Anaphylaxis to Insect Stings

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David B.K. Golden, MD

KEYWORDS

- Anaphylaxis • Venom • Insect sting • Hymenoptera • Immunotherapy
- Diagnostic tests • Mastocytosis

KEY POINTS

- Anaphylaxis to insect stings occurs in 3% of adults and less than 1% of children.
- Anaphylaxis to insect stings is generally more benign in children, but severe reactions can be associated with sustained risk for decades.
- Diagnostic tests can identify the presence of sensitization to insect venom but are poor predictors of sting anaphylaxis.
- There is a specific association between insect-sting anaphylaxis and mastocytosis, particularly when there is hypotension during the reaction.
- Venom immunotherapy is highly effective in preventing sting anaphylaxis, and leads to lasting tolerance in most patients who are treated for 5 years.

INTRODUCTION

Stinging insects of the order Hymenoptera can cause systemic allergic reactions, including anaphylaxis, but such reactions are rare with biting insects. This article describes the clinical patterns and treatment of anaphylaxis to insect stings, and how they may resemble or differ from other causes of anaphylaxis.

CLINICAL FEATURES

Transient pain, itching, and swelling are normal responses to stings, but allergic reactions can cause more severe local reactions or generalized systemic reactions. Large local sting reactions cause delayed and prolonged local inflammation increasing over 24 to 48 hours and resolving in 3 to 10 days. These reactions resemble late-phase inflammatory reactions that are immunoglobulin E (IgE) dependent. Most patients with large local reactions have detectable venom-specific IgE.[1]

Systemic (generalized) reactions may cause any one or more of the signs and symptoms of anaphylaxis. Although the definition of anaphylaxis seems to exclude reactions involving only cutaneous systemic manifestations (urticaria, angioedema, pruritus, flush), these are included in this article because they must be considered in diagnosis and treatment of insect allergy as potential precursors of more severe anaphylactic reactions. There are also reports of chronic urticaria and cold urticaria developing after insect stings, usually without any immediate hypersensitivity reaction, and with uncertain risk of anaphylaxis to a future sting.[2,3] Unusual patterns of reaction have also been reported, including nephropathy, central and peripheral neurologic syndromes, idiopathic thrombocytopenic purpura, and rhabdomyolysis, but these are not IgE related.[4]

Systemic (generalized) allergic sting reactions result in cutaneous, vascular, or respiratory symptoms and signs, either singly or in any combination, with possible involvement of other less common target tissues. Cardiac anaphylaxis can also cause bradycardia, arrhythmias, angina, or myocardial infarction.[5] Hypotension or cardiac anaphylaxis without cutaneous signs or symptoms can easily be misdiagnosed.[6] Abdominal cramps are common, resulting from gastrointestinal tract or uterine smooth muscle contraction. There may be a greater chance of systemic reaction if there are multiple stings at one time, or if there are repeated stings in the same summer.[7] The onset of reactions is generally within 10 to 30 minutes of the sting. Abrupt onset after a sting may be related to an underlying mast-cell disorder.[8] Onset of symptoms 1 to 4 hours after a sting has been reported in a small number of cases.[9] In contrast with food anaphylaxis, the slower the onset of the sting reaction, the less likely it is to be life threatening.[9,10]

Whether anaphylaxis differs clinically between children and adults is unclear for most causes, but is known for insect-sting allergy, both in the clinical history and the natural history. Cutaneous symptoms are most common overall, affecting 80% of patients with systemic reactions to stings, in both adults and children; they are the sole manifestation in 15% of adults but in 60% of affected children.[11] Almost 50% of reactions in both children and adults included respiratory complaints. Symptoms and signs of hypotension were uncommon in children but occurred in more than 30% of adults, with half experiencing loss of consciousness (which is rare in children).[9,12] The clinical presentation can be vague and uncertain both during the reaction and in the history. To aid proper diagnosis and treatment, objective documentation should be made whenever possible, including description of cutaneous findings, vital signs, pulse oximetry, and air flow measurements.

Differential Diagnosis

Although a history of insect-sting anaphylaxis might be expected to be obvious, this is not always the case. When reactions have not been observed and treated by a physician, there can be uncertainty as to the true nature of the symptoms. Objective urticaria or angioedema (distant from the site of the sting), or documented hypotension, can confirm the diagnosis of anaphylaxis. The absence of cutaneous symptoms or signs, which occurs in 15% to 30% of cases of insect-sting anaphylaxis (more in adults than in children), does not rule out anaphylaxis, and has been associated with a higher frequency of hypotension and mastocytosis (particularly in male patients).[13] Non–IgE-mediated reactions can occur in patients with mastocytosis.

Subjective symptoms can occur that are convincing (eg, throat or chest discomfort, dyspnea, light-headedness) and must be assumed to be allergic when gleaned from the patient history. However, such reactions have often occurred under monitored sting challenge conditions when no objective abnormalities were found (ie, normal physical

examination, vital signs, pulse oximetry, air flow measurement, and serum tryptase), making it unclear whether they are caused by allergic mast-cell mediator release.[14] Many of these symptoms are consistent with anxiety, but can also be related to hyperventilation or vocal cord dysfunction.

ETIOLOGY/PATHOPHYSIOLOGY

Stinging insects of the order Hymenoptera are the main cause of insect-related anaphylaxis. There are 3 families of Hymenoptera with clinical importance: the bees (honeybees, bumblebees), vespids (yellow jackets, hornets, wasps), and stinging ants (genus *Solenopsis* and others). Exposure to these insects is affected by geographic, environmental, and ecological factors. The Africanized honeybee (the so-called killer bee) is an aggressive hybrid resulting from an experiment intended to enhance honey production. The danger from the Africanized honeybees stems from the numbers of stings because of their swarm-and-attack behavior; their venom is no different from that of other honeybees. Imported fire ants arrived 75 years ago in Mobile, Alabama, and have rapidly become an increasing public health hazard in the south and southeast parts of the United States.[15,16] There have been increasing reports of anaphylaxis caused by other species of stinging ants in Asia and Australia.[17]

The immunochemical characteristics and immunogenetic relationships of the Hymenoptera venoms have been thoroughly studied.[18,19] Venoms contain multiple protein allergens, most having enzymatic activity. Honeybee venom is immunochemically distinct from that of the other Hymenoptera, but cross reactivity is often observed in serum IgE tests for honeybee and yellow jacket venoms because of the presence of cross reacting carbohydrate determinants (CCDs) on the native allergens.[20] Vespid venoms have a high degree of cross reactivity with each other and contain essentially the same allergens. Patients who are allergic to yellow jacket stings also have positive tests for hornet venom IgE in 95% of cases. *Polistes* wasps are not as closely related to the other vespids, and only 50% of patients allergic to yellow jackets or hornets have positive tests to wasp venom. Fire ant venoms are different in that they contain very little protein, in a suspension of alkaloid toxins that causes the characteristic vesicular eruption. The proteins in fire ant venoms are antigenically unique except for 1 that shows limited cross reactivity with a vespid allergen. The diagnostic and therapeutic materials currently supplied by commercial laboratories are fire ant whole-body extracts that, unlike the other insect whole-body extracts, show reasonable allergenic activity for diagnostic skin testing and for preventative immunotherapy.[21–23] The other 5 Hymenoptera products (honeybee, yellow jacket, yellow hornet, white-faced hornet, and *Polistes* wasp) are supplied as lyophilized venom protein extracts to be reconstituted using an albumin-saline diluent.

EPIDEMIOLOGY/NATURAL HISTORY

Knowledge of the epidemiology and natural history of Hymenoptera venom sensitivity is crucial in clinical decision making. Insect-sting allergy can occur at any age, often following several uneventful stings. Systemic allergic reactions are reported by up to 3% of adults, and almost 1% of children have a medical history of allergic sting reactions.[24,25] The frequency of large local reactions is uncertain, but is estimated at 10% in adults.[24,25] At least 40 fatal sting reactions occur each year in the United States.[10,26] Half of all fatal reactions occur with no history of previous sting reactions.[27] Many sting fatalities may be unrecognized and attributed to other causes. In some cases of unexplained sudden death in the summer, postmortem blood samples show the presence of both venom-specific IgE antibodies and increased serum

tryptase level, suggesting a possible fatal sting reaction as the cause of death.[27,28] However, the presence of IgE antibodies to Hymenoptera venom is common. Sensitization to Hymenoptera venoms is common, but systemic sting reactions are much less common.[29] More than 30% of adults stung in the previous 3 months showed venom-specific IgE by skin test or serum test, and more than 20% of a random sample of adults tested positive to yellow jacket or honeybee venom, even though most had no history of allergic sting reactions, and almost all had been stung in the past.[25] Venom sensitivity in asymptomatic adults is often transient, disappearing more rapidly than it does in patients with a history of anaphylaxis. Of the subjects with initial positive skin tests, 30% to 60% became negative after 3 to 6 years. Those who remained positive showed a 17% frequency of a systemic reaction to a sting.[30]

Systemic reactions become progressively more severe with each sting in some cases, but this seems to be the exception rather than the rule. In children, a prospective long-term study showed that those with cutaneous systemic reactions had about a 10% chance of a similar or milder reaction, but only a 1% to 3% chance of a more severe reaction.[31] The findings were similar in a follow-up survey of the same pediatric cohort for 15 to 20 years.[32] In that study, children with moderate or severe anaphylaxis to stings who did not receive venom immunotherapy (VIT) still had a 32% frequency of anaphylaxis to recent stings.

In adults who have had previous systemic reactions to stings, a repeat sting causes another systemic reaction in 30% to 65% of cases, depending mainly on the severity of previous reactions, the level of venom sensitivity, and the species of insect.[14] Systemic reactions are more common with honeybee than vespid stings, more with hornets than yellow jackets, and more with some yellow jacket species (*Vespula maculifrons*) than with others (*Vespula germanica*). However, it has been noted that a patient can react to one sting and not another even from the same species. This difference may be caused by a 10-fold variability in the amount of venom injected by a vespid sting,[33] which can lead to a misleading impression that the patient is no longer allergic, only to have them react to a later sting.

In adults with a history of mild systemic reactions to stings, there has been less of a consensus on the risk of more severe reactions to future stings. In prospective sting challenge studies, less than 1% of the patients had reactions more severe than their past reactions.[14,34] In 2 retrospective surveys, there were a larger number of subjects who described worsening of the reaction with subsequent stings.[9,35] Allergic reactions to stings usually follow a predictable and individual pattern in each patient with severity being variable. Anaphylactic reactions to stings can occur even decades apart, with or without intervening stings.

Table 1 shows the risk of systemic reaction in untreated patients with a history of sting anaphylaxis and positive venom skin tests.

DIAGNOSIS
History

The history is paramount in diagnosis and must be elicited with insight and attention to detail. Patients usually fail to admit sting reactions without specific inquiry, often do not seek medical attention, and typically believe the reaction was a chance occurrence that could not happen again (because they have had many previous stings without reaction).[25] The history should include all previous stings, the time course of the reactions, and all associated symptoms and treatments. The reaction to any sting can be variable in occurrence and severity, even in individuals allergic to stings. Even without intervening stings, sensitization can persist for decades and result in subsequent

Table 1
Risk of systemic reaction in untreated patients with history of sting anaphylaxis and positive venom skin tests

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 systemic	Child	10	5
	Adult	20	10
Anaphylaxis	Child	40	30
	Adult	60	40

From Golden DB. Insect Allergy. In: Adkinson NF Jr, Bochner BS, Burks AW, et al, editors. Middleton's allergy: principles and practice. 8th edition. Philadelphia: Elsevier; 2014:1266; with permission.

anaphylactic reactions to stings. If intervening stings have occurred without systemic reaction there could be less risk of subsequent severe reaction, but the species of insect is never certain to be the same as the underlying allergy, and the possibility of future anaphylaxis cannot be excluded when diagnostic tests reveal venom-specific IgE antibodies.[14]

The significance of the sting reaction can be overestimated or underestimated. Symptoms are sometimes exaggerated by fear, panic, exercise, heat, alcohol, or underlying cardiorespiratory disease. For this reason, objective documentation of the physical findings during the reaction should be sought (measurements of blood pressure or reduced air flow, observed urticaria). The history is sometimes of a sting reaction that occurred many years earlier and is poorly remembered. Even when the reaction was not severe, people have often been told by physicians that the next one will kill them.

Diagnostic Tests

Diagnostic tests are indicated in patients who have had systemic reactions to stings.[36] If the risk of future anaphylaxis is judged to be low (less than 10%) based on the history, diagnostic testing (and VIT) is not required; this is the case in patients with only large local reactions to stings, and in children who had only cutaneous systemic reactions. There are also patients who request venom testing because of fear of the reactions experienced by family members, friends, or others. Testing is not advised in such cases because of the frequent occurrence of positive venom tests in individuals who have previously been stung with no abnormal reaction.

However, skin tests are not a useful screening test and are not recommended in patients with no history of systemic allergic reaction to a sting. A screening test for insect allergy is desirable in order to prevent the morbidity and mortality of the initial anaphylactic episode; half of all fatal reactions occur without prior reactions to stings. Venom immunotherapy is indicated only in patients who have a history of a previous systemic reaction because venom skin tests are positive in many adults who have had previous stings and will have no reaction to a future sting.[29,30]

The preferred diagnostic method is venom skin testing because of its high degree of sensitivity and proven safety.[36,37] In vitro methods can be useful but are not as sensitive and can therefore yield false-negative results in more than 10% of cases. The standard method of skin testing is with the intradermal technique using the 5 Hymenoptera venom protein extracts (and/or whole-body extracts of imported fire ants). For Hymenoptera

venom testing, intradermal tests are performed with venom concentrations in the range of 0.001 to 1.0 μg/mL to find the minimum concentration giving a positive result. Puncture tests at concentrations less than or equal to 100 μg/mL may be used initially for patients with a history of severe reactions to stings. Sensitization may have occurred to multiple venoms even when there has only been a reaction to a single insect; therefore, skin testing should be performed with a complete set of 5 Hymenoptera venoms, a negative diluent (HSA-saline) control, and a positive histamine control.

Skin test results are clearly positive in 65% to 85% of patients with a convincing history. Negative skin tests in history-positive patients can occur for several possible reasons. In the case of a remote sting reaction, this can be caused by loss of sensitivity. After a recent sting there could be a temporary refractory period of anergy for several weeks.[38] Venom skin tests also show unexplained variability over time such that tests can be negative on one occasion and positive on another.[39] It may be best to perform venom skin tests (or perform both skin tests and serum tests) on separate occasions before making the final therapeutic selection of venoms. Some cases of sting anaphylaxis seem to be non–IgE mediated and may be related to underlying mastocytosis or simply toxic mast-cell mediator release. Most important, the degree of skin test sensitivity does not correlate reliably with the degree of sting reaction.[14] 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 show only weak skin test (or specific serum IgE) sensitivity. About 25% of patients presenting for systemic allergic reactions to stings are skin test positive only at the 1.0-μg/mL concentration. Again, it is the history that is most predictive.

The detection of allergen-specific IgE antibodies in serum is less sensitive than skin testing, but is useful when skin tests cannot be done (patients with a severe skin condition or unavoidable medications that suppress skin tests). Another use of the serum IgE test is to resolve the discordance when skin tests are negative in patients with a history of a severe reaction to a sting. It is not clear whether there is any difference in prognostic value of skin tests and serum tests. Patients with negative skin tests and positive serum tests have been reported to have systemic reactions to subsequent stings, although the frequency may be lower than in patients with positive venom skin tests.[14]

Some investigators have suggested that sting challenge is the most specific diagnostic test, but others find this unethical and impractical.[34,40,41] Furthermore, a single negative challenge sting does not preclude anaphylaxis to a subsequent sting.[14,42] Newer approaches include either new materials (recombinant allergens) or new techniques (basophil activation tests). Recombinant venom allergens have been studied for serum IgE measurement in patients with dual sensitization to honey bee and yellow jacket venoms, in whom the tests can distinguish whether the patient is primarily allergic to just 1 of the venoms, or is allergic to both.[43–45] The recombinant venom allergens are free of the CCDs on the native venoms that may cause the serologic cross reactivity. Serum IgE tests with recombinant venom allergens do not show improved sensitivity, and have lower diagnostic accuracy than tests with the native venom extracts.[37] When multiple recombinant allergens are combined to approximate the repertoire of allergens in the native venom, the diagnostic sensitivity is improved but still not as good that of as the whole venom.

Basophil activation tests have been under development for many years. As a marker of susceptibility to basophil mediator release, these tests may provide clinically significant evidence of reactivity with, or potentially even without, specific IgE. The expression of basophil activation markers, particularly CD63, on exposure to very low

concentrations of allergen has been reported to detect venom allergy in patients with no detectable venom-specific IgE on serum or skin tests, to predict efficacy of VIT, and to predict relapse after stopping VIT.[46–48] The methodology for performing and interpreting these tests has not yet been standardized, but it seems likely that they will become part of the diagnostic arsenal in the future.

Table 2 summarizes the diagnostic evaluation of insect-sting allergy.

RISK FACTORS FOR STING ANAPHYLAXIS

There are 2 elements of risk in insect-sting allergy: frequency and severity. The chance of a systemic reaction to stings is related to the frequency of exposure, the level of sensitivity on serum or skin tests for venom IgE, and the severity of previous reactions to stings (**Table 3**).[14] The severity of sting anaphylaxis is not predicted reliably by the level of venom sensitivity on serum or skin tests but may be correlated with markers of basophil and mast-cell responses, such as the level of baseline serum tryptase.[49] The Spanish Mastocytosis Network has described a Red Española de Mastocitosis (REMA) score that predicts underlying mastocytosis in patients with insect-sting anaphylaxis who are male and have hypotensive shock reactions to stings without cutaneous manifestations.[13] Insect stings are the most common cause of anaphylaxis in patients with indolent systemic mastocytosis.[50] Baseline serum tryptase level is increased in 25% of patients with a history of hypotension after a sting, and in about 5% of patients with other systemic reactions to stings.[51] Mastocytosis and/or increased baseline tryptase level are associated with not only increased risk of severe reactions to stings but also increased risk of systemic reactions to VIT injections, increased risk of treatment failure, and increased risk of relapse after a VIT (including fatal anaphylaxis).[49,52–56] There is also early evidence that a low level of platelet-activating factor acetylhydrolase is correlated with severe and fatal anaphylaxis to foods or insect stings.[57,58]

Antihypertensive medications, particularly β-blockers, have been reported to increase the risk of a severe allergic reaction to a sting.[49] In the case of β-blockers, the concern is mainly the potential for epinephrine resistance requiring additional

Table 2
Diagnostic evaluation of insect-sting allergy

Purpose	History	Skin Test	Specific IgE	BAT	Recombinant Allergen	RAST-Inhibition	Tryptase Baseline
Diagnosis							
No reaction	X						
LLR	X						
Mild systemic reaction	X	X	X				
Anaphylaxis	X	X	X	X	X	X	X
Predict severe reaction (to stings or VIT)	X			X			X
Cross-reactivity (honeybee/yellow jacket)					X	X	
Discontinue VIT	X			X			X

Abbreviations: BAT, basophil activation test; LLR, large local reaction; RAST, radio-allergosorbent test.

From Golden DB. Advances in diagnosis and management of insect sting allergy. Ann Allergy Asthma Immunol 2013;111:85; with permission.

Table 3
Predictors of risk of systemic reaction to insect stings

Natural History	Markers
Severity of previous reaction	Venom skin test
Insect species	Venom-specific IgE
Age/Gender	Basophil activation test
No urticaria/angioedema	Baseline serum tryptase value
Medications	PAF acetylhydrolase
Multiple or sequential stings	Angiotensin-converting enzyme

Abbreviation: PAF, platelet-activating factor.
From Golden DB. Insect Allergy. In: Adkinson NF Jr, Bochner BS, Burks AW, et al, editors. Middleton's allergy: principles and practice. 8th edition. Philadelphia: Elsevier; 2014:1266; with permission.

epinephrine and intravenous (IV) fluids. If the patient remains unresponsive to epinephrine this may be overcome with glucagon injection. Angiotensin-converting enzyme inhibitors may increase the risk of angioedema with airway obstruction. Despite the convincing evidence to support these concerns in some studies, there are other reports that find no correlations.[8] There has also been concern that stopping β-blocker medication may create a greater risk than continuing the medication during VIT.[6]

ACUTE TREATMENT

Treatment of insect-sting anaphylaxis is no different from treating other causes of anaphylaxis, requiring immediate epinephrine injection and potentially IV fluids and oxygen.[36,59] In the presence of hypotensive symptoms, recumbent posture is of critical importance.[60] Biphasic and protracted anaphylaxis have been reported with insect stings, so medical observation should extend for 3 to 6 hours depending on severity. Some individuals are resistant to epinephrine, especially those on β-blocker medication. Nevertheless, the risk of stopping β-blockers in patients with cardiac disease may exceed the risk of continuing the drugs.[6] Patients discharged from emergency care after anaphylaxis should receive instruction about the appropriate use of an epinephrine autoinjector, and recommendations for an allergy consultation and preventative treatment. Patients should be specifically informed that VIT is routinely available and gives rapid protection and ultimately a cure (tolerance) in most cases. Patients should understand that using the epinephrine is not a substitute for emergency medical attention (in case of persistent or recurrent anaphylaxis), that the epinephrine is not dangerous at the recommended dose, and that delay in the use of epinephrine can increase the risk of fatal anaphylaxis.[61]

PREVENTION
Precautions

Individuals susceptible to allergic reactions to stings should avoid related exposures, particularly outdoor foods and drinks that attract or harbor stinging insects. However, excessive fear impairs quality of life and can be considered among the indications for VIT in patients who are otherwise at low risk for anaphylaxis.[62,63] When to carry or use an epinephrine injector depends on the clinical setting. Although having an emergency injector is reassuring to some individuals, it is frightening to others and conveys a concern about possible dangerous reactions to stings. Many experts

suggest that an injector is not necessary when the chance of a systemic reaction is only 5% to 10%, such as in large local reactors, children with cutaneous systemic reactions, and patients who are receiving or have completed VIT. In contrast, some clinicians think that even a 1% chance of anaphylaxis warrants carrying epinephrine, even if it does not warrant VIT. Having an epinephrine injector does not improve the quality of life, whereas VIT does. This distinction has been shown not only in patients with moderate to severe sting anaphylaxis but even in those with cutaneous reactions.[64] Most insect allergic patients can be advised to keep an epinephrine injector at the ready when stung, but may not need to use it if the reaction does not occur or remains limited to mild (cutaneous) symptoms. Some patients have had rapid onset of severe reactions and (until immunized) should potentially use epinephrine immediately after being stung.

Venom Immunotherapy

One of the only types of anaphylaxis for which immunotherapy has been proved to be highly effective is insect-sting allergy. VIT has been the most useful model for the elucidation of the mechanisms of allergen immunotherapy. VIT has also proved to be the most highly effective form of immunotherapy at inducing full and reliable clinical protection and, ultimately, a lasting tolerance.

The indications for VIT require a history of previous systemic allergic reaction to a sting and a positive diagnostic test for venom-specific IgE. Such individuals have a 30% to 65% chance of systemic reaction to a subsequent sting.[34,65,66] This range is related to several factors as described earlier. Children do not always outgrow insect allergy, and those with moderate or severe systemic reactions should receive VIT. One study found that without VIT such children still have up to 30% chance of reaction to a sting even decades later.[32]

A low risk (<10%) has been reported in children and adults with a history of large local reactions, and in children with systemic reactions limited to cutaneous signs and symptoms (with no respiratory or circulatory manifestations).[1,31,32,67] Venom immunotherapy is not required in these low-risk cases, but some patients still request treatment because of their fear of reaction and the impact on their quality of life. Adults with cutaneous systemic reactions also seem to have a low risk of progression to anaphylaxis, but there are conflicting reports suggesting that the risk might justify the recommendation of VIT in such patients. However, there is no test that predicts which patients will progress to more severe reactions. Even intervening stings without reaction do not necessarily ensure that there will be no reaction to a later sting.

Initial VIT can follow any of several recommended schedules. The common modified-rush regimen is more rapid than traditional regimens, achieving the 100-μg maintenance dose with 8 weekly injections, instead of taking 4 to 6 months. With these regimens, adverse reactions are no more common than in traditional regimens of inhalant allergen immunotherapy, and both regimens are equally effective. Even rush regimens of 2 to 3 days are not associated with a higher frequency of adverse reactions to venom injections.[68–70] Ultrarush VIT is clearly associated with increased risk of anaphylactic adverse effects.[71]

Treatment is usually recommended with each of the venoms giving a positive skin test. Therapy is 98% effective in preventing systemic allergic reactions to stings when treatment includes mixed vespid venoms (300-μg total dose), but complete protection is achieved in only 75% to 90% of patients using 100 μg of any single venom (eg, honeybee, yellow jacket, or *Polistes* wasp). Fire ant immunotherapy using whole-body extracts has been reported to be reasonably safe and effective, and should be used in cases of significant systemic reaction, although there have been no controlled

trials.[22,23] Fire ant venoms are not available for diagnosis or treatment, but jack jumper ant VIT was very successful in a controlled clinical trial in Australia.[72]

Adverse reactions to VIT occur no more frequently than with inhalant allergen immunotherapy.[73,74] Systemic symptoms occur in 10% to 15% of patients during the initial weeks of treatment with semirush or traditional regimens. Most reactions are mild, and fewer than half require epinephrine injection. Virtually all patients can achieve the full dose even after initial systemic reactions. In the unusual case of repeated systemic reactions to injections even after adjustment of the dose schedule, VIT up to maintenance doses has been achieved using inpatient rush VIT, and in some cases with omalizumab pretreatment. Large local reactions to injections are common, occurring in up to 50% of patients. Unlike standard inhalant immunotherapy, the uniform target dose in VIT may make it necessary to advance the dose if there are large local reactions, beyond what might otherwise be considered the maximum tolerated dose. Large local reactions can be reduced by pretreatment with antihistamines and leukotriene modifiers without affecting efficacy.[75,76] Efficacy may be improved by pretreatment with antihistamines.[75]

Venom immunotherapy has been the most productive model for investigation of the mechanisms of immunotherapy. Venom IgE levels increase initially with treatment, then decline steadily over time toward very low levels after 5 to 10 years. Venom immunoglobulin G (IgG) levels generally increase with treatment, and have been correlated with clinical protection.[77,78] The IgG response is a downstream marker of interleukin-10 production, which in turn reflects changes in regulatory T-cell populations and dendritic cells.[79,80] However, the determinants and markers of long-term immune tolerance after immunotherapy remain elusive.

Maintenance doses of VIT are administered every 4 weeks for at least a year. Most experts agree that the maintenance interval then may be increased to every 6 weeks for at least a year, and later to every 8 weeks.[36] Venom skin tests or serum IgE tests are repeated periodically, usually every 2 to 3 years, to determine when there has been a significant decline in sensitivity. 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 (although most remain positive on serum IgE tests).[81,82] Patients who continue VIT beyond 4 to 5 years can be safely and effectively treated every 12 weeks.[83]

The duration of VIT is indefinite according to the recommendation in the product package insert. Initial efforts to stop treatment when the serum IgE became negative were successful, but only a few patients become IgE-negative within 5 years of treatment.[84,85] However extended study of a large number of adults has shown that when VIT is stopped after 5 years, the chance of a systemic reaction remains 10% for each sting even more than 10 years after stopping treatment, and even if skin tests become negative.[82,86] When sting reactions occur after stopping VIT, most are mild and almost always less severe than the pretreatment reaction. A higher frequency of relapse occurs in patients who had very severe (near-fatal) sting reactions before therapy, those who had a systemic reaction during therapy (to a sting or a venom injection), those with honeybee allergy, those with increased baseline serum tryptase level, and those who had less than 5 years of therapy.[82,87–89] Patients with any of these high-risk characteristics may need to be treated indefinitely, but there are no data on the outcome in these patients after more than 15 years of treatment. Some patients prefer to continue venom treatment for security and improved quality of life, especially those with frequent, unavoidable, or occupational exposure. Children who have had 3 to 5 years of VIT have a very low chance of systemic reaction even 10 to 20 years after stopping treatment.[32]

CURRENT CONTROVERSIES/FUTURE CONSIDERATIONS

There remain a few areas of controversy and ongoing investigation in insect-sting allergy. There is a need for new and better diagnostic and prognostic tests that can distinguish those individuals who will have severe reactions to future stings from those who have minimal risk despite similar levels of venom IgE. Such a test might also serve as a screening test that could prevent anaphylaxis to future stings, including the fatalities that occur on the first reaction that are currently not preventable. There is also a need for a test that could distinguish patients who have achieved permanent tolerance after years of VIT from those whose protection will wane if they stop treatment.

There is a need to clarify the relative risk of more severe reactions in adults who have had only mild systemic reactions to stings. At present, these patients are advised that it would be prudent to undergo VIT, although outside the United States this is not the case.

SUMMARY

Anaphylaxis to insect stings has occurred in 3% of adults and can be fatal even on the first reaction. Large local reactions are more frequent but rarely dangerous. The chance of a systemic reaction to a sting is low (5%–10%) in those with large local reactions and in children with mild (cutaneous) systemic reactions, and varies between 30% and 65% in adults with systemic reactions depending on the severity of previous sting reactions. Venom skin tests are most accurate for diagnosis but measurement of serum-specific IgE is an important complementary test. The level of venom IgE detected by the skin test or serum test does not reliably predict the severity of a sting reaction. Venom sensitization can be detected in 25% of adults, so the history is most important in clinical evaluation. Venom immunotherapy is 75% to 98% effective in preventing sting anaphylaxis. Most patients can discontinue treatment after 5 years, with very low residual risk of a severe sting reaction.

Anaphylaxis to insect stings is unique in some ways, especially its mode of antigen exposure, its well-described natural history, its milder relatives (large local and cutaneous reactions), and its remarkable response to immunotherapy. Familiarity with these features permits better recognition and prevention of insect-sting anaphylaxis. There is a need to educate the public and health care professionals about the availability, efficacy, and safety of VIT.

There is a need for improved accuracy in diagnostic tests for insect-sting allergy, which may be achieved with dialyzed venoms, recombinant venoms allergens, basophil activation tests, or other in vitro procedures. There remains a need to determine the best predictive factors that distinguish patients who would react to stings from those who are sensitized but do not have anaphylaxis. Such a test would identify those individuals who are at risk before their first reaction occurs, those who are immunized but have incomplete protection, and those who will have increased risk of reaction if they discontinue VIT. Clinicians could then target the therapy to those most likely to benefit and spare patients who are sensitized but are not in danger. Such insight may come from studying large local reactors (who are highly sensitized but have the lowest risk of anaphylaxis), untreated patients who do not react to a challenge sting, and patients who relapse after stopping VIT.

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