

STINGING INSECT VACCINES

Patient Selection and Administration of Hymenoptera Venom Immunotherapy

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Immunotherapy for prevention of allergic reactions to insect stings has a long history checkered by the use of whole body extracts for over 50 years,²⁴ the eventual development (25 years ago) of the first standardized extracts with specific Hymenoptera venom protein allergens,³⁸ and the refinement of arguably the most effective form of treatment available to allergists and their patients.²⁸ The appropriate clinical application of this remarkable treatment requires an understanding of the clinical patterns of reaction, the natural history of the disease, and the human immune response to insect venoms. The simple fact that whole body extracts were certified as being effective, even though they are no more effective than placebo, illustrates the importance of recognizing the distinction between natural history and therapeutic effect. Although the research of the past 20 years has revealed many of the markers and patterns of reactions that enable the statistical prediction of risk, there remains a fundamental deficiency in understanding that limits the ability to predict with precision which individuals will have a severe reaction to a sting. The current standard of practice in North America rests primarily on statistical observations that provide the framework for patient selection and for the methods of administration of venom immunotherapy.

The risk of anaphylaxis occurs primarily with stinging insects of the

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order Hymenoptera. Insect bites by numerous species can cause local inflammation, swelling (including IgE-mediated reactions), and toxic systemic reactions to envenomation, but the occurrence of anaphylaxis from biting insects is rare. There are three families of Hymenoptera with clinical importance: bees (e.g., honeybees, bumblebees), vespids (e.g., yellow jackets, hornets, wasps), and fire ants (e.g., genus *Solenopsis*). Exposure to these insects is affected by environmental and ecological changes. The predominant species of fire ants was imported inadvertently through Mobile, Alabama in the early part of the twentieth century and has rapidly become an increasing public health hazard in the southeast and southern United States.⁴ The Africanized honeybee ("killer bee") is an aggressive hybrid resulting from an ill-advised experiment to enhance honey production. The danger from the Africanized honeybee stems from the numbers of stings because of swarm-and-attack behavior rather than any greater allergenicity or toxicity of their venom, which is in fact similar to that of other honeybees. The allergens in honeybee venom are immunochemically distinct from those of the vespid venoms (see article by Weber elsewhere in this issue).⁴¹ The vespid venoms cross-react and contain essentially the same allergens.³⁶ The yellow jacket and hornet venoms are related so closely that 95% of vespid-allergic patients have positive skin tests to all three of the common vespid skin test preparations: yellow jacket, yellow hornet, and white-faced hornet. Polistes wasps are more distantly related to the other vespids, and only 50% of yellow-jacket-allergic patients have cross-reactive positive tests to wasp venom. Fire ant venoms are unique in that they contain minimal protein in a suspension of alkaloid toxins. The alkaloid component is the cause of the painful, sterile, and pustule characteristic of fire ant stings but does not cause allergic reactions. The allergenic proteins of fire ants are unique except for one that cross-reacts slightly with a vespid allergen.³⁷

PATIENT SELECTION FOR VENOM IMMUNOTHERAPY

History

The fundamental question in evaluating patients for venom immunotherapy is: "What is the chance of a future sting causing a systemic reaction and how severe will it be?" Such risk analysis requires a careful history, sensitive and specific diagnostic tests, and a knowledge of the natural history of the condition. As in all allergic conditions, the history is paramount in diagnosis and must be elicited with insight and attention to detail. The history should be reviewed with respect to the circumstances and chronology of stings in the past, the time course of the reaction, and all associated symptoms and treatments. Symptoms are sometimes exaggerated by fear, panic, exercise, heat, alcohol, or underlying cardiorespiratory disease. The identity of the stinging insect is a notoriously unreliable part of the history, but the location and timing of

the sting or the location of the nest may suggest the type of insect. Honeybee stings are much more common in children and others who are barefoot outside. Honeybees or wasps may predominate in some areas of the country, but in most of the United States the majority of stings in adults are caused by yellow jackets. Insect stings can elicit local allergic reactions, systemic symptoms, or no unusual reaction at all, even in sensitized patients. Conversely, even subjects with a normal historic reaction may have become sensitized to insect venom allergens by previous stings. Such asymptomatic (and possibly preclinical or latent) sensitivity is 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, individuals with similar levels of venom-specific IgE antibodies will experience variable reactions ranging from large local reactions to systemic anaphylaxis.

Large local sting reactions cause delayed and prolonged local inflammation. These reactions resemble "late phase reactions" that are IgE dependent. Fifty percent to 80% of patients with large local reactions have detectable venom-specific IgE.^{33, 34, 44} Systemic (generalized) allergic sting reactions result in cutaneous, vascular, or respiratory symptoms and signs, either singularly or in any combination, in addition to involvement of the less common target tissues such as the intestines, heart, and uterus. The Insect Allergy Committee of the American Academy of Allergy described the frequency of the various symptoms of allergic sting reactions in a registry of sting-allergic individuals.³ Of 2602 registrants, 16% reported only cutaneous symptoms and 24% had life-threatening reactions, including 15% with loss of consciousness. Forty-four percent had "moderate" systemic reactions. Johns Hopkins Asthma and Allergy Center's experience in a survey of over 300 adult and pediatric patients closely resembles the findings of the Insect Allergy Committee, but demonstrates the different spectrum of reaction in children (Table 1). Cutaneous symptoms are most common (affecting 80%); they are the sole manifestation in 15% of adults and in more than 60% of affected children.⁵² Almost 50% of children and adults had respiratory

Table 1. 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

From Golden DBK, Lichtenstein LM: Insect sting allergy. In Kaplan AP (ed): Allergy. New York, Churchill Livingstone, 1985; with permission.

complaints. Symptoms and signs of hypotension were uncommon in children but occurred in over 60% of adults, with half experiencing loss of consciousness.

The presentation may be less certain. The history may be remote, even decades earlier, such that medical records are unavailable and the recall of the reaction inaccurate. If intervening stings have occurred without systemic reaction there could be less risk of subsequent severe reaction, but the possibility of anaphylaxis cannot be entirely excluded with a positive history and positive skin test. Many patients describe subjective symptoms that suggest anaphylaxis but without objective signs (i.e., documented hypotension, reduced air flow, observed urticaria). Throat or chest discomfort, dyspnea, lightheadedness, nausea, and other constitutional symptoms may be caused by anxiety or panic disorder or simple fear. Many such patients have been described in insect sting challenge studies as having symptoms without signs. There also are patients who request venom testing because of fears related to the severe reactions of family members or friends or cases in the news. Testing is not advised in such cases because of the frequent occurrence of positive venom tests in individuals who have been previously stung without abnormal reaction. .

Diagnosis

A positive skin test to insect venom is confirmatory evidence of the allergic sting reaction and helps to define the allergenic specificity of the reaction. The standard method uses the intradermal skin-test technique with the five available Hymenoptera venom protein vaccines. In the case of fire ant sensitivity, whole body vaccines do contain sufficient protein allergen for testing and treatment. For Hymenoptera venom testing, prick tests at 0.001 $\mu\text{g/mL}$ may be used initially for patients with a history of very severe reactions. Intradermal tests are performed with venom concentrations beginning with 0.001 $\mu\text{g/mL}$ and increasing to 1.0 $\mu\text{g/mL}$ to find the minimum concentration giving a positive (2+ grade; 5/20 mm wheal/erythema) result. Honeybee venom is somewhat more irritating and can exhibit weak positive (1+ grade, 5/10 mm result) in some nonallergic individuals. Yellow-jacket venom causes only rare false-positive reactions at 1.0 $\mu\text{g/mL}$ concentration, and testing at 3.0 $\mu\text{g/mL}$ concentration may be useful. False-positive reactions occur in some patients at 10 $\mu\text{g/mL}$.^{7, 39, 53} Even when there has only been a single reaction to a sting, sensitization may have occurred to multiple venoms. Skin testing should be performed with a complete set of Hymenoptera venoms, and the usual negative diluent (human serum albumin [HSA]-saline) control and a positive histamine control. When fire-ant stings are suspected by identification of the typical sterile pustule and characteristic exposure, testing with fire-ant whole body vaccine is performed.

Most patients with a convincing history have positive venom tests but many are skin-test negative.¹¹ Negative skin tests can be caused by

loss of sensitivity after many years and can occur during the refractory period for several weeks after a sting reaction.⁹ Skin tests usually become positive within weeks or months after a systemic sting reaction. In the case of a negative skin test with a history of severe anaphylaxis, reasonable precautions should be continued and repeat tests for venom IgE (in vitro tests and skin tests) should be done on several occasions. Some cases of apparent sting anaphylaxis are thought to be non-IgE mediated. Possible mechanisms include subclinical mastocytosis and mast cell hyper-releasability with nonimmune (toxic) release of mast cell mediators.^{6, 46}

There are many different patterns of venom skin-test sensitivity. Most importantly, the degree of skin-test sensitivity does not correlate reliably with the degree of clinical sting reaction. The strongest skin tests often occur in patients who have had only large local reactions and have a low risk of anaphylaxis, whereas some patients who have had abrupt and near-fatal anaphylactic shock only show weak skin test or serologic sensitivity. In fact, almost 25% of patients presenting for evaluation of systemic allergic reactions to stings are skin-test positive only at the 1.0 $\mu\text{g/mL}$ concentration, demonstrating the importance of testing with the full diagnostic range of concentrations. These points emphasize the importance of the history in making the diagnosis.

The detection of allergen-specific IgE antibodies in serum by radioallergosorbent test (RAST) or similar serologic tests is potentially useful but the results are variable. A high level of venom-specific IgE is diagnostic. A decrease in venom-specific IgE has been used as a marker for the effectiveness of therapy in diminishing sensitivity. The venom skin test and RAST, however, correlate imperfectly. The RAST is negative in approximately 20% of skin-test positive subjects, and the converse is true in approximately 10% of RAST positive subjects.^{39, 57} The clinical significance of a positive RAST result with a negative skin test is unknown. Skin testing is the preferred method for diagnosing insect sting hypersensitivity.

Epidemiology/Natural History

Surveys of children and adults have shown that insect sting allergy is more common than generally recognized. In published surveys, systemic allergic reactions were reported by approximately 3% of adults, while less than 1% of children had severe sting reactions.^{27, 56} The frequency of large local reactions is uncertain but is estimated at 10% in adults. There are at least 50 fatal sting reactions each year in the United States and many other sting fatalities are probably unrecognized.^{1, 54} The presence of IgE antibodies to Hymenoptera venom is not unusual, however. Recent surveys suggest that allergic sensitization is common: over 30% of adults stung in the previous 3 months showed venom-specific IgE by skin test or RAST, and over 20% of all adults tested positive.²⁷ Other reports have confirmed that venom skin tests and RAST may be positive in 20% of normal adults.^{40, 49, 58, 62} In these normal

adults with asymptomatic sensitization, sensitivity is often transient, disappearing more rapidly than in patients with a history of anaphylaxis. Although the venom-specific IgE became undetectable in 50% of subjects after 3 to 5 years in one study, those who remained positive had a 15% to 20% risk of a systemic reaction to a sting.²⁶ Nevertheless, there is no valid screening test to identify the risk before any severe reaction occurs because of the large number of normal adults with positive skin tests who will never experience a severe reaction. Of equal importance in the author's epidemiologic studies was the observation that most affected individuals never seek medical attention. A review of medical records yields an underestimated prevalence of insect hypersensitivity and points to the need for better public education and to the value of a complete medical history.

The natural history of Hymenoptera venom sensitivity is crucial to clinical decision making but only in the last 20 years has data become available. The lack of natural history information resulted in the previous erroneous conclusion that whole body extract therapy was effective in the prevention of anaphylaxis. The apparent efficacy of whole body extracts was overestimated because many low-risk patients were studied along with patients who had recent sting anaphylaxis. The risk of systemic reaction for high-risk patients is 40% to 70% with sting challenges, even though the nonreactors may react to subsequent stings.^{2, 5, 13, 24, 38, 47, 48, 55, 60} Lower-risk patient groups include most children (because most have had strictly cutaneous sting reactions)^{51, 52, 59} and patients with large local reactions.^{33, 34, 44}

Most patients exhibit a characteristic and individual pattern of anaphylaxis that varies only slightly in severity from one sting to another. This predictability of the pattern of reaction also is found in food and drug reactions. It is of special interest that the frequency of recurrent systemic sting reactions is much lower in children. 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.^{51, 59}

The recurrence rate of large local sting reactions is not known but is probably high. A history of large local reactions, however, clearly does not predict progression to systemic reactions, as the risk of eventual anaphylaxis in large local reactors is only 5% to 10%.^{10, 19, 33, 44} Most of these individuals consistently have large local reactions on repeated stings, and some have family members who have had systemic reactions. Factors favoring a systemic reaction include multiple stings or single, sequential 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 with venom skin tests or RAST often showing a higher level of sensitivity in large local reactors than in systemic reactors.

Individuals with asymptomatic sensitization (positive venom skin test or RAST with no history of allergic sting reaction) serve as the obvious reservoir of candidates for a *first-time* systemic reaction to a future sting, but such individuals would normally be unaware of their sensitization since venom allergy testing is not indicated in persons with no prior history of a systemic reaction to a sting. This recommendation is based on the observation that one out of four normal adults has detectable venom-specific IgE antibodies, so the predictive value of the skin test in the absence of a positive history is low. Long-term observation of such individuals was possible in the author's epidemiologic studies of the natural history of venom sensitivity and insect sting allergy. In that study, the previously asymptomatic subjects with persistently positive venom skin tests had a 17% incidence of systemic reactions to subsequent stings, regardless of whether they were stung after 1 to 4 years or after 5 to 9 years.²⁶ In the same study, the venom skin tests become negative in 30% after 2 years and in an estimated 50% after 3 years. 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 owing to a lack of an intervening sting. Even among those who are stung, more than 50% will have no systemic reaction. It is, therefore, not surprising to find an historic prevalence of systemic reactions of 3.3%, despite a prevalence of immunologic sensitivity of 26%.

Because of the strong indications for immunotherapy in patients with a history of previous systemic reactions, there have been few long-term studies of the natural history of venom sensitivity in such individuals. In untreated patients who had only large local sting reactions, and in patients who stopped venom therapy against medical advice after only 12 to 24 months, venom sensitivity (5 years after the original evaluation) decreased in 60% of patients, and became negative in about 15%.^{10, 17} Skin-test results were similar in patients who completed 5 to 9 years of therapy (mean, 6 years), were negative in 20%, and showed a 10-fold decline in sensitivity in 95% of patients. After stopping venom injections these patients continued to show decreasing sensitivity with negative skin tests (at 1.0 $\mu\text{g/mL}$) and IgE (RAST) of 1 ng/mL or less in 45% to 60% after 2 additional years off treatment (mean 8 years after original evaluation).²² In other studies of untreated children and young adults, skin tests or RAST became negative in 25% to 50% after an average of 10 years.^{48, 50}

There are many variables that may affect the frequency and rate of decline of venom sensitivity. The passage of time is an important factor because venom allergy is self-limited in many cases. Venom-specific IgE antibodies identified by skin tests and RAST show a similar decline in treated and untreated patients observed for up to 10 years.²³ In treated patients who had at least 5 years of therapy, the risk of systemic reactions to inadvertent stings is 2% to 10% after 8 to 10 years. Interim stings

cause a transient increase of venom-specific IgE but do not prevent the continued decline of sensitivity.²³ Another long-term study indicates a risk of 10% per sting 10 to 15 years after discontinuing treatment, even in patients whose last known skin test was negative.¹² In untreated "high-risk" patients, however, the risk of reaction declines from 50% initially to 35% after 3 to 5 years to 20% after 10 to 20 years.^{15, 23, 47} It is important to note that there are individuals in whom the risk of anaphylaxis persists for decades even without intervening stings.

The possibility that children routinely "outgrow" sting reactivity was suggested 20 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 (personal communication). Some surveys indicate up to 50% loss of sensitivity over a 10-year period in children and young adults.^{32, 50} In a follow-up of the hundreds of children evaluated in the program 15 to 20 years ago, the author reported a survey of treated and untreated children with mild and severe reactions.¹⁹ The frequency of systemic reaction to subsequent stings was higher in untreated (15%) than treated (4%) subjects. Among the untreated patients, the reaction rate was higher in those with a history of moderate-to-severe reactions (36%) than in patients with milder reactions (11%). These are the first results suggesting a long-term benefit of venom immunotherapy in childhood with lower reaction rates persisting into adulthood.

ADMINISTRATION OF VENOM IMMUNOTHERAPY

Indications

Venom immunotherapy is the preventative treatment of choice for insect sting hypersensitivity. Successful venom immunotherapy requires the careful selection of patients, a period of initial treatment to induce a protective immune state, regular monitoring during maintenance therapy and long-term decisions about discontinuation. Current indications for venom immunotherapy (summarized in Table 2) require a history of

Table 2. CLINICAL RECOMMENDATIONS BASED ON HISTORY OF STING REACTIONS AND RESULTS OF VENOM SKIN TEST OR RAST

Reaction to Previous Sting	Skin Test or RAST	Risk of Systemic Reaction	Clinical Advice
No reaction	Positive	15%	Avoidance
Large local	Positive	10%	Avoidance
Cutaneous systemic	Positive—Child	1%–10%	No VIT
	Positive—Adult	20%	VIT
Anaphylaxis	Positive	60%	VIT
	Negative	Unknown	Repeat skin test and RAST

VIT = venom immunotherapy

previous systemic allergic reaction to a sting and evidence of a positive venom skin test. Patients with a negative skin test are not eligible regardless of history: they may have lost sensitivity or, less commonly, have non-IgE-mediated reactions. Some patients with positive skin tests do not need venom immunotherapy because they are judged to be at low risk for life-threatening anaphylaxis. Epidemiologic studies have helped to estimate the risk of reaction. The highest risk, in those with a recent history of anaphylaxis and a positive skin test, is 40% to 70% since only about half of these individuals react to a challenge sting. A low risk of anaphylaxis (<10%) has been found in some clinical subgroups such as children and adults with a history of large local reactions, or children with reactions limited to cutaneous signs and symptoms (i.e., no respiratory, cardiovascular, abdominal, or neurologic manifestations). In these cases, venom immunotherapy is not required, but some patients will still request treatment because of their fear of reaction and the impact on their lifestyle. There are insufficient data on the risk of anaphylaxis in adults with strictly cutaneous reactions, especially since this presentation is unusual in adults but predominates in children. Adults with cutaneous systemic reactions are still advised to undergo venom immunotherapy because of case reports of progression in adults from cutaneous reactions to life-threatening anaphylaxis on subsequent stings. Unfortunately, for large local and cutaneous systemic reactors, there is no test that predicts which patients will progress to more severe reactions. The decision regarding immunotherapy is complicated by factors that, in some cases, may reduce the risk of anaphylaxis. When the sting reaction was more than 10 years ago, especially when intervening stings have caused little or no reaction, even a positive skin test is not always convincing enough to require venom immunotherapy. Some patients report reactions only with multiple or sequential stings but not from isolated single stings.¹³

Initiating Treatment

Initial venom immunotherapy follows a schedule that may vary according to the recommendations of the source laboratory that has prepared the allergen extract and with the training and background of the treating physician. The common "modified rush" regimen is more rapid than traditional regimens, achieving maintenance dose in 8 weekly injections instead of the 4- to 6-month regimens that are more commonly used for inhalant allergen immunotherapy. Adverse reactions are not more common with the more rapid regimen than with traditional regimens of allergen immunotherapy. The mean venom-specific IgE antibody response is greater and more rapidly achieved with the more rapid regimen, although both regimens are equally effective in long-term comparisons.²⁹ The recommended maintenance dose is 100 µg of each venom that elicited a positive skin test. Lower doses are immunologically ineffective in 15% to 20% of patients whereas standard therapy

with mixed vespid venom is at least 98% effective in completely preventing the systemic allergic reaction.²⁰ Single venom therapy (e.g., honeybee or wasp) has been reported to give full protection in 85% of cases, and some individuals have needed a higher dose.^{20, 61} The recommended dose for children age 3 and over is the same as the adult dose. There are few reports of half-dose therapy in children, although their IgE immune response to venom immunotherapy is double that of adults (Fig. 1).¹⁸

The selection of venom vaccines to be used for immunotherapy is dependent on the venom skin test reaction to those venoms. Therapy should include all that are positive, because assurance of not reacting to the next sting is not possible without therapy if the skin test is positive. For this reason, the most common therapy when vespids are involved is with the mixed vespid venoms preparation (equal parts yellow jacket, yellow hornet, and white-faced hornet venoms). Although therapy with yellow-jacket venom alone protects against hornet stings because of the cross-reactivity of the *Vespula* venoms, there are reports that therapy with any single venom gives 15% to 20% less immune response and less reliable clinical protection than mixed-vespid venoms.³⁰ The three component venoms in mixed-vespid venom provide twice the amount of yellow-jacket allergen than single venom administration. The skin test

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Figure 1. Yellow-jacket venom-specific IgG antibody concentration ($\mu\text{g/mL}$, mean $\pm$ standard error of mean [SEM]) during venom immunotherapy in children (*dashed line*) and adults (*solid line*). Sample size (n) for each point shown in parentheses. (From Golden DBK, Valentine MD: Allergen-specific IgG antibody measurements in the management of immediate hypersensitivity to Hymenoptera venoms. *J Clin Immunoassay* 6:172, 1983; reprinted from reference 28a, p 172, by courtesy of Marcel Dekker, Inc.)

also is positive to *Polistes* wasp venoms in at least 50% of vespid-allergic patients; when positive it is usually included in therapy as a separate injection. Therapy with yellow-jacket or mixed-vespid venoms can protect against wasp stings, but this has only been established for patients whose wasp-IgE showed complete cross-reactivity with yellow-jacket venom as assessed by RAST inhibition.^{30, 35}

Fire-ant immunotherapy is less well characterized because the natural history of fire-ant allergy is still unclear.⁴ There is, however, an increasing need for effective immunotherapy. Trials suggest that fire-ant whole body extract immunotherapy is reasonably safe and effective and should be employed in cases of significant systemic reaction. Fire-ant whole body vaccines, in contrast to other Hymenoptera whole body vaccines, contain the venom allergens in sufficient concentration. More reliable clinical protection with improved safety is the goal of current studies to develop the fire-ant venoms for clinical diagnostic and therapeutic use.

The incidence of adverse reactions to venom is similar to that reported for inhalant allergen immunotherapy (see article by Kemp elsewhere in this issue).^{29, 43} Systemic symptoms occur in 5% to 15% of patients during the first weeks of treatment, regardless of the regimen used. Most reactions are mild, and fewer than 5% require epinephrine. In the unusual case of recurrent systemic reactions to injections, therapy may be streamlined to a single venom and given in divided doses, 30 minutes apart. Rarely, therapy is suspended for 6 to 12 months to facilitate advancement toward protective maintenance doses. Large local reactions occur in up to 50% of patients, especially in the dose range of 20 to 50 μ g. Attaining the uniform target dose of venom immunotherapy may result in local reactions larger (8–10 cm) than generally accepted during inhalant immunotherapy.

Maintenance Treatment

Maintenance therapy is administered every 4 weeks for at least a year and, in most cases, may then be given at intervals of 6 to 8 weeks over several years.^{8, 21} The ideal test for confirming immune protection has not been developed. Assays for venom-specific IgG correlate with clinical protection but cannot accurately predict the outcome of every sting in every individual. The test is used to confirm protective levels after initiating therapy and then to verify that the venom-IgG level is adequately maintained at the longer intervals used for maintenance treatment. In one study, the IgG level was considered protective with more than 3 μ g/mL serum levels during the first 4 years of maintenance therapy, but protection was independent of the IgG after 4 years of treatment when other mechanisms of action become more important.²⁵ Ideally, the IgG should achieve levels more than 5 μ g/mL when the monthly maintenance dose is first reached at 4 to 6 months. During long-term maintenance therapy, repeat skin tests or RASTs may be performed every 2 to 3 years to monitor for a significant decline in venom-IgE. Skin tests generally remain unchanged in the first 2 to 3

years but show a significant decline after 4 to 6 years. Less than 20% of patients are skin test negative after 5 years, but 50% to 60% become negative after 7 to 10 years.²² The venom-specific IgE and IgG antibody concentrations during venom immunotherapy are shown in Figure 2. Venom-specific IgE antibody averages 10 ng/mL in adults and 20 ng/mL in children before immunotherapy. The venom-specific IgE usually increases in the first months of therapy, returns to baseline after 12 months, and then declines steadily during maintenance treatment. This decline continues even after therapy is stopped or after a sting.^{18, 23} The venom-IgG level is well-maintained during maintenance treatment, declining only slowly during 5 years of therapy.

Discontinuing Treatment

The ideal duration of venom immunotherapy still is not defined. The question is no longer whether venom immunotherapy may be discontinued, but when and with what risk factors.³¹ The original recommendations, approved for the product insert in the United States, were that therapy should be continued indefinitely. Although treatment could be stopped if sensitivity disappears on RAST or skin test, this occurs in

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Figure 2. Yellow-jacket venom-specific IgE (*dashed line*) and IgG (*solid line*) antibody responses during 5 years of venom immunotherapy with mixed vespid venoms. (From Golden DBK, Lichtenstein LM: Insect sting allergy. In Kaplan AP (ed): Allergy. New York, Churchill Livingstone, 1985; with permission.)

only 20% of those treated for 5 years, 50% at 8 years, and up to 66% of those observed for 10 years.^{16, 22, 23, 31, 32, 47} The risk of systemic sting reaction in untreated, venom-allergic patients declines with time but remains in the range of 25% to 40% after 5 to 8 years and 20% to 30% after 7 to 12 years. If stopping venom immunotherapy allows the risk to return to this level, it may be preferable, in some cases, to continue maintenance therapy. Skin-test positive patients who prematurely discontinue therapy after 1 to 2 years still have a substantial risk of systemic reaction to a sting.^{17, 48} A study of over 100 adults and children shows that, despite the persistent presence of venom-specific IgE, venom immunotherapy may be stopped after 5 years with a 5% to 10% risk of systemic symptoms after a sting and only a 2% risk of a reaction requiring epinephrine treatment.²³ It is reassuring that, after stopping venom immunotherapy, the venom-IgE and skin tests decline steadily with time and show no persistent increase after challenge stings (Fig. 3). Venom-IgG levels fall to subtherapeutic levels, less than 3 $\mu\text{g/mL}$, within months of discontinuing long-term therapy, but clinical protection from reaction to a sting persists by some mechanism other than IgG. Current immunologic evidence supports the hypothesis that a cellular suppression is induced by 4 or 5 years of high-dose immunotherapy. Patients

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Figure 3. Mean venom 2+ skin test sensitivity (*solid line*) and venom-specific IgE antibody level (*dashed line*) shown before venom immunotherapy (–6 years), after a mean of 6 years of treatment (0 years), and 2, 4, and 5 years after stopping therapy. (From Golden DBK, Kwiterovich KA, Kagey-Sobotka A, et al: Discontinuing venom immunotherapy: Outcome after 5 years. *J Allergy Clin Immunol* 97:579, 1996; with permission.)

who lose protection after stopping venom immunotherapy were often those who experienced a systemic reaction to a sting, or to an immunotherapy injection, during treatment. Patients who have a systemic reaction to a sting after discontinuation also show less decrease in skin-test reactivity or RAST during treatment and a greater increase of venom-IgE after a sting.^{14, 22, 42, 45} These observations all indicate that the patients most likely to have adverse reactions during or after therapy are those whose allergic response is not as well suppressed by immunotherapy.

Long-term observations demonstrate a 10% sting reaction rate 10 to 15 years after discontinuation of immunotherapy. A few patients experience systemic reactions despite a negative venom skin test when immunotherapy is discontinued.^{12, 22} Some patients have no reaction to one sting after discontinuing therapy but experience systemic reactions to subsequent stings, which leads to an increase with time of the total number of patients who have had a sting reaction after discontinuation. This is the reason that the cumulative reaction rate is now reported to be up to 16.7% after 10 to 15 years off treatment. Figure 4 depicts the risk of systemic reaction to a sting over 10 to 15 years for untreated and

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Figure 4. Natural history of insect sting allergy showing the risk of systemic reaction to a sting in untreated patients (*solid line*), and during and after treatment in patients who received venom immunotherapy for a duration of either 1 to 2 years (*dotted line*) or for a mean of 6 years (*dashed line*). (From Golden DBK, Kagey-Sobotka A, Lichtenstein LM: Survey of patients after discontinuing venom immunotherapy. *J Allergy Clin Immunol* 105:385–390, 2000; with permission.)

treated patients. Without treatment, the risk declines gradually during that time to approximately 25%, whereas the risk remains only 2% during maintenance venom immunotherapy. Although the cumulative risk after stopping treatment approaches the rate observed in patients who were never treated, this lack of long-term benefit is contrasted with the reduction of reaction rate to only 2% during the years of highest risk when untreated patients had a 30% to 60% reaction rate. The only way to maintain the minimal reaction rate of 2% is to continue immunotherapy indefinitely, an option appealing to some patients and consistent with the current product package insert.

SUMMARY

Elucidation of the natural history of insect sting allergy is critical to the development of guidelines and practice parameters for the evaluation and prevention of insect sting anaphylaxis. There remains a need for long-term observations and correlations that may yet provide the indicator of clinical and immunologic factors that accurately predict the individual patient's risk of anaphylaxis to future stings. One goal to consider is the identification of subjects at risk for insect sting anaphylaxis even before the first event.

References

1. Barnard JH: Studies of 400 Hymenoptera sting deaths in the United States. *J Allergy Clin Immunol* 52:259, 1973
2. Blaauw PJ, Smithuis LOMJ: The evaluation of the common diagnostic methods of hypersensitivity for bee and yellow jacket venom by means of an in-hospital insect sting. *J Allergy Clin Immunol* 75:556, 1985
3. Insect Allergy Committee of the American Academy of Allergy: Insect sting allergy: Cooperative study. *JAMA* 193:115, 1965
4. DeShazo RD, Butcher BT, Banks WA: Reactions to the stings of the imported fire ant. *N Engl J Med* 323:462, 1990
5. Franken HH, Dubois AEJ, Minkema HJ, et al: Lack of reproducibility of a single negative sting challenge response in the assessment of anaphylactic risk in patients with suspected yellow jacket hypersensitivity. *J Allergy Clin Immunol* 93:431, 1994
6. Fricker M, Helbling L, Schwartz L, et al: Hymenoptera sting anaphylaxis and urticaria pigmentosa: Clinical findings and results of venom immunotherapy in ten patients. *J Allergy Clin Immunol* 100:11, 1997
7. Gadde J, Golden DBK, Kagey-Sobotka A, et al: Skin test sensitivity to purified vespid venom allergens. *J Allergy Clin Immunol* 73:159, 1984
8. Gadde J, Sobotka A, Valentine MD, et al: Intervals of six and eight weeks in maintenance venom immunotherapy. *Annals of Allergy* 54:348, 1985
9. Goldberg A, Confino-Cohen R: Timing of venom skin tests and IgE determinations after insect sting anaphylaxis. *J Allergy Clin Immunol* 100:183, 1997
10. Golden DBK, Johnson K, Addison B, et al: Evolution of Hymenoptera venom allergy. *J Allergy Clin Immunol* 73:159, 1984
11. Golden DBK, Kagey-Sobotka A, Bailey D, et al: Sting challenge trial IV: The history-

- positive skin test-negative patient [abstract]. *J Allergy Clin Immunol* 105:S376-S377, 2000
12. Golden DBK, Kagey-Sobotka A, Lichtenstein LM: Survey of patients after discontinuing venom immunotherapy. *J Allergy Clin Immunol* 105:385-390, 2000
 13. Golden DBK, Kagey-Sobotka A, Norman PS, et al: Sting Challenge Trial I: Spectrum of a population with insect sting allergy [abstract]. *J Allergy Clin Immunol* 101:5159, 1998
 14. Golden DBK: Immunotherapy for Hymenoptera stings. In Bierman CW, Pearlman DS, Shapiro GG, et al (eds): *Allergy Asthma and Immunology from Infancy to Adulthood*, ed 2. Philadelphia, WB Saunders, 1996, p 348
 15. Golden DBK, Addison BI, Blake K, et al: Discontinuing venom immunotherapy: Immunologic and clinical criteria. *J Allergy Clin Immunol* 79:126, 1987
 16. Golden DBK, Addison BI, Gadde J, et al: Prospective observations on patients who discontinue venom immunotherapy. *J Allergy Clin Immunol* 84:162, 1989
 17. Golden DBK, Johnson K, Addison BI, et al: Clinical and immunologic observations in patients who stop venom immunotherapy. *J Allergy Clin Immunol* 77:435, 1986
 18. Golden DBK, Kagey-Sobotka A, Hamilton RG, et al: Human immune response to Hymenoptera venoms. *J Allergy Clin Immunol* 71:140, 1983
 19. Golden DBK, Kagey-Sobotka A, Norman PS, et al: Do children outgrow insect sting allergy [abstract]? *J Allergy Clin Immunol* 103:S182, 1999
 20. Golden DBK, Kagey-Sobotka A, Valentine MD, et al: Dose dependence of Hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 67:3704, 1981
 21. Golden DBK, Kagey-Sobotka A, Valentine MD, et al: Prolonged maintenance interval in Hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 67:482, 1981
 22. Golden DBK, Kwitrovich KA, Addison BA, et al: Discontinuing venom immunotherapy: Extended observations. *J Allergy Clin Immunol* 101:298, 1998
 23. Golden DBK, Kwitrovich KA, Kagey-Sobotka A, et al: Discontinuing venom immunotherapy: Outcome after 5 years. *J Allergy Clin Immunol* 97:579, 1996
 24. Golden DBK, Langlois J, Valentine MD: Treatment failures with whole body extract therapy of insect sting allergy. *JAMA* 246:2460, 1981
 25. Golden DBK, Lawrence ID, Kagey-Sobotka A, et al: Clinical correlation of the venom-specific IgG antibody level during maintenance venom immunotherapy. *J Allergy Clin Immunol* 90:386, 1992
 - 25a. Golden DBK, Lichtenstein LM: Insect sting allergy. In Kaplan AP (ed): *Allergy*. New York, Churchill Livingstone, 1985
 26. Golden DBK, Marsh DG, Freidhoff LR, et al: Natural history of Hymenoptera venom sensitivity in adults. *J Allergy Clin Immunol* 100:760, 1997
 27. Golden DBK, Marsh DG, Kagey-Sobotka A, et al: Epidemiology of insect sting allergy. *JAMA* 262:240, 1989
 28. Golden DBK, Schwartz HJ: Guidelines for venom immunotherapy. *J Allergy Clin Immunol* 77:727, 1986
 - 28a. Golden DBK, Valentine MD: Allergen-specific IgG antibody measurements in the management of immediate hypersensitivity to Hymenoptera venoms. *J Clin Immunology* 6:172, 1983
 29. Golden DBK, Valentine MD, Kagey-Sobotka A, et al: Regimens of Hymenoptera venom immunotherapy. *Ann Intern Med* 92:620, 1980
 30. Golden DBK, Valentine MD, Kagey-Sobotka A, et al: Cross-reactivity of vespid venoms. *J Allergy Clin Immunol* 67:57, 1981
 31. Graft DF, Golden DBK, Reisman RE, et al: The discontinuation of Hymenoptera venom immunotherapy: Report from the Committee on Insects of the American Academy of Allergy Asthma and Immunology. *J Allergy Clin Immunol* 101:573, 1998
 32. Graft DF, Schuberth KC, Kagey-Sobotka A, et al: The development of negative skin tests in children treated with venom immunotherapy. *J Allergy Clin Immunol* 73:61, 1984
 33. Graft DF, Schuberth KC, Kagey-Sobotka A, et al: A prospective study of the natural history of large local reactions following Hymenoptera stings in children. *J Pediatr* 104:664, 1984
 34. Green A, Reisman R, Arbesman C: Clinical and immunologic studies of patients with large local reactions following insect stings. *J Allergy Clin Immunol* 66:186, 1980

35. Hamilton RH, Wisenauer JA, Golden DBK, et al: Selection of Hymenoptera venoms for immunotherapy based on patients' IgE antibody cross-reactivity. *J Allergy Clin Immunol* 92:651, 1993
36. Hoffman DR: Allergens in Hymenoptera venom: XXV. The amino acid sequence of Antigen 5 molecules: The structural basis of antigenic crossreactivity. *J Allergy Clin Immunol* 92:707, 1993
37. Hoffman DR, Dove DE, Moffitt JE, et al: Allergens in Hymenoptera venom: XXI. Cross-reactivity and multiple reactivity between fire ant venom and bee and wasp venoms. *J Allergy Clin Immunol* 82:828, 1988
38. Hunt KJ, Valentine MD, Sobotka AK, et al: A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 299:157, 1978
39. Hunt KJ, Valentine MD, Sobotka AK, et al: Diagnosis of allergy to stinging insects by skin testing with Hymenoptera venoms. *Ann Intern Med* 85:56, 1976
40. Jarish R, Zajc J, Buzath A: The risk of sensitization of non-allergic persons to bee venom. *Arch Dermatol Res* 273:173, 1982
41. King T, Valentine M: Allergens of Hymenopteran venoms. *Clin Rev Allergy* 5:137, 1987
42. Lerch E, Muller U: Long-term protection after stopping venom immunotherapy. *J Allergy Clin Immunol* 101:606, 1998
43. Lockey RF, Turkeltaub PC, Olive ES, et al: The Hymenoptera venom study III: Safety of venom immunotherapy. *J Allergy Clin Immunol* 86:775, 1990
44. Mauriello PM, Barde SH, Georgitis JW, et al: Natural history of large local reactions from stinging insects. *J Allergy Clin Immunol* 74:494, 1984
45. Muller U, Berchtold E, Helbling A: Honeybee venom allergy: Results of a sting challenge 1 year after stopping venom immunotherapy in 86 patients. *J Allergy Clin Immunol* 87:702, 1991
46. Oude-Elberink J, deMonchy J, Kors J, et al: Fatal anaphylaxis after a yellow jacket sting despite venom immunotherapy in two patients with mastocytosis. *J Allergy Clin Immunol* 99:153, 1997
47. Reisman RE: Natural history of insect sting allergy: Relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions. *J Allergy Clin Immunol* 90:335, 1992
48. Reisman RE, Dvorin DD, Randolph CC, et al: Stinging insect allergy: natural history and modification with venom immunotherapy. *J Allergy Clin Immunol* 75:735, 1985
49. Reisman RE, Georgitis JW: Frequency of positive venom skin tests in insect-allergic and non-allergic populations. *J Allergy Clin Immunol* 73:187, 1984
50. Savliwala MN, Reisman RE: Studies of the natural history of stinging-insect allergy: Long-term follow-up of patients without immunotherapy. *J Allergy Clin Immunol* 80:741, 1987
51. Schuberth KC: Discontinuing venom immunotherapy in skin test positive children. *J Allergy Clin Immunol* 79:126, 1987
52. Schuberth KC, Valentine MD, Kagey-Sobotka A, et al: An epidemiologic study of insect allergy in children: Characteristics of the disease. *J Pediatr* 100:546, 1982
53. Schwartz HJ, Lockey RF, Sheffer AL, et al: A multicenter study on skin test reactivity of human volunteers to venom as compared with whole body Hymenoptera antigens. *J Allergy Clin Immunol* 67:81, 1981
54. Schwartz HJ, Sutheimer C, Gauerke B, et al: Venom-specific IgE antibodies in post-mortem sera from victims of sudden unexpected death. *J Allergy Clin Immunol* 73:189, 1984
55. Settiple GA, Chafee FH: Natural history of allergy to Hymenoptera. *Clin Allergy* 9:385, 1979
56. Settiple GA, Newstead GJ, Boyd GK: Frequency of Hymenoptera allergy in an atopic and normal population. *J Allergy* 50:146, 1972
57. Sobotka A, Valentine M, Benton A, et al: Allergy to insect stings: I. Diagnosis of IgE-mediated Hymenoptera sensitivity by venom-induced histamine release. *J Allergy Clin Immunol* 53:110, 1974
58. Stuckey M, Cobain T, Sears M, et al: Bee venom hypersensitivity in Busselton. *Lancet* 2:41, 1982

59. Valentine MD, Schuberth KC, Kagey-Sobotka A, et al: The value of immunotherapy with venom in children with allergy to insect stings. *N Engl J Med* 323:1601, 1990
60. vanderLinden PG, Hack CE, Struyvenberg A, et al: Insect-sting challenge in 324 subjects with a previous anaphylactic reaction: Current criteria for insect-venom hypersensitivity do not predict the occurrence and the severity of anaphylaxis. *J Allergy Clin Immunol* 94:151, 1994
61. Yunginger JW, Dahlberg ME, Jones RT, et al: Diagnostic and therapeutic importance of individual honeybee venom allergens. *J Allergy Clin Immunol* 69:139, 1982
62. Zora JA, Swanson M, Yunginger JW: How common is unrecognized Hymenoptera venom allergy in the general population? *J Allergy Clin Immunol* 73:139, 1984

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