

Clinical correlation of the venom-specific IgG antibody level during maintenance venom immunotherapy

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Allergen immunotherapy is associated with a significant increase of specific IgG antibodies that have been suggested as a mechanism of action and as a marker of efficacy for immunotherapy. The value of venom-specific IgG antibody determinations as a measure of clinical protection against sting anaphylaxis has been difficult to prove in individual patients. We performed 211 insect sting challenges in 109 patients over a 4-year period to determine the significance of venom IgG levels $3 \mu\text{g/ml}$ or lower. Systemic symptoms occurred in only 1.6% of those with venom IgG more than $3 \mu\text{g/ml}$, but in 16% of those with less than $3 \mu\text{g/ml}$ IgG, and notably in 26% of patients with low venom IgG who had received less than 4 years of treatment. The venom IgG level had no predictive value in patients who had received more than 4 years of therapy. Honeybee sting data were inconclusive because of the small number of subjects. We conclude that low venom-specific IgG levels are associated with an elevated risk of treatment failure during the first 4 years of immunotherapy with yellow jacket or mixed vespid venoms. (J ALLERGY CLIN IMMUNOL 1992;90:386-93.)

Key words: Insect-sting allergy, venom, anaphylaxis, immunotherapy, IgG antibodies, Hymenoptera

For more than half a century it has been recognized that allergen injections (immunotherapy) cause increased production of specific IgG "blocking" antibodies.¹⁻³ Laboratory measurements of these antibodies in studies of allergic rhinitis showed no clear relationship between concentration and clinical symptom control in individual patients, but analysis of groups of patients demonstrated greater relief with higher mean serum titers of allergen-specific IgG.⁴⁻⁶ The utility of IgG determinations is most clearly recognized in patients allergic to insects in whom elevations of venom-specific IgG antibody levels are

clearly associated with protection from sting anaphylaxis in the first year of venom immunotherapy.⁷⁻¹² However, in insect sting allergy, as in allergic rhinitis, the predictive value of venom-specific IgG antibody levels measurement in individual patients has been difficult to establish.¹³⁻¹⁵ Passive immunization with venom-specific IgG antibody level infusion has successfully protected against system reactions to venoms.^{16, 17}

Patient confidence and reassurance is one of the accepted goals of venom immunotherapy. Although venom immunotherapy has a reported efficacy of 95% to 98%, the efficacy in patients treated with any single venom or with submaximal doses or at prolonged maintenance intervals has been reported as only 75% to 85%. Although deliberate sting challenge can demonstrate to patients that treatment is succeeding, a more practical method would be welcome if it correlated closely with clinical protection as judged by the outcome of sting challenge. With recent advances in immunoassay methods, current procedures to measure allergen-specific IgG antibodies are relatively rapid and precise and can provide quantitation in absolute weight units.¹⁸ To provide clinical validation of this laboratory technique, the present study was carried out to ascertain whether the subset of treated

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TABLE I. Pretreatment reactions to stings

	Venom-specific IgG ≤ 3 $\mu\text{g/ml}$	Venom-specific IgG >3 $\mu\text{g/ml}$
Skin eruptions only (including hives)	7 (15%)	10 (16%)
Respiratory symptoms	24 (52%)	35 (56%)
Vascular anaphylaxis (with hypotension or cardiovascular collapse)	15 (33%)	18 (29%)
Total patients	46	63

patients who have low venom-specific IgG antibody levels while on maintenance immunotherapy are at increased risk of systemic sting reaction when compared with the majority who have higher titers. In a previous study, patients who had a systemic reaction after sting challenges while on venom immunotherapy were found to have a lower mean level of venom-specific IgG antibody levels than those patients who did not react.¹⁴ That study, however, was retrospective and involved a small patient population. Therefore the current study was designed to more accurately evaluate the relationship between the level of venom-specific IgG antibody levels and the risk of systemic sting reaction. We have prospectively evaluated 211 stings in 109 patients to assess the ability of the venom-specific IgG antibody levels to predict the risk of systemic reaction after sting challenge in patients receiving venom immunotherapy. We also investigated whether the duration of immunotherapy affects this prediction of risk.

METHODS

Patient population

The 109 patients selected for this study were drawn from our adult clinic for venom immunotherapy of insect sting allergy. All patients had a positive history of insect sting-induced systemic allergic reactions, and their sensitivity was confirmed by positive intradermal tests with Hymenoptera venoms. Since most patients on maintenance venom immunotherapy (>85%) have levels of venom-specific IgG antibody levels greater than 3 $\mu\text{g/ml}$, we actively recruited one third of the study patients from those who had demonstrated low antibody levels, enabling us to have a large enough population of such patients to make valid comparisons. The remaining patients were volunteers from our clinic who were receiving maintenance venom immunotherapy. A venom-specific antibody level of 3 $\mu\text{g/ml}$ was chosen prospectively to define the groups because in previous studies we found that this value is one standard deviation below the average IgG level of patients on venom immunotherapy for more than 1 year (6 $\mu\text{g/ml}$).^{19, 20} This antibody level also provided the least overlap between reactors and nonreactors to sting challenge. We performed 87 challenge stings in 46 patients in the low antibody group (venom-specific IgG ≤ 3 $\mu\text{g/ml}$) and 124 stings in 63 patients in the high group (venom-specific IgG >3 $\mu\text{g/ml}$).

The two groups did not differ significantly with respect to age, gender, or skin test sensitivity. The distribution of pretreatment sting reactions in the two groups did not differ significantly (Table I), and both groups were representative of our adult insect sting clinic population as a whole. All patients had been on similar maintenance immunotherapy regimens for a minimum of 2 years. All patients gave informed consent under a protocol approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University School of Medicine.

Skin test sensitivity

Intradermal venom skin tests were graded according to the ALK (Milford, Conn.) package insert and then classified for comparison on a scale of 1 to 4 as follows: 1+ at 1.0 $\mu\text{g/ml}$, 1; 2+ at 1.0 $\mu\text{g/ml}$, 2; 2+ at 0.1 $\mu\text{g/ml}$, 3; 2+ at 0.01 $\mu\text{g/ml}$, 4.

Deliberate sting challenges

All sting challenges were carried out in a monitored setting with an intravenous line established, emergency equipment readily available, and a physician present. Informed consent for both the deliberate sting challenge and the venipuncture to obtain blood samples for the measurement of antibody levels were obtained before the start of the study. Yellow jackets, honeybees or both, collected locally, were used according to the skin test sensitivity and treatment regimen of the patient. Precise identification of the insect was always established by an entomologist. Patients were monitored closely for 1 hour, longer if a reaction occurred.

Venom-specific IgG antibody levels

Blood samples were obtained from all patients just before the sting challenge, which was performed 4 to 6 weeks after their last venom injection. Venom-specific IgG antibody levels were measured with use of the staphylococcal protein A solid phase radioimmunoassay as previously described.¹⁸ The limit of detection in this assay is 0.5 to 1 $\mu\text{g/ml}$. The mean interassay and intraassay coefficients of variation for each Hymenoptera venom antibody assay were less than 5% and 2.5%, respectively. The results from these assays have been shown to be reproducible over many years by comparison of multiple reference sera for each lot of reagents and are closely correlated with results from another major reference laboratory (Hamilton, Kagey-Sobotka, Yunginger: personal communication, November 1985).

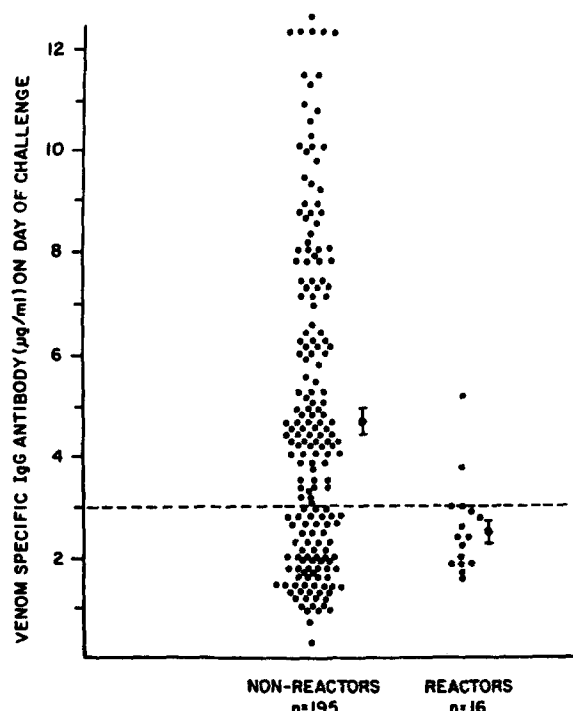


FIG. 1. Venom-specific IgG antibody level at the time of each sting challenge in patients with (reactors) and without (nonreactors) systemic reactions. Beside each column is the mean $\pm$ SEM venom-IgG for each group. Dashed line is the 3 μ g/ml cutoff between low IgG and high IgG.

Data analysis

Data were analyzed by use of the Fisher's Exact Test or the Student's *t* test.

RESULTS

The pre-sting challenge venom-specific IgG levels for all 211 stings are shown in Fig. 1. The values have been divided into two groups: nonreactors (stings causing no subjective or objective systemic symptoms) and reactors (stings causing subjective or objective evidence of a systemic reaction within 1 hour of sting challenge). One hundred ninety-five stings occurred in the nonreactor group, with a mean IgG antibody level of 4.7 ± 0.4 μ g/ml. In marked contrast, for the 16 stings in the reactor group the mean venom-specific IgG level was 2.5 ± 0.4 μ g/ml. The difference in the mean venom-specific IgG level between these two groups of patients is significant ($p < 0.001$). In the reaction group, 88% of the venom-specific IgG antibody levels were less than or equal to 3 μ g/ml in contrast to only 36% in the non-reactor group ($p < 0.001$).

In patients with low venom-specific IgG, 10 of 46 (22%) had systemic reactions, whereas 2 of 63 (3%) patients with high IgG had reactions ($p < 0.001$). When our results are adjusted for the fact that only

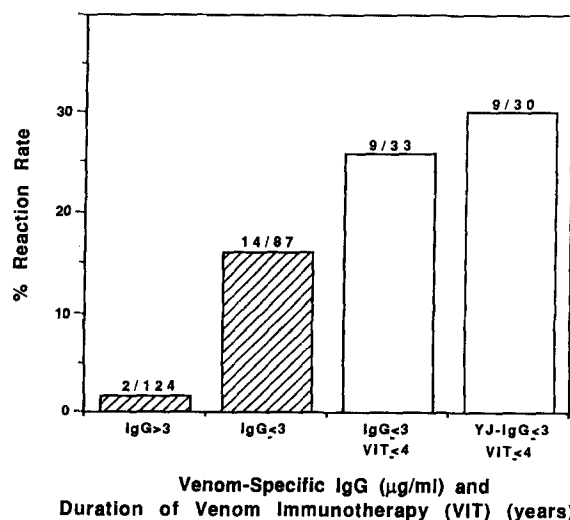


FIG. 2. Systemic reaction rate (%) in relation to venom-specific IgG level and duration of venom immunotherapy.

15% of an unselected group of patients on venom immunotherapy have IgG less than 3 μ g/ml (in contrast, 42% of our patients had low IgG), the overall reaction rate of our 109 patients would have been 4%, which is consistent with the 2% to 5% incidence reported in the literature.²¹⁻²⁴ Fig. 2 is a graphic representation of the reaction rates, expressed as a function of venom-specific IgG level. In the low IgG group, 14 of 87 stings (16%) caused a systemic reaction, whereas only 2 of 124 stings (1.6%) in the high group resulted in a reaction ($p < 0.001$). Reaction rates were higher in certain subgroups of patients treated less than 4 years (26%) and treated with yellow jacket venom (as discussed herein).

The characteristics of the 12 patients who had the 16 systemic reactions are shown in Tables II and III. The two patients with venom-specific IgG levels greater than 3 μ g/ml had the mildest reactions, with only perioral tingling, whereas the two patients with the most severe reactions (i.e., hypotension) had the lowest venom-specific IgG levels in the reactor group. All reactions, although generally less severe, were similar in pattern to the initial reactions experienced by the patients before venom immunotherapy.

Because we have previously noted that after 4 years of venom immunotherapy very few patients reacted to sting challenge regardless of their venom-specific IgG antibody level, we analyzed our data to address this question. As shown in Table IV, a total of 33 stings occurred in the low venom-specific IgG group in patients who had received immunotherapy for less than 4 years. In those patients 9 of 33 stings (26%) caused a systemic reaction (see also Fig. 2). In comparison 53 stings occurred in patients with low venom-specific IgG who had received venom immunotherapy

TABLE II. Systemic symptoms after sting challenge

	Venom-specific IgG $\leq 3 \mu\text{g/ml}$	Venom-specific IgG $> 3 \mu\text{g/ml}$
Perioral tingling	3	2
Flushing of face and trunk	4	
Generalized pruritis	3	
Dizziness without hypotension	1	
Urticaria	1	
Hypotension requiring epinephrine		
126/90 falling to 90/50	1	
130/80 falling to 80/45	1	
Total reactions (N)	14	2

TABLE III. Characteristics of patients reacting to challenge sting(S)

Patient/age	Venom immunotherapy	Duration (yr)	Challenge sting(s)	Date	IgG ($\mu\text{g/ml}$)	Challenge reaction	Pre-venom immunotherapy	
	Venoms/Dose (μg)						ST	Reaction
T.B./53	H/100, M/300, P/100	1	YJ	8/82	9.3	NR	0.1	P/E/U/A/Hy
54		2	YJ	8/83*	1.9	P		
D.B./52	Y/100	2	YJ	7/82*	1.4	P/E/U	0.1	P/E/U/A/Di
53	Y/200	3	YJ	10/83	2.6	NR		
J.C./18	M/300, P/100	1	YJ	8/82	6.5	NR	0.1	
19		2	YJ	8/83	1.8	NR		Dy/W
20		3	YJ	9/84*	1.8	Di		P/E/U/A
S.H./20	H/100, Y/100	2	YJ	9/81	4.4	NR	0.01	P/U/A
21		3		9/82	7.2	NR		
22		4		8/83*	1.8	P/E/Th/Hy/Ep		
P.L./54	M/300	8	YJ	8/84*	2.9	Di	1.0	P/E/U/A
						Dy/Di/Hy		
S.M./40	Y/100	1	YJ	9/81*	2.4	P/E/A/Th	0.1	Th/Dy/W
41	Y/200	2	YJ	9/82	1.0	NR		
42	Y/200	3	YJ	8/83*	1.9	Th/Dy/Di/Ep		
J.P./44	M/300	2	YJ	9/82*	3.8	P/E	0.01	P/E/U/A
E.R./64	M/300	4	YJ	9/81	2.9	NR	0.01	P/E/U/A
65	Y/100	5	YJ	8/82*	3.0	P/E/Th		Dy/Hy
66	Y/200	6	YJ	10/83*	1.7	P/E		
L.S./62	M/300	4	YJ	8/82*	5.2	P/E	0.1	P/E/U/Hy
S.S./45	M/300	4	YJ	8/82*	2.0	P/E	1.0	P/E/U/A
								Th/Dy/Hy
W.T./62	M/300	2	YJ	8/82	4.0	NR	1.0	P/E/U/A
63	M/300	3	YJ	9/83*	3.0	P		Dy/Hy
64	M/300	4	YJ	9/84*	2.8	P/E		
J.D./33	M/300	1	YJ	9/81*	2.8	P/E/U	1.0	P/E/U/A
34	M/300	2	YJ	9/82*	2.1	P/E/U/Th		Th

H, Honey bee; M, mixed vespid; P, Polistes wasp; YJ, yellow jacket; P, pruritus; E, erythema; U, urticaria; A, angioedema; Hy, Hypotension Di, dizziness; Dy, dyspnea; W, wheezing; Th, throat tightness; Ep, epinephrine administered; NR, no systemic reaction

*Date of sting causing systemic reaction.

†Minimum concentration of venom ($\mu\text{g/ml}$) needed for 2+ reaction.

for more than 4 years. In these patients only 5 of 53 stings (9%) caused a systemic reaction ($p < 0.05$). In the high IgG group there were fewer reactions, with no reactions occurring during the first 4 years of im-

munotheapy and only two "trivial" reactions occurring in 57 stings in patients receiving immunotherapy for greater than 4 years (3%). The difference in the reaction rates between these two high IgG groups was

TABLE IV. Relation of venom-specific IgG and duration of venom immunotherapy to outcome of sting challenge

	Duration of venom immunotherapy		
	≤4 yr	>4 yr	
Venom-specific IgG ≤3 µg/ml			
Reactors	9 (26%)	5 (9%)	$p < 0.05$
Nonreactors	24	48	
Venom-specific IgG >3 µg/ml			
Reactors	0	2 (3%)	$p = 0.2$
Nonreactors	68	55	
	$p < 0.001$	$p = 0.18$	

TABLE V. Treatment dose and venom(s) at the time of sting challenge

Venom(s)-dose	Venom-specific IgG	
	≤3 µg/ml	>3 µg/ml
YJV-100 µg	14 (16%)	32 (26%)
YJV-200 µg	11 (13%)	13 (10%)
MVV-300 µg	38 (44%)	32 (26%)
MVV/PWV	9 (10%)	22 (18%)
HBV-100 µg	15 (17%)	25 (20%)
Total	87 (100%)	124 (100%)

not significant ($p = 0.2$). When the reaction rates between the low and high venom-specific IgG groups were compared, significant difference occurred only during the first 4 years of immunotherapy ($p < 0.001$). Although the data are not shown, a similar analysis after 1, 2, and 3 years of venom immunotherapy also showed a significant difference between the high and low venom-specific IgG groups. In contrast, there was not a significant difference between the rate of systemic sting reactions in the low and high venom-specific venom IgG groups after 4 years of immunotherapy ($p = 0.18$).

Table V shows the type of venom immunotherapy given in both patient subgroups. One third (29% to 36%) received yellow jacket venom: 22% at maintenance doses of 100 µg and 11% at 200 µg maintenance doses. Half the stings (44% to 54%) were performed in patients who received mixed vespid venom (33% mixed vespid venom only and 15% mixed vespid venom with *Polistes* [ALK] wasp venom), but low IgG was more common with mixed vespid venom than with combined mixed vespid venom with *Polistes* wasp venom therapy. As shown in Table V, 40 of the 211 stings were honey bee stings, although 37 were in patients who were also being challenged separately with yellow jackets. No reaction

occurred from any of the honey bee stings: no conclusions can be drawn regarding the discontinuation of honey bee venom immunotherapy because of the small number of subjects. In patients treated with yellow jacket or mixed vespid venom for less than 4 years, the frequency of systemic reaction to challenge sting was 30% (Fig. 2).

DISCUSSION

Venom immunotherapy benefits patients not only by preventing sting anaphylaxis but also by preventing the psychologic morbidity that often interferes dramatically with normal activities through the warm weather seasons. The importance of a laboratory parameter that would enable clinicians to assure patients receiving venom-specific immunotherapy that they can assume normal activities without danger is obvious.

IgG antibodies to allergens—"blocking antibodies"—have long been thought to be associated with the clinical efficacy of allergen immunotherapy, but this has been difficult to prove in an inhalant allergy.¹⁻⁶ In insect allergy, we had data that suggested that the quantity of venom used for initial immunotherapy, and therefore the antibody level, was related to clinical success.^{8, 21-25} Passive immunization with hyperimmune IgG/globulin has also been effective.^{16, 17} Other investigators have confirmed the clinical significance of this venom-specific IgG assay.^{10, 13, 26} However, the literature remains divided on the predictive value and clinical utility of venom-specific IgG determinations in individual patients.^{22, 27, 28}

Evidence to support this hypothesis has been difficult to obtain for two reasons. The remarkable efficacy of venom immunotherapy, which confers complete protection on more than 98% of patients, has made evaluation of this parameter tedious.^{8, 10, 12, 14, 23} Further complicating this issue is the fact that even in untreated patients, only 30% to 60% will react to

subsequent sting challenge regardless of age, gender, or skin test sensitivity.^{19, 21, 29-32} Thus it has been difficult to find sufficient numbers of reactors to draw meaningful conclusions. In our previous studies we reported that 15% of patients on venom immunotherapy have venom-specific IgG 3 µg/ml or less, and that the frequency of systemic reactions was significantly greater in those patients. The present study was carried out to finally provide definitive prospective data to correlate our venom IgG assay results with clinical reactivity to sting.

In this study we chose an antibody level of 3 µg/ml or less to define patients with low levels of antibody to venom, on the basis of previous retrospective studies.^{14, 24} Three micrograms per milliliter of antibody is one SD below the average value (6 µg/ml) for patients who have received venom immunotherapy for greater than 1 year.^{23, 24} These patients represent the lowest 15% for venom-specific IgG antibody level response to venom immunotherapy. To obtain adequate numbers of patients we performed 87 challenge stings in patients with antibody levels 3 µg/ml or less, including those selected from our clinic and compared their reactions with those of 124 challenge stings in patients who had antibody levels greater than 3 µg/ml.

A systemic reaction was defined as any subjective or objective deviation from the patient pre-sting-challenge baseline, which occurred within the first hour after challenge. Although all reactions were mild, they occurred with the same pattern and type of symptoms as experienced by the patient before immunotherapy and demonstrate "incomplete protection" to a single sting. This would be reason for concern about the potential for more severe reactions, and we are unable to predict the effect that multiple natural stings might have on magnifying these mild reactions. In addition, it has always been our goal in venom immunotherapy to confer complete protection on our patients so that any reaction is judged to be a suboptimal response to therapy.

In the low venom-specific IgG group there was a reaction rate of 16%, which is significantly higher than the high venom-specific IgG group and the general population of patients receiving venom immunotherapy (1.6% and <2%, respectively). This reaction rate is less than the approximately 30% to 60% seen in untreated patients, but is clearly undesirable. Moreover, in that subset of patients for whom IgG antibody measurements are indicated (i.e., those in their first 4 years of treatment), the true reaction rate was 26%. There were no reactions to honey bee stings; in patients treated with yellow jacket or mixed vespid venoms for less than 4 years the reaction rate was

30%. This reaction rate is similar to the 25% reaction rate reported as unacceptable by some investigators for patients who have discontinued immunotherapy after 1 to 2 years.^{19, 33, 34} This study and other data indicate that these reactions can be avoided by monitoring IgG antibody levels and increasing the venom dosage in that subset of patients who respond in a below-average fashion.^{8, 13, 14} The number of honeybee stings in our study is too small for meaningful analysis. Although no reactions occurred to honeybee stings, others have reported a similar correlation of venom-specific IgG with clinical protection in honeybee-treated patients.^{9, 13, 17}

The two patients with the lowest levels of venom-specific IgG antibody levels in the reactor group had the most severe reactions, in marked contrast to the two patients with the highest venom-specific IgG in the reactor group who had two of the mildest reactions (Table III). Although we cannot state that the absolute level of venom-specific IgG antibody levels predicts the actual severity of the systemic reaction, the contrast between these patients is interesting. These data enable clinicians to reassure those patients with venom-specific IgG antibody levels greater than 3 µg/ml that there is a negligible risk of anaphylaxis and to talk to patients with venom-specific IgG antibody levels less than 3 µg/ml about the relative indication to improve their incomplete protection by more intensive therapy (more frequent injections or higher doses).

The loss of predictive value of venom-specific IgG in patients treated for more than 4 years seems to be a result of a decline in the reaction rate of the low venom-specific IgG group, as shown in Table IV. It appears, therefore, that after 4 years of therapy, venom immunotherapy may confer protection by a mechanism independent of venom-specific IgG. Although this study demonstrates that the IgG antibody level is a critical parameter for the first several years of venom immunotherapy, it also indicates that it ceases to be of utility thereafter. Recent work indicates that after 5 years of venom immunotherapy, patients can stop treatment and remain protected regardless of their IgG antibody level.^{33, 35, 36} Thus while documenting clearly for the first time in studies of human allergy the protective role of IgG antibody, we also recognize that with time other mechanisms may be operative. Reports have been published confirming this observation that the protective/suppressive effects after 4 years of venom immunotherapy are more persistent and unrelated to venom-specific IgG levels even after therapy is discontinued.^{36, 37, 38} Several parameters, including changes in lymphocyte populations, are under investigation.

Whether variables other than IgG antibodies might affect the risk of sting reaction during venom immunotherapy is not apparent from the current study data. We did not evaluate the level of venom-specific IgE antibodies: our aim was to determine the value of venom-specific IgG as an isolated measurement. Several investigators have confirmed our observation that IgG has greater predictive value than specific IgE antibody levels and that the IgE/IgG ratio is of very little additional value, except in rare individuals with high IgG but disproportionately higher IgE antibodies.^{10, 13, 14, 23} We note that the range of pretreatment sting reaction and skin test sensitivity of the 12 reactors were no different from nonreactors (Table III). The mean age of the reactors was 47.5 years, and the mean duration of venom immunotherapy at the time of challenge sting was 3.3 years: both are similar to nonreacting patients. This suggests that both groups were likely to have persistent venom sensitivity by skin test or RAST with the frequency previously reported: 90% remain positive after 2 years of venom immunotherapy, 75% after 5 years, and 50% are still positive after 8 years.^{35, 36} Although venom skin test and IgE data are not available, the specific IgE antibody level would appear to have little or no impact on the observed relationship of venom-IgG level to challenge sting reaction in these very comparable groups of patients. We also considered whether a prior sting within 1 year before the challenge sting might confer either heightened sensitivity or residual protection on the patient and, therefore, skew the data obtained from a subsequent challenge sting. Nine (16%) of 57 subjects who reported a sting within the previous year had systemic reactions to challenge sting, whereas 7 of 154 (5%) without a prior sting had a reaction to challenge sting ($p = 0.015$). These data are consistent with the hypothesis that sting reactivity decreases over a period of years, but may be sustained by intervening stings. Although others have reported a higher risk of persistent systemic reactivity in patients with more severe reactions, this was not apparent in the patients reported here.

In summary, these data suggest that the level of venom-specific IgG antibody levels in patients receiving venom immunotherapy is of value in predicting residual risk of a systemic reaction after a sting. The clinical utility of the venom-specific IgG antibody measurement is restricted to the first 4 years of therapy, but in this subgroup (Fig. 2 and Table IV) the sensitivity of the test was 100% (9 of [9 + 0]). The specificity of the test was 27% (9 of 33), which would appear to be of limited clinical significance, but the concept of statistical risk applies to each category as a whole, not only to affected individuals.

Thus the risk of reaction is not 100% for the nine reactors and 0% for the 24 nonreactors in this group, it is 27% for every patient with a low venom-specific IgG (treated <4 years). Whether increasing the maintenance treatment dose in all patients with low venom-specific IgG (and <4 years venom therapy) is justified will depend on the clinician's judgement as to whether the 27% risk is too high or is acceptable. In those patients in whom the venom-specific IgG level was less than 3 $\mu\text{g/ml}$, there was a significantly increased risk of systemic symptoms after even a single sting. We currently think that monitoring the level of venom-specific IgG in patients receiving venom immunotherapy is of definite benefit in identifying those patients who are at risk of developing a systemic reaction after a sting: the test should be performed after maintenance treatment is established (usually 4 to 6 months), and again after 1 to 2 years of therapy. In those patients in whom the venom-specific IgG antibody level is less than 3 $\mu\text{g/ml}$, adjustments in the dose or frequency of venom immunotherapy are warranted to raise the level and the clinical protection. The data are presented as a clinical validation of this laboratory method. Clinical application is a matter of professional judgement and has been observed to provide great reassurance and improved life-style to patients on venom immunotherapy.

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