

Natural History of Insect Sting Allergy: The Rhode Island Experience

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ABSTRACT

The frequency of insect sting allergy in a given population varies depending on the age group of the population and the type of criteria used (history, skin test or RAST). In a pediatric population with a mean age of 13 years (boy scouts), the frequency is 0.8% using history as the only criteria. With this same criteria in an adult population, other authors found the frequency to be higher, 3.3%. The difference is probably due to the prolonged exposure rate to insect stings in adults. Using skin test or RAST as the criteria, the frequency of sting allergy is much higher because of many false-positive reactions. With history alone, the frequency of sting reaction is similar in atopic and nonatopic populations. Sting-sensitive asthmatic patients usually have a severe reaction to a sting with the added symptom of acute bronchospasm. Our RAST studies to venoms revealed that false-positive reactions do occur; a higher frequency of positive reactions occurs within five years of the sting and cross-reactivity among Hymenoptera insects is common except for honey bee. Negative RAST may have more clinical validity than a positive RAST. Our past and present re-sting

data reveal that a large percentage of initially sting-sensitive patients have no reaction on being re-stung.

Our new study on untreated sting-sensitive patients revealed that 37% (7/19) had an improved response and 42% (8/19) had the same response on re-sting. Four (21.1%) had a worse reaction. In children under 16 years of age with a cardiovascular/respiratory response on the initial sting, 75% had an improved response on re-sting and of these 63% had no systemic reaction on re-sting and 25% had the same type of reaction. Many other authors reported that a large percentage of children under 16-years old who had a generalized cutaneous reaction to the initial sting had no generalized reaction on re-sting. Those sting-sensitive patients who were re-stung over five years from the initial sting that produced a systemic reaction have more improvement than those re-stung within five years. Although a large percentage of sting-sensitive patients improve without venom desensitization, especially children under 16 years of age, all sting-sensitive patients should be evaluated for possible immunotherapy especially those with cardiovascular/respiratory (Grade III/IV) symptoms and positive skin test or RAST to venoms.

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We became interested in insect sting allergy in 1965 while serving as camp physicians in a large boy scout summer camp in Rhode Island.¹ The total population of this camp was 4,922 boy scouts ranging in age from 11–16 years old. Reviewing health records of these boy scouts and subsequently 2,010 girl scouts (age range 11–16) who attended a similar camp in

Rhode Island, we were able to deduce that the frequency of systemic allergic reactions to insect stings in this age group was under 1%, and there was no difference in male and female children with similar outdoor lifestyles.² In this initial study (1965) and later, we devised a grading system^{1,3} for classifying symptoms of allergic reactions to insect stings. These correspond to the classical symptoms of Grade I (local reaction), Grade II (generalized urticaria), Grade III (wheezing or shortness of breath), and Grade IV (unconsciousness).

In 1969, we were able to modify the boy scout health card for summer camp with specific questions about insect sting allergy, asthma, and hay fever.⁴ Affirmative answers to these questions were followed-up using detailed questionnaires to parents and family physicians. From this information, we concluded that the frequency of insect sting allergy among boy scouts with a mean age of 13 years was 0.8%, and that the frequency of insect allergy in the normal and atopic (asthma/hay fever) segments of this population was similar. Indeed, it is apparent that the vast majority of patients with insect allergy are nonatopic by any criteria used.

The Johns Hopkins group, studying a random, stratified sample of industrial employees, determined the prevalence of insect-sting systemic reactions to be 3.3% by history and 26% by RAST or skin testing procedures.⁵ Their adult population had repeatedly more insect stings than our 13-year old boy scouts and therefore were able to develop insect allergy at a higher frequency because of many more years of exposure. Since only about 20% or more of subjects with positive RAST or skin tests to insect venoms have systemic reactions on re-sting in untreated patients, it is apparent that RAST or skin tests to venoms are not satisfactory procedures for determining frequency of insect allergy in a given population.⁵

The Johns Hopkins group is in agreement that the frequency of sting reactions is similar in atopic and nonatopic unselected populations when history alone is used, but they believe that venom sensitivity on skin test seems to occur somewhat more frequently in persons with skin test sensitivity to inhalant allergy.⁵ However, false-positive reactions to skin tests may account for this difference.

In 1980, we reported on 587 cases with systemic reactions to insect sting from the Rhode Island Hospital Allergy Clinic and from records of six board certified allergists in private practice in Rhode Island.³ In this population, the frequency of asthma/hay fever was only 22% and resembled the expected frequency in a general population. We noted an important finding that although asthmatic patients do not have an increased risk of developing systemic reactions to insect stings, they do have a significantly more severe ana-

phylactic reaction to an insect sting than nonatopic patients (60.7% (34/56) vs 30.5% (139/456), $p < 0.001$). Those severe reactions were manifested primarily by the additional symptom of acute dyspnea (Grade III). This is not surprising since asthmatic lungs are extremely sensitive to endogenous histamine and other mediators of anaphylaxis produced by the acute allergic reaction of the sting. Earlier reports that support our findings are that of Curry and others who have shown that asthmatic patients respond with acute bronchospasm when histamine was administered intravenously.^{6,7}

In 1980, as part of the ongoing study, we reported our RAST results to one or more venoms in 80 sting-sensitive patients (history) and 28 normal controls (no history of insect sting sensitivity).^{8,9} Fifty-one percent (41/80) of our insect-sensitive patients had a positive RAST compared to 7% (2/88) of our normal controls. These tests were repeated in a blinded fashion one and one-half years later on the other half of the saved sera and the results were similar. RAST scores of two to four were remarkably reproducible while scores of one were not consistently reproducible. The most frequent positive RAST was to yellowjacket followed by hornet, wasp, and honey bee. A high degree of cross-reactivity occurred between venoms of hornet, wasp, and yellowjacket. This cross-reactivity was demonstrated in our previous animal studies using immunized rabbits.¹⁰ This latter study confirms Loveless¹¹ early work which was one of the first papers to demonstrate that honey bee contained unique antigens different from the rest of the Hymenoptera. Subsequently, the major uniqueness of the honey bee antigen was shown to be phospholipase A₂. A positive RAST to venoms was frequently found in sera of patients stung within five years, although we did obtain some positive RAST in sera in patients stung over five years previously.

Golden states that there are many false-positive and false-negative reactions to RAST and that RAST is negative in approximately 20% of skin test positive subjects and approximately 10% of RAST-positive subjects have negative skin test.⁵ Reisman¹² reported that in 18 untreated patients with positive RAST and large local reactions, only 6% (1/18) had a systemic reaction on re-sting while none of the 38 patients with large local reactions and negative RAST had systemic reactions on re-sting. It appears, therefore, that a negative RAST may have more clinical validity than a positive RAST to venoms, and this is in agreement with Bousquet's¹³ conclusions as to when to stop venom immunotherapy. Both Golden and Bousquet state that although positive RAST can occur in those stung over five years previously, RAST titers tend to decrease after five years.^{5,13} Our findings are similar.⁹

Table I

General Characteristics of 19 Untreated Patients with Initial Systemic Reactions to Stings and Who Were Later Re-Stung		
	Under 16 Years-Old	Over 16 Years-Old
Total patients	8	11
Initial sting:		
Age range (yrs)	3-15	22-66
Mean age (yrs)	8.0	47.3
Male/female	7/1	4/7
Past/present Hx of asthma	0	2
Interval between initial sting and re-sting		
Range	1 mo to 20 yrs	1 mo to 26 yrs
Mean	5.01 years	4.11 years

In 1979, we completed a study of natural history of allergy to insect allergy and reported on 119 patients who initially had a generalized reaction to insect stings and subsequently had a history of being re-stung before treatment with venoms.⁸ We found that 40% had only local reactions to the re-sting and that 45% had an improved grade of reaction on the re-sting. In addition, 43% had the same grade of reaction and 13% had a

worse grade of reaction on re-sting. We noted that a significantly greater proportion of patients who were re-stung after five years had a milder reaction than those who were re-stung within five years [63% (12/19) vs 34% (25/74), $p < 0.02$]. Only one out of 19 (5.3%) of those re-stung over five years from the initial reaction had a worse response.

Reisman¹² recently found similar results in that he reported that the loss of clinical sensitivity appears to be related to the time interval between the initial sting reaction and the subsequent bee sting. He states that as the time interval increased, the percent of individuals who have re-sting reactions decreased.

NEW STUDY

Our new and unpublished data on insect sting sensitivity covers a period between 1980 and 1985 when 87 patients with a history of generalized insect sting allergy were evaluated by history and skin test to venoms, (venom skin test titer of 0.1 μ g or less was considered positive). Of these 87 patients, 19 (21.8%) had a history of being re-stung before venom immunotherapy was instituted, Table I. All 19 of these re-sting patients had positive skin test to one or more Hymenoptera venom. Most had positive skin test to more than one venom, Tables II and III. Children who were under age 16 years old and who had only generalized urticaria/angioedema with their initial sting were not included in this study, because venom treatment was not a consideration. It is of interest that five children who had cardiovascular/respiratory reaction in their initial sting and who had positive skin tests to venoms had no reaction on being re-stung before treatment. Therefore,

Table II

Individual Characteristics of Eight Untreated, Sting-Sensitive Patients Who Were under 16 Years of Age on Initial Sting and Were Later Re-Stung

Patients	Age (yr) 1st Sting	Age Re-sting	Grade of Reaction		Interval 1-2 Sting (years)	Venom Titer .1 μ g or less	Hx of Asthma
			1st Sting	Re-sting			
M.V.	3	5	3.5	1	2	YJ	NO
D.M.	5	13	3.5	1	8	YJ, WH, W	NO
J.S.	6	6	3	1	.08	YJ	NO
C.O.	7	9	3	1	2	YJ	NO
L.A.	8	9	3	2	1	YJ, YH, WH, W	NO
K.W.	8	12	4	1	4	YJ, W	NO
D.K.	12	15	3	3	3	YJ	NO
P.R.	15	35	3	3	20	YJ, WFH	NO

YJ = yellowjacket, WH = white faced hornet, YH = yellow hornet, W = wasp, Hon Bee = honeybee.

Table III

Individual Characteristics of 11 Untreated, Sting-Sensitive Patients Who Were over 16 Years of Age on Initial Sting and Were Later Re-Stung

Patients	Age (yr) 1st Sting	Age Re-Sting	Grade of Reaction		Interval 1-2 Sting (years)	Venom Titer .1 µg or Less	Hx of Asthma
			1st Sting	Re-Sting			
B.B.	22	48	4	4	26	YJ	YES
R.V.	37	42	4	4	5	YJ	NO
R.R.	38	42	2	3	4	YJ, YH, WH	NO
B.D.	39	39	2	3	.08	YJ, YH, WH, W	YES
R.R.	42	42	4	3	.08	YJ, YH, WH, W	NO
N.S.	44	47	2	4	3	YJ, W	NO
S.B.	52	55	2.5	2.5	3	YH, WH	NO
G.L.	55	55	3	3	.08	HON BEE	NO
F.D.	59	60	3	2	1	YJ	NO
F.P.	66	68	2	4	2	YJ, YH, WH, W	NO
M.W.	66	67	3	3	1	YJ, YH, WH, W	NO

Table IV

Relationship of Age at Time of Initial Sting and Re-Sting Reaction in 19 Untreated Patients

	<16 Yrs			>16 Yrs				
	Total Patients	Cardiovascular/ Respiratory		Total Patients	Urticaria/ Angioedema		Cardiovascular/ Respiratory	
		#	%		#	%	#	%
Initial Systemic Reaction	8	8	100%	11	4	36.4%	7	63.6%
Re-sting Reactions:	8			11				
Urticarial/Angioedema	—	1	12.5		0	0	1	9.1%
Cardiovascular/Respiratory	—	2	25.0		4	36.4%	6	54.5%
No Reaction	—	5	62.5		0	0	0	
Re-sting summary:								
Improvement		6	75%				1	9.1%
Same		2	25%				6	54.5%
Worse		0					4	36.4%
Total patients	19	8					11	

similar to the RAST, there are false-positive skin tests to venoms, and that negative skin tests may have more clinical validity than positive skin tests. The age range of these 19 patients was three–66 years with a mean age of 31 years old. The mean interval between the initial sting that caused a generalized reaction and the re-sting was 4.5 years with a range of one month to 26 years. Thirty-seven percent (7/19) had an improved response

on re-sting: 26.3% (5/19) having no systemic reactions and two patients had a Grade II or urticaria reaction only. The number that had the same grade of reaction on re-sting was 42% (8/19). Four of these patients had worse reactions according to our classification (Table IV) which places Grade III/IV in the same category and so that we would have a similar criteria as Reisman.¹²

When subdividing our re-sting population into those

under 16 years of age, and those over 16 years of age, the re-sting information becomes dramatically different, Table IV. In children, under 16-years old with cardiovascular/respiratory reaction to the initial sting, the improvement rate on re-sting was 75% (6/8) with 62.5% (5/8) having no systemic reaction to re-sting. A same reaction to the re-sting as in the initial reaction was found in 25.0% (2/8), Table IV. The mean age of the children in the under 16-years old category was eight years, with a range 3–15 years. The mean re-sting interval in these children was 5.01 years with a range of one month to 20 years.

In sharp contrast, the older children and adults (those over 16 years of age), only 9.1% (1/11) had an improved reaction on re-sting and 36.4% (4/11) became worse, Table IV. However, 54.5% (6/11) had the same reaction on re-sting. The mean age of those in the category of over 16 years of age was 47.3 years with a range of 22–66 years. The mean interval between the initial sting that caused a systemic reaction and the re-sting was 4.1 years with a range of one month to 26 years.

It is well known that a vast majority of children under 16 years of age who have only cutaneous symptoms as their initial reaction to insect sting have no reaction on re-sting.^{5,12,13,14} Reisman¹² reported that 76% (19/25) of children who had initial systemic sting reactions and who were under 16 years of age had no reaction on being re-stung. In a subpopulation of children who had an interval between initial sting with a systemic reaction and re-sting under five years ago, his frequency of no reaction on re-sting was 60% (9/15). In those children with an interval between stings of over five years, the no reaction rate on re-sting was 100%

(10/10). These children had a mixed grade of initial reaction. However, he also reports that his data suggests that children with cardiovascular/respiratory reactions also may have a lower re-sting reaction rate. Our data confirms this suggestion.

REFERENCES

1. Settupane GA, Boyd GK. Prevalence of bee sting allergy in 4,992 boy scouts. *Acta Allergologica* 25:286–291, 1970.
2. Abrishami MA, Boyd GK, Settupane GA. Prevalence of bee sting allergy in 2,010 girl scouts. *Acta Allergologica* 26:117–120, 1971.
3. Settupane GA, Chafee FH, Klein DE, Boyd GK, Sturam JH, Freye HB. Anaphylactic reactions to Hymenoptera stings in asthmatic patients. *Clin Allergy* 10:659–665, 1980.
4. Settupane GA, Newstead GJ, Boyd GK. Frequency of Hymenoptera allergy in an atopic and normal population. *J Allergy Clin Immunol* 50:146–150, 1972.
5. Golden DBK. Epidemiology of allergy to insect venoms and stings. *Allergy Proc* 10:103–107, 1989.
6. Curry JJ. The action of histamine on the respiratory tract in normal and asthmatic subjects. *J Clin Invest* 25:785, 1946.
7. Weiss S, Robb GP, Blumgart HL. The velocity of blood flow in health and disease as measured by the effect of histamine on the minute vessels. *Am Heart J* 4:664–1929.
8. Settupane GA, Chafee FH. Natural history of allergy to Hymenoptera. *Clin Allergy* 9:385–390, 1979.
9. Settupane GA, Carlisle CC. A critical evaluation of RAST to venoms of Hymenoptera. *Clin Allergy* 10:667–673, 1980.
10. Settupane GA, Hopson CN. Hymenoptera allergy: Precipitin and passive cutaneous anaphylaxis tests in human and rabbit sera. *Acta Allergologica* 26:121–130, 1971.
11. Loveless MH, Fackler WR. Wasp venom allergy and immunity. *Ann Allergy* 14:347–366, 1956, (Sept/Oct).
12. Reisman RE. Studies of the natural history of insect allergy. *Allergy Proc* 10:97–102, 1989.
13. Bousquet J, Velasquez G, Francois-Bernard M. Evolution of sensitivity to Hymenoptera venoms during maintenance immunotherapy. *Allergy Proc* 10:115–118, 1989.
14. Schuberth KC, Graft DE, Kagey-Sobotka A, et al. Do all children with insect allergy need venom therapy? *J Allergy Clin Immunol* 71:140, 1983. (abst) □

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