

Current reviews of allergy and clinical immunology

(Supported by a grant from GlaxoSmithKline, Inc, Research Triangle Park, NC)

Series editor: Harold S. Nelson, MD

Insect sting allergy and venom immunotherapy: A model and a mystery

David B. K. Golden, MD *Baltimore, Md*

This activity is available for CME credit. See page 28A for important information.

Whole-body extracts of Hymenoptera were used for diagnosis and treatment until controlled clinical trials proved them no better than placebo, whereas venom is 85% to 98% effective. Studies of natural history reveal why whole-body extracts were thought to work. The chance of future systemic reactions is low in large local reactors and in most children and varies between 20% and 70% in adults. Venom skin tests are most accurate, but RAST is an important complementary test. The degree of sensitivity on skin tests or RASTs does not reliably predict the severity of a sting reaction. Venom immunotherapy is recommended for patients at high risk for sting reactions. Rapid regimens are as safe as slower regimens. The recommended dose is 100 µg, but some patients require higher doses for full protection. Venom immunotherapy is continued every 4 to 8 weeks for at least 5 years in most cases. Skin test results become negative in only 25% after 5 years of therapy but in 60% to 70% after 7 to 10 years. When treatment is stopped after 5 years or more, there is a 10% chance of systemic reaction to each future sting, but most reactions are mild. Some patients have a higher risk of relapse and should continue treatment for an extended period. (*J Allergy Clin Immunol* 2005;115:439-47.)

Key words: *Venom immunotherapy, insect sting, Hymenoptera, anaphylaxis, immunotherapy*

Allergic reactions to stinging insects of the order Hymenoptera have been recognized for millennia, but only in the last century have they been subject to scientific investigation. Since we began our investigations at Johns Hopkins more than 30 years ago, the diagnosis and treatment of insect sting allergy has been viewed as

Abbreviations used

VIT: Venom immunotherapy
WBE: Whole-body extract

a model in many ways.¹ As a model of anaphylaxis, insect sting allergy illustrates most of the dilemmas in the immunology, pathophysiology, diagnosis, and prevention of anaphylaxis.² This condition and its treatment have also been a model for the use of standardized allergens, a model for allergen challenge procedures, and a model for the study and application of immunotherapy. After 3 decades, this model has lived up to many of these expectations, but some mysteries remain.³

The spectrum of reactions to insect stings includes nonallergic pain, itching and swelling, and allergic reactions. Localized allergic swelling (large local reaction) is a late-phase IgE-dependent reaction that develops after 12 to 48 hours to a diameter often exceeding 15 cm and subsiding slowly over 5 to 10 days. These reactions cause great morbidity but are only dangerous if the sting occurs in the oropharynx. Systemic allergic reactions might be limited to cutaneous manifestations (generalized urticaria, angioedema, flushing, or pruritus) or can be more severe with involvement of the airway (laryngeal edema or asthma) or circulation (hypotensive shock). Less common systemic manifestations include abdominal or pelvic pain and cardiac changes (bradycardia, tachyarrhythmias, or coronary vasospasm). Biphasic or protracted anaphylaxis can occur and is generally associated with the most severe reactions.

Allergic reactions to stings cause significant morbidity, cause impairment in quality of life, and are sometimes fatal. In a study of 400 fatal sting reactions, Barnard⁴ found that many occurred in individuals with no previous abnormal reactions to stings. Although fatalities occurred mostly in those older than 40 years, they can also affect children. The estimated incidence of 40 fatal reactions each year in the United States is probably an underestimate

From Johns Hopkins Asthma and Allergy Center.

Supported by National Institutes of Health grant AI08270 and National Institutes of Health GCRC grant 5MO1-RR02719.

Disclosure of potential conflict of interest: D. B. K. Golden—none disclosed. Received for publication November 21, 2004; accepted for publication December 22, 2004.

Reprint requests: David B. K. Golden, MD, Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Blvd, Baltimore, MD 21224. E-mail: dgolden1@jhmi.edu.

0091-6749/\$30.00

© 2005 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2005.01.005

because of the failure to recognize or report many fatal reactions. Postmortem studies identified both increased tryptase levels and venom-specific IgE antibodies in the serum of many healthy individuals who experienced unexplained summertime deaths.^{5,6}

HISTORICAL PERSPECTIVE

An early investigation of insect sting allergy by Benson and Semenov⁷ reasoned that because beekeepers demonstrated allergic sensitivity to both body proteins and venom, the allergenic component ("intrinsic bee protein") must be present in both. On this basis, whole-body extract (WBE) therapy became the standard treatment for prevention of allergic reactions to stings for almost 50 years. Loveless and Fackler⁸ challenged this when they demonstrated the efficacy of venom. Their unorthodox approach (including live stings in Loveless' courtyard) and uncontrolled studies did not succeed in changing the standard of practice. Even the American Academy of Allergy endorsed WBE therapy in 1965 on the basis of the observation that most treated individuals had less severe reactions to stings.⁹ The faults of this analysis did not become apparent until the natural history of insect sting allergy was elucidated.

The efficacy of WBE was questioned in reports of treatment failures, including fatalities.¹⁰ In a retrospective analysis of WBE therapy in 250 patients with previous systemic reactions, 75 of the 115 who were subsequently stung had systemic reactions.¹¹ A tragic fatality in a child led to the successful use of purified venom to prevent anaphylaxis in his sibling.¹² The ensuing program of investigation included the application of laboratory methods to characterize the clinical condition, the development of the first standardized allergen extracts, and a controlled clinical trial of immunotherapy.¹³⁻¹⁶ In that study venom immunotherapy (VIT) prevented systemic reactions to stings in 98% of treated patients. There were several other notable observations in that report that remain a mystery many years later. There was no difference between WBE and placebo in the outcome of sting challenge, but the frequency of systemic reaction was only 60% rather than the expected 100%. Even those who did react to a sting challenge did not react to prior subcutaneous injection of a dose of venom extract antigenically equivalent to multiple stings. Two of the patients who experienced anaphylaxis to a sting challenge required intensive care for an extended period because they showed no response to immediate treatment with large doses of epinephrine and large volumes of intravenous fluids.¹⁷ It was also surprising that one third of the candidates who had a convincing history of systemic sting reaction had to be excluded from the study because they had negative venom skin test responses. These observations led to decades of continuing research. The demonstrated efficacy of VIT led to the approval in 1979 of commercial venom extracts for the diagnosis and treatment of insect sting allergy. Venoms have also been shown to be superior for the prevention of

fire ant allergy, but unlike the other Hymenoptera, fire ant WBE does contain sufficient venom allergens to have acceptable efficacy.¹⁸

For many years, there have been sometimes conflicting popular beliefs that have influenced the treatment decisions and expectations of the lay public and medical professionals. Many assume that someone who had a systemic reaction would certainly react to any future sting, but other affected individuals believe it was a fluke and will not happen again. Many expect that future reactions will be more severe than previous reactions (viz, "the next one will probably kill you"), but others believe that patients always outgrow the allergy and will have milder or no reactions to subsequent stings. It is often assumed that owning an epinephrine injector will prevent any dangerous consequences of a sting. These beliefs have come under scrutiny as research in this area has evolved.

HYMENOPTERA

Although biting insects can cause local allergic swelling, they rarely cause anaphylaxis. Systemic allergic reactions can be caused by several distinct families of the order Hymenoptera: the bees (honeybees and bumblebees), the vespids (yellow jackets, hornets, and wasps), and the stinging ants. Fig 1 shows examples of the honeybee and a common species of *Polistes* wasp. The yellow jacket is shown on the cover of this issue. Fire ants (*Solenopsis* species) have become a rapidly increasing public health hazard in the southeast and south-central United States and in Asia (*Pachycondyla* species), as have harvester ants (*Pogonomyrmex* species) and jack jumper ants (*Myrmecia* species) in other parts of the world.^{19,20} Yellow jackets are the most common causes of allergic reactions to stings in most areas. *Polistes* wasp stings are more common in the Gulf Coast states of the United States and in the Mediterranean countries of Europe. Sensitization to fire ant venom has become the most prevalent stinging insect problem in the southeast United States because of their high attack rate.²¹ Africanized honeybees differ from other honeybees not in their size or venom but in their behavior. Their propensity to swarm and attack has earned them the moniker "killer bees." All the stinging insects are capable of inducing anaphylactic reactions. The stinger remains embedded in the skin after a honeybee sting, but this also occurs with some species of vespids.

Hymenoptera venoms contain protein allergens, as well as nonallergenic components, including toxins, vasoactive amines, acetylcholine, and kinins.²² Among the multiple allergens in Hymenoptera venoms, the major allergen of honeybee venom is phospholipase A2 (Api m 1), and that of the vespid venoms is antigen 5 (Ves v 5). Fire ant venom is a unique suspension of alkaloids containing several allergens. Allergenic cross-reactivity between the Hymenoptera venoms closely follows the entomologic relationships. The yellow jackets and hornets (*Vespula*,



FIG 1. Photographs showing the honeybee (*Apis mellifera*; **A**) and a common species of wasp (*Polistes exclamans*; **B**). Reproduced with permission from Vespa-ALK-Abello Labs.

Dolichovespula, and *Vespa*) are highly cross-reactive. In patients with allergy to *Polistes* venom, less than half show complete cross-reactivity with yellow jacket venom, and honeybee and fire ant venoms show infrequent and limited cross-reactivity with vespid venoms or with venoms of other bees (bumblebee) or stinging ants, respectively. The major protein allergens have been sequenced, and recombinant allergens have been described.²²⁻²⁴

CLINICAL CONSIDERATIONS

Natural history

Sensitization to venom occurs in more than 30% of adults in the weeks after a sting. Venom-specific IgE antibodies to honeybee or yellow jacket were identified in serum or skin in 26% of an adult population, and 3.3%

had a history of systemic reaction to a sting.²⁵ Those who are sensitized but asymptomatic constitute a reservoir of individuals, some of whom will have a systemic reaction for the first time when stung in the future. Sensitization can be self-limited, disappearing in 30% to 50% of cases after 5 to 10 years, but can also persist for decades, even with no intervening sting exposure.²⁶ Asymptomatic sensitization was associated with a 17% incidence of systemic reaction to a subsequent sting. Thus the mere presence of venom-specific IgE antibodies constitutes a risk for future systemic reaction, but no parameter has been identified that can predict which sensitized individuals will ultimately have a systemic reaction.

Once an allergic reaction to a sting has occurred, the risk of a repeat reaction is much higher. The natural history of insect sting allergy has been studied over the past 25

TABLE I. Risk of systemic reaction in untreated patients with a history of sting anaphylaxis and positive venom skin test responses

Original sting reaction		Risk of systemic reaction	
Severity	Age	1-9 y	10-20 y
No reaction	Adult	17%	
Large local	All	10%	10%
Cutaneous	Child	10%	5%
Systemic	Adult	20%	10%
Anaphylaxis	Child	40%	30%
	Adult	60%	40%

Reprinted with permission from Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER, editors. Insect allergy. In: *Middleton's Allergy: Principles and Practice*. 6th ed. St Louis: Mosby; 2003. p. 1475-86.

years. Observations have been reported in relation to the severity of the index reaction and the age of the patient (Table I).^{2,27-29} Future reactions in the same patient usually follow the same pattern, with some variation in severity but not usually in the manifestations.^{11,16,28,29} One of the earliest observations was that children have a much higher proportion than adults of cutaneous systemic reactions (with no respiratory or circulatory manifestations).³⁰ With field stings occurring over a period of 3 to 9 years, only 2% of these children had a sting reaction more severe than the original reaction, and almost 90% had no systemic reaction at all.³¹ In a recent 10- to 20-year follow-up of children with insect allergy, 7% of the children with a history of cutaneous systemic reactions had a more severe reaction to a later sting.³² No one in that cohort of children with mild systemic reactions had a severe reaction to a sting during 5 to 30 years of observation. However, among untreated children who originally had a moderate or severe systemic reaction to a sting, as many as 32% had a systemic reaction to a sting during the extended follow-up survey, and most were moderate or severe.

Adults with a history of systemic reactions to stings have an increased risk of future systemic reactions for an indefinite period of time. Adults with a recent history of severe anaphylaxis have a 60% to 70% chance of reaction to a future sting, but adults with moderately severe systemic reactions have an intermediate risk in the range of 40%, and those with mild systemic reactions might have only a 20% chance of subsequent systemic reactions to stings.^{28,33} The relative risk is also related to the insect species. Patients with honeybee allergy seem to have a risk 1.5 to 2 times greater than that of patients with yellow jacket allergy.^{29,34} The statistical chance of reaction diminishes gradually with time but does not appear to decrease to less than that of asymptomatic sensitized individuals (ie, 15% to 20%).^{11,26,28} Adults and children who have had large local reactions to stings have a 4% to 10% chance of future systemic reactions, which is (inexplicably) less than the 17% frequency reported in individuals with asymptomatic sensitization.^{26,32,35,36}

TABLE II. Projected outcome in 1000 patients, such as those surveyed in 1965, whether treated with WBE or placebo

Previous reaction	N	Subsequent sting reaction*	
		Systemic (%)	Severe/worse (%)
Nonallergic	91	0	0
Large local	133	13 (10)	13 (10)
SR/child/mild	157	16 (10)	5 (3)
SR/child/severe	129	52 (40)	8 (16)
SR/adult/mild	186	37 (20)	5 (3)
SR/adult/severe	304	188 (62)	76 (25)
Total	1000	306 (31)	107 (11) (89% better)

*On the basis of current diagnosis and natural history.
SR, Systemic reaction.

The variability in reaction rates among patients with positive histories and positive skin test results is shown in Table I.

Studies of natural history have provided some insight into why WBEs were endorsed for 50 years as being effective. The patients described in most studies of WBEs included many we now know to be at very low risk for anaphylaxis, including children and large local reactors. Also, many were given diagnoses on the basis of skin tests with WBEs that are actually unable to distinguish allergic from nonallergic patients. Finally, efficacy was defined as a lessening in severity of reaction to a sting (rather than total absence of reaction), which is now known to occur commonly in untreated patients. The combined effect of these factors was a placebo effect, suggesting more than 85% efficacy (Table II). This demonstrates the value of a complete understanding of the natural history of the disease in determining the efficacy and indications for treatment and the importance of controlled clinical trials.

Diagnostic tests

When standardized Hymenoptera venoms were used to develop diagnostic skin tests and serologic tests, they were a model for optimal sensitivity and specificity in allergy diagnosis.^{14,15,37} It has since been recognized that diagnostic venom test results are positive in 15% to 25% of healthy adults and that even patients with a positive history and positive venom skin test responses do not necessarily have allergic reactions to subsequent stings.^{16,25,29} Thus the presence of venom-specific IgE antibodies is not uncommon and must be considered in the context of the clinical history to establish the diagnosis and risk of future reactions. The presence of venom sensitivity without a history of reaction (asymptomatic sensitization) carries a definite, albeit low, risk for future systemic reactions to stings.²⁶ Conversely, a prior history of systemic reaction confers a risk for future reactions, even in patients with negative venom skin test responses. One observation that might be related to the clinical significance of tests for venom-specific IgE antibodies is the fact that a variable proportion of these antibodies are

directed against carbohydrate determinants that cross-react with a variety of foods and inhalants.³⁸

Since the introduction of venom diagnostic tests, it has been evident that, as with other allergens, 15% to 20% of patients with positive skin test responses have negative RAST results.^{14,25} Because of this greater sensitivity, skin tests are the preferred diagnostic test. However, the converse is also true: 5% to 10% of those with negative skin test responses have a positive RAST result (Table III). Among patients with a history of previous allergic reactions who are found to have negative venom skin test responses, many are no longer sensitive to stings, but some will have a subsequent systemic reaction.³⁹ Most of these sting-reactive patients with negative skin test responses have venom-specific IgE detectable in the serum. It is important to use the skin test and serologic tests in a complementary fashion to detect all cases. Even then, approximately 1% of patients with a history of systemic reaction to a sting will have negative skin test and RAST results but will still react to a challenge sting. Although this might occur in relation to mast cell disorders, some cases cannot be explained.⁴⁰ For fire ant allergy, venom is the most accurate diagnostic material, but WBEs have shown adequate diagnostic sensitivity.⁴¹

The degree of sensitivity on diagnostic tests correlates statistically but not reliably with the severity of reactions to stings.^{27,42} For example, large local reactors often have very high levels of venom skin test or RAST sensitivity, but they have a low risk of anaphylaxis. Conversely, some patients with rapid-onset hypotensive shock after a sting are found to have barely detectable sensitivity on testing. It might be possible to improve the diagnostic accuracy of venom tests by the use of dialyzed venom or recombinant allergens.⁴³ It had been suggested that deliberate sting challenge was the best diagnostic test, but this has been judged impractical and unethical.^{29,44} Even when the sting challenge causes no reaction, there remains a 15% to 20% chance of a systemic reaction from a subsequent sting.⁴⁵ Recent developments in cellular diagnostic methodology include measurements of allergen-induced leukotriene release, flow cytometry-based assays, and measurement of basophil activation markers.^{46,47} These techniques have not yet shown improved diagnostic accuracy compared with standard techniques.⁴⁸

Who needs VIT

VIT is indicated in patients with positive venom skin test responses (or positive RAST results) and a history of systemic reaction to a sting.³ It was believed that any patient who meets these criteria is at risk for more severe anaphylaxis from future stings and therefore should be advised to undergo VIT. We now recognize that there is a spectrum of risk in patients with different clinical characteristics and that we must consider the natural history of the condition in our clinical recommendation. In addition, a therapeutic plan should reflect the goals of treatment. VIT should reduce the mortality and morbidity of insect sting allergy and should prevent an impaired quality of life. The ultimate reason to recommend VIT is to

TABLE III. Comparison of venom skin test and RAST results in a healthy adult population

RAST (ng/L)	Venom skin test	
	Positive	Negative
<1 (negative)	9 (24%)	190 (89%)
≥1 (positive)	29 (76%)	23 (11%)
1.0-1.9	8	9
2.0-2.9	5	4
3.0-4.9	4	5
≥5.0	12	5
Total	38	213

Reproduced with permission from Golden DBK, Marsh DG, Kagey-Sobotka A, Addison BI, Freidhoff L, Szkló M, et al. Epidemiology of insect venom sensitivity. JAMA 1989;262:240-4.

prevent fatal anaphylaxis. This is most clear in patients who had a near-fatal reaction. Unfortunately, half of the cases of fatal sting reactions could not be prevented because the patients had no previous history of allergic reactions and therefore were not eligible for VIT.^{4,6} The only available screening test, the venom skin test (or the RAST), can have positive results in 15% to 25% of the population, and more than 80% of those who have been sensitized do not react to future stings.

The risk of nontreatment includes the chance of future stings causing either mild reactions or life-threatening anaphylaxis, as well as impaired health-related quality of life. Prediction of risk on future stings is based primarily on the severity of the past reaction, the level of sensitivity measured by skin test or RAST, the age of the patient, and the degree of exposure (Table I). Risk can only be expressed statistically because no test exists that accurately predicts the outcome of the next sting in each patient. Skin tests, serologic tests, cellular response tests, and sting challenges have all shown limited predictive value. There is a need for professional clinical judgment in the recommendations made to patients. We no longer believe all patients are at the highest risk, but indicators of low risk cannot guarantee that there will be no reaction to a sting. It is difficult to specify what level of statistical risk would justify VIT and what level might be acceptable. Most clinicians judge the risk of systemic reaction acceptable when it is less than 10%, and even when it is 10% to 20%, as in those who have asymptomatic sensitization or who have completed a course of VIT. Clearly, a 40% to 70% chance of systemic reaction is unacceptable, even though not all the reactions will be severe. The intermediate levels of risk (20% to 40%) also seem to be the most prevalent and are generally thought to justify prophylaxis.

Quality of life must be considered, as well as the patient's physical well-being. Quality of life generally improves with VIT and deteriorates when the patient is only given an Epi-Pen.⁴⁹ However, there are patients who simply do not believe they will have a severe reaction, express no fears of future stings, do not engage in excessive avoidance behaviors, and do not have a reduced quality of life. These patients might choose the Epi-Pen

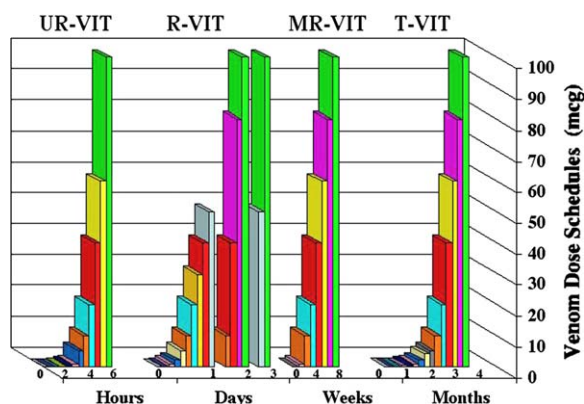


FIG 2. Four dose regimens reported for VIT depicting each dose given during the initial build-up stage of treatment. In the ultrarush schedule (UR-VIT) doses are given every 30 minutes to reach the full dose in 6 hours. In the rush schedule (R-VIT) doses are given every 30 minutes for 10 doses on day 1, 4 doses on day 2, and 2 doses on day 3. The modified rush schedule (MR-VIT) is given once weekly for 8 weeks, and the traditional schedule (T-VIT) is given weekly for 4 months or more.

over VIT and do not show any deterioration of quality of life. Unfortunately, many of those who believe their reaction was a fluke will not seek medical advice and refuse it when offered, even though they might experience anaphylaxis from future stings.

VIT

At the time of its approval by the US Food and Drug Administration 25 years ago, VIT was a model for future allergen immunotherapy.¹ Hymenoptera venoms were the first standardized allergens on the market, with their promise of greater safety and reliable efficacy. It had been demonstrated that clinical protection could be accomplished in less than 2 months with a safety profile similar to that seen with other types of allergen immunotherapy. The dose of the primary allergen (Ves v 5 or Api m 1) administered in each injection is 3 to 8 μ g (8–12 μ g for mixed vespid venom), which is now known to be in the range necessary for optimal clinical response. The efficacy of VIT was reported to be 95%, which is superior to that of any other type of allergen immunotherapy. The original model of VIT relied on a number of assumptions thought to be reasonable at that time. These assumptions (indications, venom species selection, dose, regimen, interval, and duration) are reflected in the product package insert for commercial Hymenoptera venoms in the United States but remain under investigation.

Venom species

It remains prudent to prescribe all venoms resulting in a positive skin test or RAST result. There have been cases in which immunotherapy was targeted toward the primary culprit (1 venom only), but the patient subsequently had reactions to other insects to which they had been previously sensitized. The cross-reactivity of *Polistes* wasp venom with other vespid venoms allows the omission

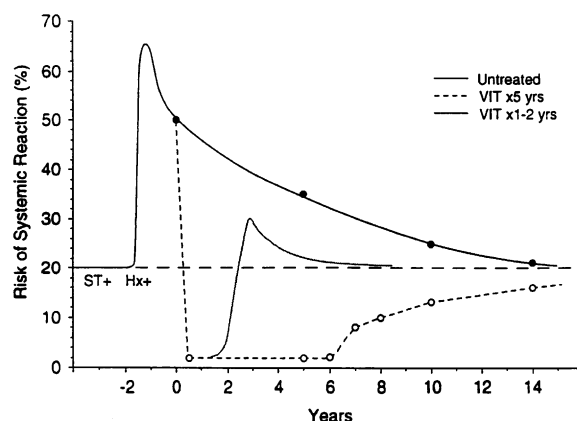


FIG 3. Natural history of insect sting allergy showing the risk of systemic reaction to a sting in untreated patients (solid line) and in patients who received VIT (dashed lines) for a duration of either 1 to 2 years or for a mean of 6 years. Reprinted with permission from Golden DBK, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. *J Allergy Clin Immunol* 2000;105:389.

of wasp venom when the RAST inhibition tests shows complete cross-reactivity (observed in 40% of dual yellow jacket- and wasp-sensitive patients).⁵⁰ Fire ant immunotherapy is performed with WBEs that contain sufficient venom allergens to provide reasonable clinical protection.¹⁸ There are no approved diagnostic or therapeutic extracts for the bumblebee (genus *Bombus*), sweat bee (genus *Halictidae*), or Mediterranean wasp (*Polistes dominulus*), which has become dominant in much of the eastern United States.

Dose and efficacy

VIT has been considered a model for the efficacy of allergen immunotherapy because it can prevent systemic reactions in more than 95% of treated patients. Indeed, there have been few reports of treatment failures, and the only fatalities have been in patients with mastocytosis.⁵¹ The target dose is 100 μ g of each venom in adults and children. Doses lower than 100 μ g are not fully and reliably effective in adults; there are no specific data on the effective dose in children. Although VIT with 300- μ g doses of mixed vespid venom provides 98% efficacy, treatment with 100 μ g of any single venom is less reliably effective.^{52–54} Single vespid venom treatment provides complete protection in 85% to 90% of cases, whereas honeybee VIT is 75% to 85% effective. In patients not fully protected by 100- μ g doses, the response can be improved by administering 150 to 250 μ g of each venom.⁵⁴

Regimen

Many regimens for initial VIT have been reported (Fig 2). The 2 standard regimens in the United States aim to achieve the 100- μ g dose in either 8 weeks or 15 weeks. The regimen used in early studies was described as a “modified rush regimen” in that the target dose was

achieved with 7 to 10 weekly injections, which was intermediate between a 2- to 3-day rush regimen and a 15- to 20-week traditional regimen.⁵⁵ Unlike the reports on inhalant allergen immunotherapy, the more rapid regimens of VIT appear to have the same or greater safety as the traditional regimen.⁵⁶⁻⁵⁸ Rush VIT is indicated in some patients and is routinely used at core treatment centers in Europe, but it is not a readily available option at most medical centers in the United States. There is suggestive evidence that a rush regimen can affect the long-term response, with earlier loss of skin test sensitivity and greater IL-10 response.⁵⁹⁻⁶¹

Safety

Given the severity of insect sting allergy, it is remarkable that VIT is both highly effective and acceptably safe.⁵⁵⁻⁶² The frequency of systemic reactions to VIT is similar to that observed with inhalant allergen immunotherapy, although local swelling is a more frequent problem. One difference that might contribute to both the efficacy and the problems with local swelling is the uniform target dose in VIT. Similar local reactions during inhalant allergen immunotherapy would usually lead to a dose reduction. An increasingly frequent problem is the patient receiving VIT who must take β -blocker medication. Although this is a relative contraindication in VIT, the risk of nontreatment might outweigh the risk of continued treatment.

Interval

The product package insert recommends that VIT should be maintained every 4 weeks for an indefinite period of time. Only a few patients seem to need a 2- to 3-week interval to avoid adverse reactions. There are almost no published studies of longer treatment intervals. Most experts have found it equally effective to administer VIT every 4 weeks for the first 18 to 24 months, then every 6 weeks for 18 to 24 months, and every 8 weeks thereafter.³ One group of investigators has reported good results with a 12-week interval for long-term maintenance treatment.⁶³

Duration

The duration of VIT was first thought to be indefinite, and discontinuing VIT after just 1 to 2 years was associated with a 25% relapse rate (Fig 3). Subsequent studies reported that 3 to 5 years of treatment was sufficient, but many studies included other criteria, such as the RAST result becoming negative, an uneventful sting during treatment, or both.⁶⁴⁻⁶⁸ Continued observations revealed that the risk of relapse is greatest in certain types of patients: those who had a systemic reaction during VIT, those with honeybee allergy, those with the most severe reactions by history, and those who had less than 5 years of treatment.^{34,69-73} These clinical characteristics have been more predictive of relapse than any immunologic parameters. Even some patients with negative venom skin test responses will have a systemic reaction to a sting after discontinuing VIT.⁷⁰ Reports describe patients having no reaction to some stings and systemic reactions to others,

even 8 to 13 years after stopping VIT. The chance of a systemic reaction is 10% per sting, but this might diminish with time. Most systemic reactions after stopping VIT are much milder than those before treatment. The cumulative relapse rate approaches 20%, as does the reaction rate, in untreated patients after 15 years (Fig 3).

Mechanism

VIT has also been a model for the understanding of immunotherapy and its mechanism of action. Early evidence supported the role of IgG antibodies in clinical protection shown by the passive transfer of immunity by infusion of IgG derived from beekeepers.^{74,75} Venom-specific IgG antibody levels greater than 3 μ g/mL were associated with protection but were not reliably able to predict the outcome of a sting in each individual patient.⁷⁶ After 4 years of VIT, even patients with low IgG levels did not react to stings, suggesting a different mechanism for tolerance induced by long-term VIT. More recent studies demonstrate a T_H2 to T_H1 shift in cytokine responses during initial VIT, with a prominent role for IL-10.^{59,61,77} The mechanism of long-term immune tolerance remains uncertain but might involve other regulatory cells, cytokines, and pathways.⁷⁸ There is renewed interest in the role of IgG-blocking antibodies on the basis of observations of altered specificity and affinity during immunotherapy and effects on memory B cells and antigen-presenting cells.⁷⁹

MYSTERIES UNRESOLVED AND MODELS FOR THE FUTURE

Research in insect sting allergy and VIT has led to great advances in our understanding of this condition, but many mysteries remain. Insect sting allergy and VIT remain an excellent model for the study of anaphylaxis and immune tolerance. There is no other form of anaphylaxis for which allergen-specific immunotherapy is currently available. The mechanism of immune tolerance induced by long-term immunotherapy can be investigated most easily in VIT. The mystery of why some sensitized patients react to a sting and others do not remains unsolved. The factors that enable or amplify the anaphylactic reaction have yet to be elucidated. By studying insect venom-sensitive patients who have high risk of reaction and others with a low risk of reaction, the determining factors might be identified.

REFERENCES

1. Lichtenstein LM. Insect allergy: the state of the art. *J Allergy Clin Immunol* 1979;64:5-12.
2. Golden DBK. Patterns of anaphylaxis: acute and late phase features of allergic reactions. In: Bock G, Goode J, editors. *Anaphylaxis*. Novartis Foundation Symposium 257. Chichester (United Kingdom): John Wiley and Sons; 2004. p. 101-15.
3. Moffitt JE, Golden DBK, Reisman RE, Lee R, Nicklas R. Stinging insect hypersensitivity: a practice parameter update. *J Allergy Clin Immunol* 2004;114:869-86.
4. Barnard JH. Studies of 400 Hymenoptera sting deaths in the United States. *J Allergy Clin Immunol* 1973;52:259-64.

5. Schwartz HJ, Sutheimer C, Gauerke B, Zora JA, Yunginger JW. Venom-specific IgE antibodies in postmortem sera from victims of sudden unexpected death. *J Allergy Clin Immunol* 1984;73:189.
6. Hoffman DR. Fatal reactions to Hymenoptera stings. *Asthma Allergy Proc* 2003;24:1-5.
7. Benson R, Semenov H. Allergy in its relation to bee sting. *J Allergy Clin Immunol* 1930;1:105-11.
8. Loveless MH, Fackler WR. Wasp venom allergy and immunity. *Ann Allergy* 1956;14:347-66.
9. Insect Allergy Committee, American Academy of Allergy. Insect sting allergy, cooperative study. *JAMA* 1965;193:115-20.
10. Brown H, Bernton HS. Allergy to the Hymenoptera: V. Clinical study of 400 patients. *Arch Intern Med* 1970;125:665-9.
11. Golden DBK, Langlois J, Valentine MD. Treatment failures with whole body extract therapy of insect sting allergy. *JAMA* 1981;246:2460-3.
12. Lichtenstein LM, Valentine MD, Sobotka AK. A case for venom treatment in anaphylactic sensitivity to Hymenoptera sting. *N Engl J Med* 1974;290:1223-7.
13. Sobotka A, Valentine M, Benton A, Lichtenstein L. Allergy to insect stings: I. Diagnosis of IgE-mediated Hymenoptera sensitivity by venom-induced histamine release. *J Allergy Clin Immunol* 1974;53:110-7.
14. Sobotka AK, Adkinson NFJ, Valentine MD, Lichtenstein LM. Allergy to insect stings, IV: diagnosis by radioallergosorbent tests (RAST). *J Immunol* 1978;121:2477-84.
15. Hunt KJ, Valentine MD, Sobotka AK, Lichtenstein LM. Diagnosis of allergy to stinging insects by skin testing with Hymenoptera venoms. *Ann Intern Med* 1976;85:56-9.
16. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978;299:157-61.
17. Smith P, Kagey-Sobotka A, Bleecker ER, Traystman R, Kaplan AP, Gralnick H, et al. Physiologic manifestations of human anaphylaxis. *J Clin Invest* 1980;66:1072-80.
18. Freeman TM, Hyghlander R, Ortiz A, Martin ME. Imported fire ant immunotherapy: effectiveness of whole body extracts. *J Allergy Clin Immunol* 1992;90:210-5.
19. Cho YS, Lee YM, Lee CK, et al. Prevalence of *Pachycondyla chinensis* venom allergy in an ant infested area in Korea. *J Allergy Clin Immunol* 2002;110:54-7.
20. Brown SG, Franks RW, Baldo BA, Heddl RJ. Prevalence, severity and natural history of jack jumper ant venom allergy in Tasmania. *J Allergy Clin Immunol* 2003;111:187-92.
21. Tracy JM, Demain JG, Quinn JM, et al. The natural history of exposure to the imported fire ant. *J Allergy Clin Immunol* 1995;95:824-8.
22. Hoffman DR. Hymenoptera venoms: composition, standardization, stability. In: Levine MI, Lockey RF, editors. *Monograph on insect allergy*. 4th ed. Milwaukee (WI): American Academy of Allergy Asthma and Immunology; 2004. p. 37-53.
23. King TP, Jim SY, Monsalve RI, Kagey-Sobotka A, Lichtenstein LM. Recombinant allergens with reduced allergenicity but retaining immunogenicity of the natural allergens: hybrids of yellow jacket and paper wasp venom allergen antigen 5s. *J Immunol* 2001;166:6057-65.
24. Muller UR. Recombinant Hymenoptera venom allergens. *Allergy* 2002;57:570-6.
25. Golden DBK, Marsh DG, Kagey-Sobotka A, Addison BI, Freidhoff L, Szklo M, et al. Epidemiology of insect venom sensitivity. *JAMA* 1989;262:240-4.
26. Golden DBK, Marsh DG, Freidhoff LR, Kwiterovich KA, Addison B, Kagey-Sobotka A, et al. Natural history of Hymenoptera venom sensitivity in adults. *J Allergy Clin Immunol* 1997;100:760-6.
27. Day J, Buckeridge D, Welsh A. Risk assessment in determining systemic reactivity to honeybee stings in sting-threatened individuals. *J Allergy Clin Immunol* 1994;93:691-705.
28. 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* 1992;90:335-9.
29. vanderLinden PG, Hack CE, Struyvenberg A, vanderZwan JK. 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* 1994;94:151-9.
30. Schuberth KC, Lichtenstein LM, Kagey-Sobotka A, Szklo M, Kwiterovich KA, Valentine MD. An epidemiologic study of insect allergy in children. I. Characteristics of the disease. *J Pediatr* 1982;100:546-51.
31. Valentine MD, Schuberth KC, Kagey-Sobotka A, Graft DF, Kwiterovich KA, Szklo M, et al. The value of immunotherapy with venom in children with allergy to insect stings. *N Engl J Med* 1990;323:1601-3.
32. Golden DBK, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children with and without venom immunotherapy. *N Engl J Med* 2004;351:668-74.
33. Golden DBK, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Sting Challenge Trial I: spectrum of a population with insect sting allergy [abstract]. *J Allergy Clin Immunol* 1998;101(suppl):S159.
34. Muller U, Helbling A, Berchtold E. Immunotherapy with honeybee venom and yellow jacket venom is different regarding efficacy and safety. *J Allergy Clin Immunol* 1992;89:529-35.
35. Mauriello PM, Barde SH, Georgitis JW, Reisman RE. Natural history of large local reactions from stinging insects. *J Allergy Clin Immunol* 1984;74:494-8.
36. Graft DF, Schuberth KC, Kagey-Sobotka A, Kwiterovich KA, Niv Y, Lichtenstein LM, et al. A Prospective study of the natural history of large local reactions following Hymenoptera stings in children. *J Pediatr* 1984;104:664-8.
37. Schwartz HJ, Lockey RF, Sheffer AL, Parrino J, Busse WW, Yunginger JW. A multicenter study on skin test reactivity of human volunteers to venom as compared with whole body Hymenoptera antigens. *J Allergy Clin Immunol* 1981;67:81-5.
38. Hemmer W, Frocke M, Kolarich K, Wilson IBH, Altmann F, Wohrl S, et al. Antibody binding to venom carbohydrates is a frequent cause for double positivity to honeybee and yellow jacket venom in patients with stinging insect allergy. *J Allergy Clin Immunol* 2001;108:1045-52.
39. Golden DBK, Kagey-Sobotka A, Hamilton RG, Norman PS, Lichtenstein LM. Insect allergy with negative venom skin tests. *J Allergy Clin Immunol* 2001;107:897-901.
40. Fricker M, Helbling L, Schwartz L, Muller U. Hymenoptera sting anaphylaxis and urticaria pigmentosa: clinical findings and results of venom immunotherapy in ten patients. *J Allergy Clin Immunol* 1997;100:11-5.
41. Paull BR, Coghlan TH, Vinson SB. Fire ant venom hypersensitivity. I. Comparison of fire ant venom and whole body extract in the diagnosis of fire ant allergy. *J Allergy Clin Immunol* 1983;71:448-53.
42. Day J. A comparison of venom concentrations of 0.1 mcg/ml and 1.0 mcg/ml as indicator of sensitivity to honeybee stings [abstract]. *J Allergy Clin Immunol* 1986;77:142.
43. Golden DBK, Kagey-Sobotka A, Hamilton RG, et al. Dialyzed venom improves sensitivity of skin tests in yellow jacket allergic patients [abstract]. *J Allergy Clin Immunol* 2001;107(suppl):S222.
44. Reisman RE. Intentional diagnostic insect sting challenges: a medical and ethical issue [letter]. *J Allergy Clin Immunol* 1993;91:1100.
45. Franken HH, Dubois AEJ, Minkema HJ, vanderHeide S, deMonchy JGR. 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* 1994;93:431-6.
46. Sainte-Laudy J, Sabbah A, Drouet M, et al. Diagnosis of venom allergy by flow cytometry. Correlation with clinical history, skin tests, specific IgE, histamine and leukotriene C4 release. *Clin Exp Allergy* 2000;30:1166-71.
47. Eberlein-Konig B, Rakoski J, Behrendt H, Ring J. Use of CD63 expression as marker of in vitro basophil activation in identifying insect venom allergy. *J Investig Allergol Clin Immunol* 2004;14:10-6.
48. Hamilton RG. Diagnostic methods for insect sting allergy. *Curr Opin Allergy Clin Immunol* 2004;4:297-306.
49. Oude-Elberink JNG, deMonchy JGR, vanderHeide S, Guyatt GH, Dubois AEJ. Venom immunotherapy improves health-related quality of life in yellow jacket allergic patients. *J Allergy Clin Immunol* 2002;110:174-82.
50. Hamilton RH, Wisenauer JA, Golden DBK, Valentine MD, Adkinson NF. Selection of Hymenoptera venoms for immunotherapy based on patients' IgE antibody cross-reactivity. *J Allergy Clin Immunol* 1993;92:651-9.
51. Oude-Elberink J, deMonchy J, Kors J, vanDoormaal J, Dubois A. Fatal anaphylaxis after a yellow jacket sting despite venom immunotherapy in two patients with mastocytosis. *J Allergy Clin Immunol* 1997;99:153-4.

52. Golden DBK, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Dose dependence of Hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 1981;67:370-4.
53. Yunginger JW, Dahlberg ME, Jones RT, Parker JL, Carey TL. Diagnostic and therapeutic importance of individual honeybee venom allergens [abstract]. *J Allergy Clin Immunol* 1982;69:139.
54. Rueff F, Wenderoth A, Przybilla B. Patients still reacting to a sting challenge while receiving conventional Hymenoptera venom immunotherapy are protected by increased venom doses. *J Allergy Clin Immunol* 2001;108:1027-32.
55. Golden DBK, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of Hymenoptera venom immunotherapy. *Ann Intern Med* 1980;92:620-4.
56. Bernstein JA, Kagan SL, Bernstein DI, Bernstein IL. Rapid venom immunotherapy is safe for routine use in the treatment of patients with Hymenoptera anaphylaxis. *Ann Allergy* 1994;73:423-8.
57. Birnbaum J, Charpin D, Vervloet D. Rapid Hymenoptera venom immunotherapy: comparative safety of three protocols. *Clin Exp Allergy* 1993;23:226-30.
58. Yunginger JW, Paull BR, Jones RT, Santrach PJ. Rush venom immunotherapy program for honeybee sting sensitivity. *J Allergy Clin Immunol* 1979;63:340-7.
59. Akdis CA, Blesken T, Akdis M, et al. Role of interleukin 10 in specific immunotherapy. *J Clin Invest* 1998;102:98-106.
60. Bousquet J, Knani J, Velasquez G, et al. Evolution of sensitivity to Hymenoptera venom in 200 allergic patients followed for up to 3 years. *J Allergy Clin Immunol* 1989;84:944-50.
61. McHugh SM, Deighton J, Stewart AG, Ewan P. Bee venom immunotherapy induces a shift in cytokine responses from a TH2 to a TH1 dominant pattern: comparison of rush and conventional immunotherapy. *Clin Exp Allergy* 1995;25:828-38.
62. Lockey RF, Turkeltaub PC, Olive ES, Hubbard JM, Baird-Warren IA, Bukantz SC. The Hymenoptera venom study III: safety of venom immunotherapy. *J Allergy Clin Immunol* 1990;86:775-80.
63. Goldberg A, Confino-Cohen R. Maintenance venom immunotherapy administered at 3-month intervals is both safe and efficacious. *J Allergy Clin Immunol* 2001;107:902-6.
64. Graft DF, Golden DBK, Reisman RE, Valentine MD, Yunginger JW. 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* 1998;101:573-5.
65. Reisman RE, Lantner R. Further observations of stopping venom immunotherapy: comparison of patients stopped because of a fall in serum venom-specific IgE to insignificant levels with patients stopped prematurely by self-choice. *J Allergy Clin Immunol* 1989;83:1049-54.
66. 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* 1991;87:702-9.
67. Urbanek R, Forster J, Kuhn W. Discontinuation of bee venom immunotherapy in children and adolescents. *J Pediatr* 1985;107:367-71.
68. vanHalteren HK, vanderLinden PWG, Burgers JA, Bartelink AKM. Discontinuation of yellow jacket venom immunotherapy: follow-up of 75 patients by means of deliberate sting challenge. *J Allergy Clin Immunol* 1997;100:767-70.
69. Golden DBK, Kwiterovich KA, Addison BA, Kagey-Sobotka A, Lichtenstein LM. Discontinuing venom immunotherapy: extended observations. *J Allergy Clin Immunol* 1998;101:298-305.
70. Golden DBK, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. *J Allergy Clin Immunol* 2000;105:385-90.
71. Lerch E, Muller U. Long-term protection after stopping venom immunotherapy. *J Allergy Clin Immunol* 1998;101:606-12.
72. Reisman RE. Duration of venom immunotherapy: Relationship to the severity of symptoms of initial insect sting anaphylaxis. *J Allergy Clin Immunol* 1993;92:831-6.
73. Keating MU, Kagey-Sobotka A, Hamilton RG, Yunginger JW. Clinical and immunologic follow-up of patients who stop venom immunotherapy. *J Allergy Clin Immunol* 1991;88:339-48.
74. Lessof MH, Sobotka AK, Lichtenstein LM. Effects of passive antibody in bee venom anaphylaxis. *Johns Hopkins Med J* 1978;142:1-7.
75. Muller UR, Morris T, Bischof M, Friedli H, Skarvil F. Combined active and passive immunotherapy in honeybee-sting allergy. *J Allergy Clin Immunol* 1986;78:115-22.
76. Golden DBK, Lawrence ID, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Clinical correlation of the venom-specific IgG antibody level during maintenance venom immunotherapy. *J Allergy Clin Immunol* 1992;90:386-93.
77. Jutel M, Pichler WJ, Skrbic D, Urwyler A, Dahinden C, Muller UR. Bee venom immunotherapy results in decrease of IL-4 and IL-5 and increase of IFN- γ secretion in specific allergen stimulated T cell cultures. *J Immunol* 1995;154:4187-94.
78. Konno S, Golden DBK, Schroeder J, King TP, Hamilton RG, Creticos PS, et al. Osteopontin: a potential biomarker for successful allergen immunotherapy [abstract]. *J Allergy Clin Immunol* 2004;113(suppl):S215.
79. Wachholz PA, Durham SR. Mechanisms of immunotherapy: IgG revisited. *Curr Opin Allergy Clin Immunol* 2004;4:313-8.