm the Johns Hopkins University experience and support the recommendation that venom immunotherapy is not necessary in children with dermal symptoms as the only manifestation of venom allergy, there are individuals in this group who may have worsening systemic sting reactions.

There were 90 patients in whom the effect of repeated re-stings could be observed, again in the absence of venom immunotherapy. Most of these patients (60) had reactions from these repeated stings that were similar to those that occurred after the initial re-sting. Six patients ultimately had more severe reactions after repeated re-stings.

In his monograph, Mueller<sup>7</sup> has reviewed other studies addressing the natural history of insect sting allergy. He also found that the nature or severity of the anaphylactic symptoms after a re-sting tend to be similar to the symptoms of the initial sting reaction. Specifically, in a large retrospective study of 400 patients by Woermann,<sup>8</sup> systemic reactions were classified by severity into four categories (I to IV). Symptoms similar to the symptoms of the initial sting reaction occurred after re-stings in 43% (I), 40% (II), 59% (III), and 51% (IV) of patients in each category, respectively.

In a small group of 20 untreated adults, Mueller reported a low systemic re-sting reaction rate (20%). In our earlier report of small population groups,<sup>3</sup> the systemic reaction rate in adults was 62% and decreased as the time interval between the initial sting reaction and re-sting increased. In his larger series Woermann<sup>7,8</sup> reported an overall reaction rate similar to the incidence of re-sting reactions in adults in this study.

As noted, in our prior studies of small patient groups, a relationship appeared to exist between the time interval between the initial sting reaction and likelihood of a reaction after the re-sting. Settupane and Chafee<sup>9</sup> also reported a tendency for risk of decreased reactions after a 5-year or greater interval in a small group of patients. On the other hand, in Woermann's<sup>7,8</sup> large study the re-sting reaction after 5 years was comparable to the data presented in this study.

The results of this study of the natural history of insect sting allergy and the interpretation of other reported data can be summarized as follows:

1. In unselected patients with insect sting anaphylaxis, approximately one half continue to react to subsequent stings. The prognosis is much better in children with mild symptoms of anaphylaxis than in adults.
2. When reactions do occur, the nature of the symptoms that follow a re-sting is likely to be the same as that which occurred with the first sting reaction. A small number of patients have reactions of increasing severity.
3. After repeated re-stings, most of the patients have reactions similar to those that have followed the first re-sting. A small number of patients eventually have a worse reaction.
4. The likelihood of a re-sting reaction does not appear to be related to the time interval between the initial sting reaction and re-sting.

The major clinical implication of these findings is that patients who have had mild or moderate insect sting reactions may be managed with the availability of emergency medication without venom immunotherapy. This decision requires evaluation of other risk factors, such as coexisting medical problems, concomitant medication use, and patient life-style, along with a full discussion of relevant risk factors with the patient. All patients who have had severe sting reactions and have positive venom skin tests should receive venom immunotherapy, regardless of the time interval since the sting reaction.

## REFERENCES

1. Valentine MD. Insect venom allergy: diagnoses and treatment. *J ALLERGY CLIN IMMUNOL* 1984;73:299-304.
2. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978;299:157-61.
3. Reisman RE. Studies of the natural history of insect sting allergy. *Allergy Proc* 1989;10:97-101.
4. Schuberth KC, Lichtenstein LM, Kagey-Sobotka A, Szklo M, Kwitrovich KA, Valentine MD. An epidemiologic study of insect allergy in children. II. Characteristics of the disease. *J Pediatr* 1983;102:361-5.
5. Lantner R, Reisman RE. Clinical and immunologic features and subsequent course of patients with severe insect sting anaphylaxis. *J ALLERGY CLIN IMMUNOL* 1989;84:900-6.
6. Valentine MD, Schuberth KC, Kagey-Sobotka A, et al. The value of immunotherapy with venom in children with allergy to insect stings. *N Engl J Med* 1991;23:1601-3.
7. Mueller UR. *Insect sting allergy*. New York: Gustav Fischer, Verlag, 1990.
8. Woermann U. *Untersuchungen zur Naturgeschichte der Insektenstichallergie*. Diss Bern 1985.
9. Settupane GA, Chafee FH. Natural history of allergy to Hymenoptera. *Clin Allergy* 1979;9:385-90.