

Review Article

Stinging insect allergy

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ABSTRACT

Stinging insect allergy is a relatively common medical problem, responsible for an estimated 40 fatalities per year in the USA and considerable anxiety and lifestyle modification. There are no criteria to identify people at risk of initial venom anaphylaxis. Reactions may occur at any age and are unrelated to the time interval of prior venom exposure. There is an approximate 60% re-sting reaction rate in people who have had sting anaphylaxis and have positive venom skin tests. Re-sting reactions are more likely to occur in adults than in children and in people who have had more severe anaphylactic symptoms. Positive venom intradermal skin tests confirm the diagnosis of potential stinging insect allergy in people who have had sting reactions. Venom immunotherapy provides almost 100% protection from further sting reactions. It is recommended for all people who have had venom anaphylaxis and have positive skin tests, except for children who have dermal reactions only. Details of venom dosing are well established. The adequate duration of venom immunotherapy is still an unresolved issue. Conversion to a negative skin test appears to be an absolute criterion to discontinue treatment. In the presence of a persistent positive skin test, 3–5 years of immunotherapy is generally sufficient. People who have had severe reactions, such as loss of consciousness, may require indefinite therapy.

Key words: clinical reactions, diagnosis, immunotherapy, natural history, venom allergy.

INTRODUCTION

Over the past 20 years, the pathogenesis, diagnosis and treatment of allergic reactions due to insect stings have been clarified and reliable guidelines established for the assessment of this allergic disease. The availability of purified insect venoms and the clinical application of measurements of venom specific IgE (skin test, radioallergosorbent test (RAST)) and serum venom specific IgG provided the appropriate tools to understand and modulate this disease process. Criteria have been established for the use of venom as a diagnostic skin test reagent, correlating with the clinical presence of potential insect sting allergy. Insect venom immunotherapy (VIT) is a remarkably effective therapy for individuals at potential risk of insect sting anaphylaxis, inducing a permanent 'cure' in many individuals.

There are still pertinent unresolved issues. These include the identification of individuals who may be at risk for initial insect sting anaphylaxis, further insight into the factors which affect the natural history of venom allergy, and objective criteria to define the adequate length of immunotherapy.

DEVELOPMENT OF INSECT STING ALLERGY

At present there are no predictive criteria that identify individuals at risk of acquiring an insect sting allergy. The majority of individuals who have insect sting anaphylaxis have tolerated prior stings without reaction. In our experience, there is no time relationship between the last uneventful sting and the subsequent sting which leads to an allergic reaction. A further confusing observation is the fact that some individuals, primarily children, have had venom anaphylaxis after the first known insect sting. As insect stings always cause pain, in contrast to insect bites, the history in this regard seems reliable. This occurrence raises the issue regarding the cause of sensitization or the pathogenesis of this initial reaction.

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In the past, there was a common accepted concept that large local reactions following insect stings, particularly those that were increasing in size with each sting, might precede an anaphylactic reaction. These large local reactions are defined as reactions extending from the sting site, often peaking in 24–48 h and lasting up to one week. For example, a sting on the finger may extend to the wrist or elbow. Clinical observations in recent years indicate that these large local reactions tend to be repetitive, with a very low incidence, perhaps less than 5%, of subsequent systemic allergic reactions.¹

Venoms are highly potent sensitizing substances when there is significant exposure. Observations in the past, such as individuals who collect snake venoms, indicate a high incidence of the development of an inhalant type allergy to venom. The occurrence of many simultaneous stings such as 100–200 stings, can sensitize individuals for subsequent single sting anaphylaxis. This potential problem is now recognized more often because of the increasing spread of the so called 'killer bees', which may inflict several hundred stings at one time.²

Demographic studies suggest that the incidence of insect sting allergy in the general population ranges between 0.4 and 3%.^{3–5} Approximately 33–40% of individuals who have insect sting anaphylaxis are atopic. There is a 2:1 male to female ratio which is probably a reflection of exposure rather than any specific sex prevalence. The majority of the reactions which do occur are in younger individuals although fatalities are greater in adults.

Severe anaphylactic symptoms following insect stings may occur at any age. In one large study, potentially fatal anaphylaxis as defined by hypotension, loss of consciousness, upper airway swelling, and marked respiratory distress occurred in individuals who had a fairly uniform age distribution, including children.⁶ The majority of the individuals who had severe reactions were not aware of their potential allergic sensitivity.

It is estimated that there are 40–50 deaths per year in the United States as a result of insect sting anaphylaxis.⁷ Most individuals had no warning or indication of their sensitivity and had tolerated prior stings with no difficulty.

NATURAL HISTORY OF INSECT STING ANAPHYLAXIS

In order to assess appropriate intervention, it is necessary to understand the natural history of any disease process. This is particularly true of insect sting allergy. Extracts prepared by crushing or grinding old insect bodies, so called

whole-body insect extracts, were used for over 40 years for diagnosis and treatment. It was generally accepted that these extracts were therapeutically potent and provided protection against further sting reactions. It is now clear that these whole-body extracts are impotent, lack sufficient venom content, are unreliable for diagnosis and ineffective for treatment. The only explanation for this mistaken confidence was the failure to understand the natural history of insect sting allergy. Individuals may spontaneously lose their allergic sensitivity.

More recent observations of individuals who have had allergic reactions from insect stings and who do not receive VIT have provided insights into the natural history of insect sting allergy and suggest that this allergy is a self-limiting process for many individuals. In the initial study which documented the efficacy of venom therapy, 40% of individuals treated with placebo or whole body extracts failed to react to subsequent re-stings.⁸ In a subpopulation of children who have had dermal (hives, angioedema) symptoms as the only manifestation of an allergic reaction from an insect sting, there is an extraordinarily low re-sting reaction rate.⁹

These observations were extended in a study of a large number of individuals who had insect sting reactions and were observed without treatment.¹⁰ Overall, the incidence of re-sting reactions was higher in adults than in children, but did average about 60%. There was no relationship between the time interval between the sting reaction and the subsequent re-sting. The severity of the anaphylactic symptoms was an important criterion. Those individuals with more severe reactions had a higher incidence of re-sting reactions. Finally, when a re-sting reaction did occur, the symptoms generally were similar to those which had occurred previously. These observations confirmed the frequent self-limiting course of insect sting allergy, especially in children, and the repetitive nature of the specific anaphylactic symptoms.

CLINICAL REACTIONS

The clinical symptoms of insect sting anaphylaxis are similar to those occurring from other causes of anaphylaxis. Cutaneous reactions, urticaria and angioedema, occur in a large majority of individuals. Other symptoms include upper airway obstruction, asthma, circulatory collapse with shock and hypotension, nausea, diarrhea, bowel contractions, cardiac arrhythmias and, on rare occasions, uterine contractions. Milder symptoms such as the dermal reactions are self-limited and usually resolve within several hours in the absence of any medical therapy.

As noted above, severe symptoms may occur at any age.⁶ In the group of people who had loss of consciousness, individuals were older and had a higher incidence of cardiac disease and beta blocker use. The majority of these individuals had no warning or indication of potential anaphylaxis.

Anaphylactic symptoms usually occur within minutes after the insect sting. In general, the shorter the time interval between the insect sting and the onset of symptoms, the greater the severity of the reaction. On occasion, however, reactions, primarily urticaria, may start 6–24 h after the sting. On rare occasions these delayed onset reactions are also associated with more acute symptoms such as throat edema and shortness of breath.

Serum sickness such as reactions characterized by hives and arthralgia and fever may occur seven to 14 days after an insect sting.¹¹ These late onset reactions are mediated by IgE antibodies. These individuals are candidates for VIT.

DIAGNOSIS-DETECTION OF VENOM SPECIFIC IGE

Venom skin tests

The diagnosis of potential venom allergy is dependent upon the history of insect sting anaphylaxis and the presence of venom specific IgE, usually detected by the immediate skin test reaction. Both of these components are necessary to substantiate the diagnosis of insect sting allergy and the possibility of administering VIT.

A positive venom skin test without a history of an allergic reaction does not indicate that there is a risk for venom anaphylaxis. The majority of individuals who have had large local insect sting reactions do have positive venom skin tests, but as noted above, have a small risk of anaphylaxis. Some individuals who tolerate insect stings with no problem will have a transient positive skin test.

In the United States there are five commercial venoms. These are honeybee, yellow jacket, *Polistes* wasp, yellow hornet and white faced hornet. The yellow jacket and *Polistes* are mixed species preparations. Individuals suspected of having insect sting allergy are usually tested with all five venoms. Intradermal tests are performed, starting with venom doses usually in the range of 0.0001 µg/mL and testing up to concentrations of 0.1–1.0 µg/mL.^{12,13} Greater venom concentrations may cause irritative reactions, which are not immunologically specific. Skin test reactions which occur only at the 1 µg/mL dose must be

carefully evaluated for clinical relevance. In our own experience there have been no systemic reactions from venom testing and only rare local reactions.

In vitro measurement of venom specific IgE

Venom specific IgE can also be measured in the serum by *in vitro* tests (RAST). In general, the skin test is a more sensitive test for detection of venom specific IgE than the *in vitro* test. In addition, the sensitivity of the *in vitro* test may vary considerably from laboratory to laboratory. The skin test remains the preferred test for diagnosis of venom allergy. When skin tests cannot be performed or cannot be reliably interpreted, such as in individuals with dermatographia, or when they give equivocal results in the presence of a highly suspect history, measurement of serum venom specific IgE may be helpful.

IMMUNITY

An important aspect related to the understanding and treatment of venom allergy is the development of immunity. Initial studies of immunity were carried out with beekeepers who represent an immune population, the antithesis to the allergic individual. Beekeepers may be stung on multiple occasions with little local reaction. They have even expressed the thought that 'I would rather be stung by a bee than bitten by a mosquito'. Investigation of beekeepers has shown the presence of high titers of venom specific IgG, often correlating with the amount of venom exposure (stings).¹⁴

More specific documentation of the role of venom specific IgG came from studies which showed that passive administration of hyperimmune gamma globulin obtained from beekeepers protected honeybee allergic individuals from allergic reactions due to venom challenge.¹⁵ Finally, the protective effects of VIT, at least during early treatment, appear to be related to the stimulation of venom specific IgG.

TREATMENT

Acute reaction

The medical treatment for acute anaphylaxis is the same as that for anaphylaxis due to any cause. Epinephrine is the drug of choice and should be administered as soon as possible, even if symptoms are mild. The use of other medications depends upon the symptom complex and

includes antihistamines, steroids, oxygen and vasopressors. Specific attention should be directed at the upper airway, as upper airway swelling has been a major cause of death. Airway patency must be maintained.

If the insect stinger remains in the skin, which most frequently occurs after honeybee stings, it should be gently flicked off. Care should be taken to avoid squeezing the sac which could deposit more venom. Because the majority of venom is deposited very quickly after the sting, this procedure may not be very helpful unless done immediately after the sting.¹⁶

Prophylaxis

Individuals at risk of an allergic reaction are advised to use precautions to avoid subsequent stings. When outside, especially when involved with activities which might increase insect exposure such as gardening, these individuals should wear slacks, long-sleeved shirts and shoes. Cosmetics, perfumes and hair sprays which attract insects should be avoided. Dark or drab clothing is less likely to attract insects. Particular care should be taken outside around food and garbage, which especially attract yellow jackets. Individuals at risk are advised to carry epinephrine, available in preloaded syringes, for self-administration. Epinephrine should be administered at the earliest sign of an allergic reaction from an insect sting. Studies comparing individuals who have had fatal allergic reactions with individuals who have had serious, non-fatal reactions suggest that the use of epinephrine may be the critical, decisive factor in determining the outcome.⁷

Venom immunotherapy

Insect venom extracts for diagnosis and therapy have been available for approximately 20 years. While some questions remain, the concepts of treatment have been well established. Venom immunotherapy is remarkably effective, preventing subsequent allergic reactions in over 98% of treated patients and, in many instances, providing a permanent 'cure'.^{17,18} The major remaining issues relate to refining of the selection process for individuals requiring VIT and refining criteria for the duration of treatment.

Patient selection (Table 1)

Potential candidates for VIT are individuals who have had an allergic reaction from an insect sting and have a positive venom skin test or elevated levels of serum venom specific IgE. As noted above, studies of the natural history of insect sting allergy have shown that only approximately

60% of these individuals will have a subsequent reaction when re-stung. The incidence of these re-sting reactions is influenced by age and the nature of the anaphylactic symptoms. Adults are more likely to have re-sting reactions than children and the more severe the symptoms, the more likely the reaction will re-occur. These observations influence the decision regarding patient selection for immunotherapy.

Children with dermal (hives, angioedema) reactions only have a very benign prognosis and do not require immunotherapy. The incidence of re-sting reactions is low and when the reactions do occur, they are almost always similar in intensity.⁹ Individuals of any age who have had severe allergic reactions should be advised to receive VIT. This is particularly true of individuals who have had loss of consciousness. Current recommendations are to administer VIT to adults who have had mild to moderate allergic sting reactions. This decision may require evaluation of other risk factors such as coexisting medical problems, concomitant medication use, patient lifestyle and risk of sting exposure.

Individuals who have had serum sickness like reactions are also candidates for VIT.¹¹ These individuals have elevated levels of venom specific IgE and usually undetectable or low levels of venom specific IgG. As with individuals who have had classic serum sickness from horse serum products, they are now at risk for anaphylaxis if re-exposed to venom. Venom immunotherapy has been administered with no adverse consequences, in particular no signs of immune complex disease.

A diagnostic sting challenge has been suggested as a criterion for initiating venom immunotherapy.^{19,20} This approach has been suggested because of the repeated observation that only 60% of individuals thought to be at risk for a sting reaction, because of a history of a prior reaction and the presence of a positive skin test, do react when re-stung. The problems with the sting challenge

Table 1. Indications for venom immunotherapy in patients with positive venom skin tests

Insect sting reaction	Venom immunotherapy
Normal – transient pain, swelling	No
Extensive local swelling	No
Anaphylaxis – severe	Yes
Anaphylaxis – mild; dermal reaction only	
Children	No
Adults	Yes
Serum sickness	Yes
Toxic	Yes

relate to its safety and reliability. Observations of both field stings and intentional sting challenges have shown similar results. Approximately 20% of individuals who initially tolerate a re-sting with no difficulty react following a subsequent re-sting.^{10,21} More importantly, this diagnostic sting challenge raises serious medical and ethical issues. Life threatening reactions have occurred after intentional sting challenges in patients who did not receive VIT.^{20,22} It is my opinion that patients who have a high risk of serious anaphylaxis, such as adults who have had prior severe reactions, should not be intentionally rechallenged and should be given immunotherapy on the basis of their history and skin test reactivity, recognizing that some of these patients may not need therapy.

Venom selection

The commercial venom product brochure recommends treatment with all venoms to which there are positive skin tests. As a result, many individuals are treated with multiple venoms, despite the history of a single sting reaction. The basic issue is really whether multiple venom skin test reactions represent specific venom allergy or antigenic cross reactivity among different venoms. Extensive studies of venom cross reactivity may be summarized as follows:

1 There is extensive cross reactivity between the two major North American hornet venoms, yellow hornet and bald-faced hornet.²³

2 There is extensive cross reactivity between yellow jacket venom and hornet venom.²⁴

3 There is limited cross reactivity between yellow jacket and *Polistes* venom.²⁵

4 There is a more complex relationship between honeybee venom and vespid venom. There may be no cross reaction, extensive cross reaction or reaction to a major allergen in one venom cross reacting with a minor allergen in the other venom.²⁶

The practical application of these data suggests that almost all individuals who have had allergic reactions due to yellow jacket or hornet stings should be expected to

have positive skin test reactions to both of these venoms. In this situation, our clinical studies have suggested that immunotherapy with one venom, more commonly yellow jacket, provides adequate protection.¹⁸ Approximately 50% of individuals who have had yellow jacket or hornet sting reactions will also have positive skin test reactions to *Polistes* venom. *Polistes* VIT is not necessary. The contrast is also true. About half of the individuals who had *Polistes* sting reactions will have a positive skin test to yellow jacket or hornet venoms. These individuals can be adequately treated with *Polistes* venom only.

Individuals who have positive tests to both yellow jacket and honeybee venoms are more difficult to treat with single venoms unless the history of the offending insect is clear.

The implications of these observations for therapy are clear. If the offending insect can be identified accurately or if there is a significant difference in degree of skin test reactivity, knowledge of these cross reactions should lead to single venom therapy whenever possible despite the presence of multiple positive venom skin test reactions.

Dosing schedule

Venom immunotherapy is administered in a similar manner to other forms of immunotherapy (Table 2). Treatment is initiated in small doses, usually from 0.01 to 0.1 μg and incremental doses are given until the maintenance dose is reached, traditionally 100 μg . The selection of a starting dose is really based on the intensity of the skin test reaction rather than the nature of the anaphylactic symptoms. A number of dosing regimens have been suggested. A commonly used schedule suggests two or three injections during the weekly build-up phase with doses doubled or tripled at 30 min intervals. Maintenance doses can then be reached in 6–8 weeks. Rush desensitization therapy has also been given with multiple doses administered, often in a hospital setting, over a period of 2–3 days to one week. The more rapid schedules appear to be accompanied by a more rapid increase in venom specific IgG. Reported immunotherapy reaction rates with both rapid and slower

Table 2. General venom immunotherapy dosing guidelines

Initial dose	Administer 0.01–0.1 mg, depending on degree of skin test reaction
Incremental doses	Schedules vary from 'rush' therapy, administering multiple venom injections over several days, to traditional once-weekly injections
Maintenance dose	Administer 50–100 μg of single venom or 300 μg of mixed vespid venom
Maintenance interval	Every 4 weeks for the first year; every 6 weeks for the second year; every 8 weeks for the third year
Duration of therapy	Stop when skin test becomes negative, or after 3–5 years

schedules vary, but are not significantly different. The critical issue is to reach the top maintenance dose.

Once the top maintenance dose is reached, it can be administered every four weeks during the first year. Our approach is to extend the maintenance interval to six weeks after the first year and to eight weeks after the second year.^{27,28} This has been done with no loss of clinical effectiveness or increase in reaction rate. The top recommended maintenance dose of a single venom is 100 µg. We have given 50 µg as a top dose with good results. There is a mixed vespid preparation which contains the two hornet venoms and yellow jacket venom available for therapy. The top dose is 300 µg.

Venom immunotherapy reactions

Venom immunotherapy may cause reactions similar to those induced by other types of allergenic extracts. These reactions may pose a more difficult clinical problem because, to insure protection, it is necessary to administer maximum venom doses. Reduction of dosing, as done with other forms of allergenic extracts, may not be clinically effective. Fortunately, reactions to VIT are uncommon and the majority of individuals are able to reach maintenance doses.

Large local reactions

Venoms are intrinsically irritating and cause pain at the injection site. Local swelling may occur and can cause considerable morbidity. There are several approaches to minimize these reactions. The venom dose can be split into two injections, thus limiting the amount of venom delivered at one site. The addition of a small amount of epinephrine with the venom may minimize the immediate local swelling. If the swelling is extensive and particularly delayed in onset, the addition of a small amount of steroid with the venom usually effectively inhibits the large local reaction.

Systemic reactions

Systemic reactions due to VIT are quite rare and much less common than those induced by pollen immunotherapy. After a reaction, the next dose is usually reduced by approximately 25% and subsequent doses are slowly increased. If individuals are receiving multiple venoms, it might be advisable to administer individual venoms on separate days.

Generalized fatigue

Another reaction occasionally noted after injections of other allergenic extracts such as molds and dust, but more frequently with venom, is the occurrence of generalized fatigue and aching, sometimes associated with a large local swelling. Successful treatment of this reaction is usually accomplished with the administration of 650 mg of aspirin, approximately 30 min before the injection and every four hours thereafter for 24–48 h. If symptoms persist, then steroids such as 40 mg of Prednisone administered daily for several days is usually helpful.²⁹

Other reactions

There have been no identified adverse reactions caused by long-term VIT. Injections appear to be safe during pregnancy with no effect on the pregnancy or the fetus.³⁰

Monitoring of venom immunotherapy

Venom immunotherapy is associated with initial increasing titers of serum venom specific IgG, occasional increasing and subsequent decreasing titers of serum venom specific IgE, and an extremely high, successful clinical response. A minority of patients will develop negative venom skin tests while receiving immunotherapy. As noted below, this is one criterion for stopping treatment. I do recommend repeat venom tests approximately every two years.

Stimulation of venom specific IgG has been associated with clinical immunity to insect stings.³¹ For individual patients, however, there is no absolute titer which is directly related to successful treatment. In my opinion, the overall success rate of VIT and review of relative data does not support the routine measurement of venom specific IgG.³²

Treatment failures

Venom immunotherapy is very effective, protecting approximately 98% of treated individuals. If a re-sting reaction does occur, it is initially advisable to determine whether the appropriate venom is being administered. Culprit insect identification is important and repeat allergy tests may be necessary to verify specific venom sensitivity. If the specific venom treatment is correct, then the dose should be increased by 50–100%. For example, if the maintenance dose is 100 µg, it should be increased to 150 or 200 µg.

Table 3. Venom immunotherapy – when to stop

Suggested criteria for stopping venom immunotherapy
Conversion to a negative venom skin test
Persistence of positive venom skin test; 3–5 years of therapy
Factors which may influence decision to stop therapy
Severe anaphylactic symptoms, such as loss of consciousness, due to insect sting
Systemic reactions to venom immunotherapy
Unchanged venom skin test sensitivity during venom immunotherapy
Honey bee venom allergy (as compared to vespid venoms)

Duration of therapy (Table 3)

The question of duration of treatment or when is it safe to discontinue immunotherapy has posed a persistent issue. Several criteria have been suggested as reliable guidelines. These include conversion to a negative venom skin test, a fall in serum venom specific IgE to undetectable levels and a finite period of treatment, three or five years, regardless of the persistence of skin test reactivity or serum antibody.

A recent position statement from the Insect Committee of the American Academy of Allergy, Asthma, and Immunology has addressed this issue³³ and these conclusions are supported by three recently published studies.^{34–36} In my opinion, these data strongly suggest that conversion to a negative venom skin test is an absolute criterion for stopping VIT.^{35–37} However, there have been several anecdotal reports of individuals who continue to have allergic reactions from insect stings apparently despite the presence of a negative venom skin test, which suggests the need for continued monitoring of this guideline.

Three to five years of VIT appears adequate for the large majority of individuals who have had mild to moderate anaphylactic reactions, despite the persistence of a positive venom skin test.^{33–37} The re-sting reaction rate after cessation of VIT is low, generally in the range of 5–10%. Individuals who have had severe anaphylactic symptoms such as hypotension, laryngeal edema or loss of consciousness have a higher risk of a repeat severe systemic reaction if therapy is discontinued. For this reason I currently recommend that individuals who have had severe symptoms and retain positive venom skin tests, receive immunotherapy indefinitely, which at this point can be administered every eight to 12 weeks. Other suggested factors which have been associated with the occurrence of re-sting reactions after cessation of VIT include systemic reactions to VIT, persistence of significant skin test reactivity and honey bee venom allergy as compared to vespid venom allergy. These decisions

regarding cessation of therapy should include consideration of other medical problems, concomitant medication, patient lifestyle, and patient preference.

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