Clinical and immunologic features and subsequent course of patients with severe insect-sting anaphylaxis

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One hundred fifty-eight patients were evaluated because of symptoms of potentially fatal venom anaphylaxis, as defined by hypotension, including loss of consciousness (LOC), throat/laryngeal edema, or marked respiratory distress. The demographic characteristics were 118 male and 40 female patients; age range, 3 to 80 years; mean, 29.7 years; 33 patients less than 10 years; and incidence of atopy, 20%. One hundred twenty-seven patients had had prior stings; 27 had prior systemic reactions (SR), including one with LOC. Almost all patients had venom-specific IgE; RAST titers covered a wide range. As compared to the total group, the subset of 45 patients with LOC were older, had an increased incidence of cardiac disease and β-blocker use, stings in the head area, and re-sting reactions in patients who did not receive venom immunotherapy (VIT). One hundred six re-stings occurred in 37 patients receiving VIT with no SR. There were 38 re-stings in 18 patients who refused VIT, with 14 SRs in 11 patients. These studies suggest no distinguishing characteristics, including age, that would identify patients susceptible to severe venom anaphylaxis and confirm the prophylactic effectiveness of VIT. (J ALLERGY CLIN IMMUNOL 1989;84:900-6.)

Understanding the natural history of insect-sting anaphylaxis has important clinical ramifications. Until they are better defined, controversial or unsettled issues, such as selection of individuals at risk for sting anaphylaxis, criteria for VIT, amount and type of VIT, and duration of VIT cannot be resolved. Immunologic markers, such as the presence of venom-specific IgE as an indicator of clinical allergy and the presence of venom-specific IgG as an indicator of immunity, have poor clinical correlates. For example, at least 50% of individuals who have had venom anaphylaxis and have venom-specific IgE when they are tested, do not react to subsequent stings in the absence of VIT.[1, 2] The results of intentional sting challenges in presumed venom-allergic individuals have demonstrated no correlation with preexisting titers of serum-venom specific IgE.[3, 4] The observation that children who have dermal reactions as the only manifestation of sting anaphylaxis have remarkably low re-sting reaction rates[5] suggests that the nature of the clinical symptoms may reflect the natural history of the allergic process.

Abbreviations used

VIT: Venom immunotherapy
SR: Systemic reactions
LOC: Loss of consciousness
CV: Cardiovascular

To investigate further the natural history of insect-sting anaphylaxis, we reviewed our experience with a large number of patients who had severe life-threatening anaphylactic reactions. The purpose of the study was to identify any risk factors and detail the natural history and its modification with VIT.

MATERIAL AND METHODS

Records were reviewed of all patients who were evaluated during the past 10 years because of an allergic reaction after an insect sting. Patients were selected who had symptoms of severe anaphylaxis as defined by upper airway edema, hypotension, including LOC, or severe respiratory distress. Patients were not included who had mild respiratory symptoms or dermal reactions only.

The following information was obtained: identification of the culprit sting insect, location of the sting, anaphylactic symptoms, history of prior stings, and history of other al-

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lergic or medical problems. Skin tests were performed with freshly prepared dilutions of honeybee, yellow jacket, white-faced hornet, and *Polistes* venoms. A positive test was considered a reaction to 0.1 μg/ml or less, with a negative diluent control.[6] Serum venom-specific IgE was measured by the RAST.[7]

Follow-up information was obtained from most patients. The results of subsequent re-stings were analyzed, grouping patients according to their VIT status: (1) receiving VIT, (2) received and stopped VIT, and (3) never received VIT.

RESULTS

Of the 158 individuals that were identified who had severe insect-sting anaphylaxis, there were 118 male and 40 female subjects, ranging in age from 3 to 80 years, with a mean age of 29.7 years. The patients were fairly evenly distributed among all ages. Thirty-three patients (21%) were younger than 10 years of age; 29 patients (18%) were older than 50 years of age. Approximately 20% of the patients had a history of atopic disease (eczema, rhinitis, or asthma). The yellow jacket was identified as the causative insect in 85 patients (54%), followed by the honeybee (10%), hornet (7%), wasp (3%), and bumblebee (1%). Twenty-five percent of the patients were unable to identify the causative insect. The most frequent sting site was the arm in 49 individuals, followed by the head and leg in 33 individuals each. These data are tabulated in Table I.

The symptoms of the anaphylactic reaction are detailed in Table II. Nearly three fourths of the patients had CV symptoms, including 45 (20%) with LOC. Two of these patients suffered cardiac arrest and recovered. One patient had a seizure. Sixty-nine patients (44%) had respiratory symptoms; 48 (30%) complained of throat and upper airway-related symptoms.

There were 36 patients who received multiple stings (2 to 30), causing anaphylaxis (Table III). There was no correlation between the number of stings and the severity of the reaction. None of the four patients who had more than 10 stings lost consciousness. Conversely, most patients with LOC had less than five stings.

Eighteen patients had other medical problems. Thirteen patients had cardiac-related disorders; six patients, hypertension; one patient, coronary disease; one patient, aortic stenosis; one patient, idiopathic hypertrophic subaortic stenosis; two patients, nonspecified valvular disease; one patient, rheumatic heart disease; and one patient, tachycardia. Other medical problems included gout, seizure disorder, peptic ulcer disease, attention-deficit disorder, diabetes mellitus, and glaucoma. Fifteen patients were taking medications for these disorders; five were taking β-blockers at the time of the sting reaction, four orally and one patient topically (timolol). Other medications included cimetidine, phenytoin, digoxin, allopurinol, methylphenidate, clonidine, aspirin, and other nonsteroidal anti-inflammatory drugs, and butalbital (Fiorinal; Sandoz Pharmaceuticals, East Hanover, N.J.).

TABLE I. Demographic data—158 patients with severe insect-sting anaphylaxis

	No. of pts	%
Age*		
0-10	33	21
11-20	30	19
21-30	20	13
31-40	23	14
41-50	23	14
51-60	14	9
>60	15	10
Sex (M/F)	118/40	
Atopy	32	20
Insect ID		
Yellow jacket	85	54
Honeybee	15	10
Hornet	11	7
Wasp	5	3
Bumblebee	1	1
Unknown	40	25
Sting site		
Arm	49	31
Head	33	21
Leg	33	21
Trunk	14	9
Neck	9	6
Unknown	20	13

Pts, Patients; *ID*, identification.
Thirty-sex patients had multiple stings. The sting site is recorded once; 26 patients had multiple stings at the same body site. The other 10 patients had stings at different sites, and the site closest to the head is listed.
*Age range, 3 to 80 years; mean, 29.7 years.

Information concerning prior insect stings was obtained from 134 patients (Table IV). Seven of these patients reported no prior stings. Of 97 patients with a known time interval between the prior sting and the sting causing anaphylaxis, most patients (62 patients, 64%) had been stung within 2 years. Thirty-four of these patients had had no reactions, 18 had local reactions, and 10 patients had SRs with prior stings. Twelve patients had a prior sting between 2 and 5 years preceding the insect-sting anaphylaxis. Four of these patients had no reaction, three had local reactions, and five patients had SRs. No patient stung within 5 years had LOC from the prior sting. Twenty-three patients had prior stings more than 5 years before their anaphylactic-sting reaction. Local reactions oc-

TABLE II. Details of anaphylactic symptoms after insect stings

Reactions	No. of pts	%	Pts included with LOC
Symptoms			
CV, U	38	24.0	13*
CV, R, U	25	15.8	8*
CV	20	12.6	13
T, R, U	16	10.0	0
T, U	14	8.9	0
CV, R	12	7.6	4†
CV, T, U	5	3.2	1
R, U	5	3.2	0
CV, GI	4	2.5	3
T, R	4	2.5	0
CV, GI, U	4	2.5	0
CV, T	3	1.9	1
CV, R, GI, U	2	1.3	1
CV, T, R	2	1.3	1
CV, T, R, U	2	1.3	0
T, GI, U	1	0.6	0
T, R, GI	1	0.6	0
Total	158		
Summary			
Total CV reactions	116	73.4	
Including LOC	45	28.5	
Total T reactions	48	30.4	
Total R reactions	69	43.7	

Pts, Patients; *R*, respiratory; *GI*, gastrointestinal; *T*, throat and upper airway; *U*, urticaria.
*Includes one patient with cardiac arrest.
†Includes one patients with seizure.

TABLE III. Reactions after multiple insect stings

	No. of stings			
	2-4	5-10	11-20	>20
SRs	24	8	2	2
LOC	8	4	0	0

curred in five and systemic reactions in eight patients, including one episode of LOC. To summarize these data, 68 of 127 patients (54%) had no reaction to the prior sting, 32 patients (25%) had local reactions, and 27 patients (21%) had SRs, with one patient having LOC. These data are tabulated in Table IV.

The results of venom skin tests were available in 149 patients. These results are tabulated in Table V. Most patients (69%) were tested within 1 to 2 months of the anaphylactic-sting reaction. Nineteen patients (13%) were tested more than 1 year after the reaction. Fifty-eight patients reacted to a venom concentration of 0.0001 μg/ml, three patients to a venom concentration of 0.001 μg/ml, 59 patients to 0.01 μg/ml, and 19 patients reacted to 0.1 μg/ml. Only five patients had positive skin tests at 1.0 μg/ml. Five patients had negative skin tests (0.01 to 0.1 μg/ml). Of these five patients, three had positive RASTs and one had a borderline positive RAST. The one patient with negative skin tests (0.1 μg/ml) and negative RASTs was tested 10 years after the sting reaction.

Venom-specific IgE was measured by the RAST in 151 patients, and these data are presented in Table VI. Most patients (66%) had RAST analysis within 2 months of the sting reaction. There was a fairly equal distribution of RAST titers in the usual range between 6 and 100 U/ml; 22 patients (15%) had negligible titers, and 12 patients (7%) had titers >100 U/ml.

One hundred twenty-nine (72%) of the 158 patients did receive VIT. At the time of this review, 86 were still receiving VIT, and 43 patients had stopped VIT, 28 by self-choice and 15 because of a fall in serum venom-specific IgE to insignificant levels.[8] The results of re-stings are presented in Table VII. There were 106 re-stings in 37 patients who were receiving VIT with no SRs and 10 local reactions. There were 14

TABLE IV. Data concerning insect stings before insect sting that caused severe anaphylaxis: Time interval and reaction

Time interval from last sting	No. of Pts	Reactions			
		None	Local	SR	LOC
0 - 3 mo	25	12	10	3	0
3 - 12 mo	19	12	3	4	0
1 - 2 yr	18	10	5	3	0
2 - 5 yr	12	4	3	5	0
5 - 10 yr	14	5	5	4	1
>10 yr	9	5	0	4	0
Unknown	30	20	6	4	0
TOTAL	127	68 (54%)	32 (25%)	27 (21%)	1
No prior stings	7				
No data	24				

Pts, Patients.

TABLE V. Results of venom skin tests

Venom dilution (μg/ml)	Time interval between insect sting anaphylaxis and venom skin tests* (mo)				
	0-1	1-2	2-6	6-12	>12
1.0	3†	1	1	0	0
0.1	12	0	1	4	2
0.01	37	8	7	5	2
0.001	1	1	1	0	0
0.0001	32	5	4	4	13
Negative‡	2	1	0	0	2

No information on nine patients.

*Results are tabulated for venom most likely to have caused reaction; not all patients had venom skin tests titrated to end point.

†Number of patients.

‡Of these five patients, three had positive RASTs and one had a borderline positive RAST. The one patient with negative skin tests (0.1 μg/ml) and negative RASTs was tested 10 years after the sting reaction.

re-stings in six patients who had stopped by self-choice. These patients had received VIT for an average of 1.2 years, and the average interval between cessation of therapy and the first re-sting exposure was 2.8 years. In this group, there were five SRs in three patients. In the patients who stopped VIT because of a fall in serum venom-specific IgE, there were 16 re-stings in five patients with no SRs. These patients had received VIT for an average of 2 years, and the average interval between cessation of therapy and the first re-sting exposure was 2.4 years.

A subset of 45 patients who had LOC as a result of the insect-sting reaction was evaluated separately. These data are presented in Table VIII. The patients ranged in age from 4 to 80 years, similar to the total group. Although the numbers were small, there was a greater percentage of patients older than 60 years and fewer patients younger than 20 years of age in this group. The other demographic features, such as sex ratio, incidence of atopy, and insect identification, also were similar to the total group.

In the group with LOC, there were eight patients who had significant medical illness; seven patients had a history of cardiac disease. Other medical problems included gout, peptic ulcer disease, and attention-deficit disorder. There were five patients taking medication; three patients were taking β-blockers. In addition, four patients were taking other medications, allopurinol, methylphenidate, digoxin, and nonsteroidal anti-inflammatory drugs.

Information concerning prior stings was available in 40 of 45 patients who had LOC. Two patients reported no prior stings. Of the remaining 38 patients, 18 were stung within 2 years of the sting reaction. Of

TABLE VI. Results of venom RASTs

RAST (IgE U/ml)	Time interval between insect sting anaphylaxis and RAST (mo)				
	0-1	1-2	2-6	6-10	>12
0-5	12*	2	1	3	4
6-20	25	8	6	6	8
21-50	18	5	3	3	6
51-100	17	2	4	5	1
101-200	8	1	1	0	1
200	1	0	0	0	0

No information on seven patients.
*Number of patients.

TABLE VII. Summary of re-sting data

	Receiving VIT	VIT stopped		No VIT
		Self-choice	Drop in specific IgE	
No. of pts	86	28	15	41*
Re-stings				
No. of Pts	37	6	5	18
No. of stings	106	14	16	38
Reactions				
None	96	3	7	23
Local	10	6	9	1
SR	0	5 (3 pts)	0	14 (11 pts)
LOC	0	0	0	5 (3 pts)

Pts, Patients.
*Twelve of these 41 patients eventually did receive VIT.

these patients, 11 had no reaction, four had local reactions only, and three patients had SRs. Five patients had been stung between 2 and 5 years before their sting reaction with only one SR occurring from a prior sting. Of five patients stung more than 5 years before their sting reaction, there had been two SRs, including one with LOC. The time interval between the prior sting and the sting causing the anaphylaxis was unknown for the 10 remaining patients. Of the total group, 23 of 38 patients had no reactions to prior stings, nine had local reactions, and six patients had SRs, including one with LOC.

The skin test reactivity and RAST titers in the patients with LOC also were similar to the skin test reactivity reported in the total group.

Re-sting data were obtained in 20 of 45 patients. Twelve patients had a total of 37 re-stings while they were receiving VIT, with no SRs. Three patients who stopped VIT by self-choice had six re-stings with one SR. There were three re-stings in two patients who stopped VIT because of a fall in RAST titers, with no SRs. In five patients who did not receive VIT, there were five SRs in four patients.

DISCUSSION

Allergic reactions caused by insect stings manifest a wide range of symptoms, ranging from mild urticaria to profound CV collapse, respiratory distress, and even death. The nature of the symptoms may influence subsequent management recommendations. For example, children with dermal reactions only are not considered candidates for VIT.[5] The purpose of this study was to examine the clinical and immunologic features of a large number of individuals who had severe insect-sting anaphylaxis with the goal of defining risk factors and establishing subsequent therapeutic guidelines.

Patients were selected who had potentially fatal reactions, either hypotension, including LOC, severe respiratory distress, or upper airway and throat edema. Of approximately 600 patients evaluated because of venom allergy, 158 patients had one or more of these

symptoms. Approximately 75% had CV symptoms, 30% had upper airway edema, and 44% had marked lower respiratory tract symptoms. As noted above, patients with mild respiratory symptoms were not included in the study.

The demographic data demonstrated an equal prevalence of severe anaphylaxis in all age groups. For example, 21% of the reactions occurred in children younger than 10 years of age, and 18% occurred in adults more than 50 years of age. This was somewhat unanticipated, since severe reactions, particularly fatalities, usually are associated with older subjects.[9-13] The actual incidence of severe anaphylaxis is probably higher in the older age groups because there is a greater frequency of sting reactions in individuals younger than 20 years.[14, 15]

The presence of atopy was not a relevant factor. Prior observations had suggested that sting location might be relevant, with most reactions following stings about the face and neck.[14] In this study, sting location was diversified. For the total group, the arm was the most common location; in the subgroup of patients with LOC, most stings did occur in the head.

The yellow jacket was the major culprit insect, probably a reflection of the sting incidence rather than any specific characteristic of yellow jacket venom. Multiple stings did lead to reactions in 36 patients; there was no relationship to severity of the reaction, using LOC as the criterion. Other studies also have demonstrated no relationship between the number of stings and the severity of the reactions.[9, 15, 16]

Thirteen patients had CV disease, and five patients were receiving β-blockers. The incidence of LOC was particularly high in these patients.

Most patients had no forewarning of anaphylaxis; only 20% had had prior SRs, one reaction with LOC. Studies of fatalities caused by insect-sting anaphylaxis also indicate most of these individuals had no prior sting reactions and were unaware of their potential allergy.[10] Furthermore, seven patients in this study had their severe anaphylactic reaction after their first insect-sting exposure. Reactions after initial stings have been reported previously.[14, 17]

The occurrence of anaphylactic sting reactions had no relationship to the time of the prior sting, regardless of whether the prior sting had caused a reaction or was well tolerated.

The degree of immunologic reactivity, measured by skin test or RAST after the reaction, did not demonstrate any specific trend. Skin test reactions and serum venom-specific IgE titers covered a wide range and did not distinguish this group of patients from other unselected patients with sting anaphylaxis or with large local reactions.[18, 19]

TABLE VIII. Comparison of patients with and without LOC

	LOC	No LOC
No. of pts	45	113
Age		
Range	4-80 yr	3-80 yr
Mean	38 yr	30 yr
>60 yr	18%	6%
<20 yr	24%	46%
Sting location		
Head	36%	15%
Arm	24%	11%
Leg	11%	25%
Cardiac disease	16%	5%
Use of β-blockers	7%	2%
Pts with prior SRs from stings	13%	18%
Re-sting SRs		
Receiving VIT		
%/patient	0% (0/12)	0% (0/25)
%/sting	0% (0/37)	0% (0/69)
Stopped VIT		
Self-choice		
%/patient	33% (1/3)	67% (2/3)
%/sting	17% (1/6)	50% (4/8)
Drop in IgE		
%/patient	0% (0/2)	0% (0/3)
%/sting	0% (0/3)	0% (0/13)
No VIT		
%/patient	80% (4/5)	50% (7/13)
%/sting	63% (5/8)	30% (9/30)

Pts. Patients.

VIT was extremely effective in preventing subsequent re-sting reactions. There were no SRs after 106 re-stings in 37 patients receiving VIT. In a relatively small number of patients, VIT was stopped, using the criterion of a fall in venom-specific IgE to insignificant titers.[8] Sixteen re-stings were tolerated without reaction, suggesting that VIT can be safely stopped in this group of patients. In contrast, three of six patients who had stopped VIT by self-choice did have re-sting reactions.

One of the most impressive observations of this study is the high re-sting reaction rate in patients who did not receive VIT. As mentioned earlier, the re-sting reaction rate in unselected patients who have had venom anaphylaxis is approximately 50%.[1, 2] This rate is influenced by the time interval between the sting causing anaphylaxis and the subsequent sting, by the age of the individual, and by the nature of the anaphylactic symptoms.[5, 20] In this group of patients with severe anaphylaxis, there were 14 SRs in 11 patients

after 38 re-stings in 18 patients, a reaction rate of 61% per patient and 39% per sting. The subgroup of patients with LOC had an even higher incidence of re-sting reactions, 80% per patient and 63% per sting. Prior studies of the natural history of insect-sting allergy also suggested an increased re-sting reaction rate in patients who have initial CV/respiratory symptoms as compared to patients who have urticaria/angioedema only.[2, 20]

These observations have very important clinical ramifications. Patients with severe insect-sting anaphylaxis, if they are untreated, have a high risk of re-sting anaphylaxis, not greatly influenced by the time interval between the sting exposures. In contrast to an unselected group of patients with sting anaphylaxis who appeared to lose their sensitivity during a period of time, patients with severe anaphylaxis remain at risk and should receive VIT. These preliminary observations also suggest that VIT may eventually be stopped using criteria such as the fall in serum venom-specific IgE to insignificant titers. It is not clear whether the suggestion that 5 years of VIT,[21] another of the criteria for stopping therapy, applies to this group of patients.

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