

Epidemiology of Allergy to Insect Venoms and Stings

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ABSTRACT

Stings by bees, yellow jackets, hornets or wasps may cause allergic reactions in sensitized individuals, including systemic or anaphylactic reactions. The epidemiology and natural history of insect venom allergy is emerging in the past decade and has clarified the reasons for the false perceptions that whole body extracts of the insects were considered effective for therapy. Up to 3% of adults have had a systemic sting reaction but 25% show venom sensitivity on skin test or RAST. Sensitization is common after a sting but is transient in 50% of cases. The risk (and pattern) of systemic reaction differs in children, but is 50% for those with positive history and skin test. Lower risk of reaction is expected in those with positive skin tests and large local reactions (5–10%), no previous reaction (10–20%), children with strictly cutaneous generalized reaction (1–10%), or for those with no stings for over ten years (15–25%). These observations have profound impact on the evaluation of patients for initiation or discontinuation of venom immunotherapy.

SPECTRUM OF STING REACTIONS

Insect stings can elicit a wide range of possible reactions. Non-allergic people usually experience local

pain, irritation, itching, redness, and swelling for a short while after a sting, resolving gradually, usually within hours. Some individuals are quite sensitive to toxic venom constituents and will develop pronounced local reactions and even mild constitutional symptoms, such as nausea, malaise, headache, or fatigue. These people often have similar reactions to insect bites and may report skin sensitivity to a variety of irritants. Venom allergic individuals may have localized reactions, systemic symptoms, or no unusual reaction at all to any particular sting. Even those with a normal reaction may have been sensitized to insect venom allergens. Such asymptomatic (and possibly pre-clinical) sensitivity will be discussed below. Many patients give a history of predictable large local reactions to stings, while others have had local swelling on some occasions and systemic reactions at other times. Even within a family, some members have only large local reactions and others have reproducible patterns of systemic anaphylaxis.

Large local sting reactions cause delayed and prolonged local inflammation. These reactions resemble “late phase reactions” which are IgE dependent. In fact, 50% to 80% of these patients have detectable venom-specific IgE.¹⁻³

Systemic (generalized) allergic sting reactions cause the typical manifestations of anaphylaxis. Cutaneous, vascular or respiratory symptoms and signs may be present singly or in any combination, in addition to involvement of the less common target tissues. The Insect Allergy Committee of the American Academy of Allergy described the frequency of the various symp-

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Table I

Symptoms and Signs of Insect Sting Anaphylaxis in Adults and Children

Symptom or Sign	Frequency	
	Adults	Children
Cutaneous only	15	60
Urticaria/angioedema	80	95
Dizziness/hypotension	60	10
Dyspnea/wheezing	50	40
Throat tightness/hoarseness	40	40
Loss of consciousness	30	5

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toms of allergic sting reactions in a registry of sting-allergic individuals.⁴ Of 2602 registrants, 16% reported only cutaneous symptoms and 24% had life-threatening reactions, including 15% with loss of consciousness; 44% had "moderate" systemic reactions. Our own experience in a survey of over 300 adult and pediatric patients (Table I) closely resembles the findings of the Insect Allergy Committee,⁵ but demonstrates the different spectrum of reaction in children. Cutaneous symptoms are most common (affecting 80%); they are the sole manifestation in 15% of adults, but in more than 60% of affected children.⁶ Almost 50% of children and adults had respiratory complaints. Symptoms and signs of hypotension were uncommon in children, but occurred in over 60% of adults, and half of these experienced loss of consciousness. These differences between adults and children, as well as the difference in natural history (discussed later), are of great clinical importance.

Although fatal sting reactions are unusual, there are more deaths in the United States from insect stings than from all other venomous animals. Fatal reactions often occur without a past history of sting reactions.⁷ Although deaths have been reported in children, they are far more common in adults, the risk increasing with age. This is consistent with the relative intolerance of older individuals to hypotension and hypoxia.

PREVALENCE

There have been very few studies of the epidemiology of insect sting allergy. The only published sur-

veys were performed 20 years ago by reviewing the medical forms of boys attending a Boy Scout summer camp. Two such surveys reported the frequency of systemic sting reactions in children at 0.4% to 0.8%.^{8,9} These data probably underestimated the true frequency due to selection factors in medical reporting and camp attendance. The prevalence of sting reactions in adults was entirely unknown until very recent studies were reported. In a stratified random sample of a population of industrial employees, the prevalence of systemic allergic sting reactions was found to be 3.3%; either RAST or skin-test evidence of sensitization to Hymenoptera venom was present in 26%.¹⁰ This study suggested that venom sensitization after a sting is common, occurring in 30-40% of those who had been recently stung. However, the sensitivity was half as common in subjects stung more than three years prior to testing. This suggests that sensitization is often transient.

Of equal importance is the observation from these studies that most affected individuals never seek medical attention. This explains why a review of medical records would yield an estimated prevalence of less than 1%, and points to the need for better public education. Various studies have shown that the frequency of sting reactions is similar in atopic, non-atopic and unselected populations, but venom sensitivity on skin test seems to occur more frequently in persons with skin test sensitivity to inhalant allergens.¹⁰ The frequency and the risk of insect sting allergy is clearly related to exposure to insects and is, therefore, greater in children, in males and in those adults who work or play outdoors, particularly beekeepers and their families.

In the survey of a population of industrial employees (described above), skin tests were positive to honey bee venom in 5% of subjects, and to yellowjacket venom in 14%; 17% were positive to at least one venom. In children however, honey bee venom sensitivity is much more common, occurring in half of affected pediatric patients.⁶ Some areas of the country have larger populations of different insects such that honey bee sensitivity is more common in agricultural and fruit-belt regions, whereas *Polistes* wasp sensitivity is more frequent in the central Gulf coast (Texas and Louisiana). The venom RAST showed a similar pattern in the above survey, with 6% positive to honey bee, 21% positive to yellowjacket and 27% positive to at least one venom. The venom skin test and RAST showed an imperfect correlation. As previously reported, the RAST is negative in approximately 20% of skin-test positive subjects. However the converse is true in approximately 10% of RAST positive subjects. The clinical significance of positive RAST with a negative skin test is unknown. Other reports have confirmed that

venom skin tests and RAST may be positive in 20% of adults.¹¹⁻¹⁴

Deaths from insect sting allergy are probably somewhat more frequent than the estimated 40-50 per year in the United States, but many cases are unsuspected and unrecognized since the end results of anaphylaxis may lead to the recording of the cause of death as "myocardial infarction" or "cerebrovascular accident." Postmortem RAST analysis may support a final diagnosis of insect sting anaphylaxis in suspicious cases.^{15,16}

NATURAL HISTORY

The fate of patients with insect sting allergy upon subsequent stings is somewhat unpredictable, especially since systemic reactions seem to recur as often as not. Although this variability is not well understood, it is clear that only 30-60% of sting-allergic patients have systemic reactions when deliberately challenged even though the non-reactors may react to subsequent stings.¹⁷⁻²⁰ This is similar to the case of penicillin and food allergies, in which only half of the skin test-positive patients react to a specific allergen challenge. Although it is widely believed that allergic reactions become progressively worse with each subsequent sting, the majority of patients exhibit a characteristic and individual pattern of anaphylaxis which varies only slightly in severity from one sting to another. This predictability of the pattern of reaction is also found in food and drug reactions.

It is of special interest that the frequency of recurrent systemic sting reactions is much lower in children. In fact children who have had strictly cutaneous systemic reactions have only a 10% incidence of subsequent systemic reactions, and only 0.4% incidence of more severe reactions (with respiratory or circulatory symptoms).²¹

The recurrence rate of large local sting reactions is not known, but appears rather high. However, a history of large local reaction does not clearly predict progression to systemic reactions as the risk of eventual anaphylaxis in such people is only 5-10%.^{2,3,22,23} Most such individuals consistently have large local reactions on repeated stings, even some whose family members have had systemic reactions. Factors favoring a systemic reaction include multiple stings, or repeated stings in close temporal proximity (only weeks apart). There are no known clinical or laboratory characteristics that differentiate those who will progress to systemic reactions, just as there are no characteristics that distinguish systemic reactors from those who have only large local sting reactions; both groups have venom-specific IgE

antibodies. In fact, venom skin tests or RAST often show a higher level of sensitivity in large local reactions.

The incidence of systemic reactions in individuals with asymptomatic sensitization (positive venom skin test or RAST with no history of allergic sting reaction) is unknown. Prospective studies are in progress, and preliminary observations show a 15-25% frequency of systemic reactions, especially in those with positive skin tests.²⁴

Long-term observations of venom skin test sensitivity and specific IgE antibody levels have shown a gradual but linear decline over a period of years in almost all subjects. In those with asymptomatic sensitization, the tests become negative in 30% after two years, and in an estimated 50% after three years.²⁴ Because most people are stung only infrequently, these data indicate that the majority of sensitized individuals will lose their sensitivity without ever knowing they had it, or will have persistent sensitivity that remains asymptomatic due to a lack of sting challenge. Of course, even among those who are stung, more than half will have no systemic reaction (as previously observed in deliberate challenge studies). It is, therefore, not surprising to find a prevalence of systemic reactions of 3.3% despite a prevalence of immunologic sensitivity of 26%.

There have been few long-term studies of venom sensitivity in untreated patients, especially because of the strong indications for immunotherapy in such individuals. In untreated patients who had only large local sting reactions, as well as in patients who stopped venom therapy against medical advice after only 12-24 months, venom sensitivity (five years after the original evaluation) was found to have decreased in 60% and became negative in about 15%.^{22,25} Results were quite similar in patients who completed five years of therapy: after stopping venom injections these patients continued to show declining sensitivity with negative skin tests (at 1.0 mcg/ml) and IgE (RAST) of 1 ng/ml or less occurring in 15-20% after six years therapy and 45-60% after two additional years off treatment (eight years after original evaluation) (26). In other studies of untreated children and young adults, skin tests or RAST became negative in 25-50% after an average of ten years of follow-up.^{27,28}

There are many variables that may affect the frequency and rate of decline of venom sensitivity. The mere passage of time is clearly an important factor as described above. Although skin tests and RAST show a similar decline in treated and untreated patients observed for up to ten years, the frequency of systemic reactions to stings after eight to ten years is 2-10% in those who had at least five years therapy, but is 15-25% in untreated patients.^{26,29} Interim stings cause a tran-

Table II

Epidemiology of Insect Sting Allergy

Sting Reaction	Skin test (or RAST)	Prevalence (Estimated)	Risk of Systemic Sting Reaction (Estimated)
Normal	Negative	74%	<1%
	Positive	12%	10–15% (?)
Large local	Negative	4%	<1%
	Positive	7%	5–10%
Systemic	Negative	1%	<1%
	Positive	2%	50%

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sient increase of venom IgE but do not seem to prevent the continued decline of sensitivity.^{29,30}

Clinical Significance

The clinical significance of the epidemiology and natural history of insect sting allergy has not been appreciated until the 1980's. A better knowledge of the high frequency of asymptomatic sensitization and the self-limited nature of this allergy in many sub-groups of affected individuals, would have altered the history of insect sting allergy in this century. The reported efficacy of whole body extract (WBE) therapy was based on small collections of patients by individuals and on the registry for insect allergy of the American Academy of Allergy. These reports show that 80% to 95% of WBE-treated patients did "better" on their next sting, as opposed to only 10% to 40% of untreated patients.⁴ There were however many short-comings to these studies since they were multicenter, retrospective and poorly controlled. The definition of "better" was not clearly made, and many of these "better" patients still had systemic reactions. Increasing knowledge of the natural history of the disease has revealed the inherent variability of systemic reactions, so that "better" or "worse" have little clinical or prognostic significance. In the largest study for example, 38% of the treated patients received epinephrine when stung, compared to only 14.7% of the untreated patients.⁴ This alone may account for some of the apparent "success" of WBE therapy. Furthermore, 40% of the patients in that report were children, who are now known to be much less reactive than adults, with a very low risk of recurrent systemic reactions.²¹ It was also not appreciated at that time that many of the adults who had had their sys-

temic sting reactions in the remote past, may well have lost their sensitivity in the intervening years, although there was no way of detecting this at that time for lack of an accurate diagnostic agent. It was also unknown until ten years ago that (as noted above) even allergic individuals will not always react to a sting. Thus, these are many indications that the alleged efficacy of WBE treatment was due entirely to the characteristics and natural history of the disease itself.

Clinical decisions on the initiation or discontinuation of venom immunotherapy must also take into account the epidemiology and natural history of insect sting allergy. The fundamental question in evaluating patients for venom immunotherapy is: "What is the chance of a future sting causing a systemic reaction?" Such risk analysis requires accurate diagnostic criteria to determine the presence and clinical significance of venom sensitivity (Table II). It has become clear that additional information is also required. The lessons learned from experience with whole body extract treatment showed that an intimate knowledge of the natural history of insect sting allergy is necessary for meaningful risk analysis.³¹ The mere presence of venom hypersensitivity is not a certain sign of a risk of anaphylaxis; the frequency of systemic sting reactions in various subgroups of sensitized subjects ranges from 10% to 50%. Moreover, this risk, like the underlying sensitivity, changes with time. It is therefore imperative that more comprehensive data on the natural history of this disease be developed as a basis for clinical practice.

Whether and when to initiate venom immunotherapy is determined primarily by the presence of venom-specific IgE antibodies and a history of systemic allergic reaction to a sting. Epidemiologic studies have helped to clarify that the risk of systemic reaction is less than 10% in children who have had only cutaneous systemic sting reactions²¹ and in adults or children who have had only large local reactions.^{1–3,22,23} Adults with strictly cutaneous systemic reactions have not been available in sufficient number to determine the true risk of progression to respiratory or circulatory anaphylaxis to subsequent stings. Questions frequently arise when the systemic reaction was remote or in childhood, especially if interim stings have caused only minimal or local reactions. Better long-term observations of such individuals will be necessary to determine if the risk is significantly reduced in some types of affected individuals simply by the passage of time or the transition into adulthood. The possibility that children routinely "outgrow" sting reactivity was suggested ten years ago by Dr. Lichtenstein based on the observation that virtually none of the hundreds of affected adults he had seen gave a history of sting reactions in childhood. Some surveys indicate up to 50% loss of sensitivity over

a ten year period in children and young adults.^{27,28} Nevertheless, some individuals report severe reactions 20 years or more apart. The recent observation that venom sensitization is rather common suggests that a positive skin test or RAST is inconclusive in a patient with a questionable history, but that persistent sensitivity may carry a significant risk for future systemic sting reactions.

Similarly, data on the natural history of venom sensitivity and sting reactivity in treated and untreated patients is required for evaluation of when it might be safe to discontinue therapy. Although treatment can apparently be stopped if sensitivity disappears on RAST or skin test, this occurs in only 20% of those treated five years, 50% after eight years and up to 66% of those observed for ten years.^{26-29,32-34} The risk of systemic sting reaction in affected but-untreated-patients does seem to decline with the passage of time but remains in the range of 25-40% after five to eight years follow-up. The mere passage of time would therefore not justify stopping treatment unless the risk is significantly reduced by the therapy itself. This indeed does seem to occur in studies revealing only 2-8% sting reactivity up to five years after stopping venom immunotherapy of five years or more duration.²⁹

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