Practice parameter

Stinging insect hypersensitivity: A Practice Parameter Update

Chief Editors: **John E. Moffitt, MD, David B.K. Golden, MD, Robert E. Reisman, MD, Rufus Lee, MD, Richard Nicklas, MD***

Associate Editors: **Theodore Freeman, MD, Richard deShazo, MD, James Tracy, MD, I. Leonard Bernstein, MD, Joann Blessing-Moore, MD, David A. Khan, MD, David M. Lang, MD, Jay M. Portnoy, MD, Diane E. Schuller, MD, Sheldon L. Spector, MD, and Steven A. Tilles, MD**

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the "Stinging insect hypersensitivity: A Practice Parameter Update." Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology.

This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients.

Published practice parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology include the following:

1. Practice parameters for the diagnosis and treatment of asthma. J Allergy Clin Immunol 1995;96(suppl): S707-S870.
2. Practice parameters for allergy diagnostic testing. Ann Allergy 1995;75:543-625.
3. Practice parameters for the diagnosis and management of immunodeficiency. Ann Allergy 1996;76:282-94.
4. Practice parameters for allergen immunotherapy. J Allergy Clin Immunol 1996;98:1001-11.
5. Disease management of atopic dermatitis: a practice parameter. Ann Allergy 1997;79:197-211.
6. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-S528.
7. Algorithm for the diagnosis and management of asthma: a practice parameter update. Ann Allergy 1998;81:415-20.
8. Diagnosis and management of rhinitis: parameter documents of the Joint Task Force on Practice parameters in Allergy, Asthma and Immunology. Ann Allergy 1998;81(suppl):S463-S518.
9. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol 1998;102(suppl): S107-S144.
10. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80.
11. Disease management of drug hypersensitivity: a practice parameter. Ann Allergy 1999;83(suppl): S665–S700.
12. Diagnosis and management of urticaria: a practice parameter. Ann Allergy 2000;85(suppl):S521-S544.
13. Allergen immunotherapy: a practice parameter. Ann Allergy 2003;90(suppl):S1-S54.
14. Symptom severity assessment of allergic rhinitis: part I. Ann Allergy 2003;91:105-14.

These parameters are also available on the Internet at: http://www.jcaai.org

CONTRIBUTORS

The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

*This parameter was edited by Dr Nicklas in his private capacity and not in his capacity as a medical officer with the Food and Drug Administration. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

Reprint requests: Joint Council of Allergy, Asthma and Immunology, 50 N Brockway St, #3-3, Palatine, IL 60067.

J Allergy Clin Immunol 2004;114;869-86.
0091-6749/$30.00

doi:10.1016/j.jaci.2004.07.046

Stinging insect hypersensitivity: A practice parameter update

Table of Contents

PREFACE

The objective of ''Stinging insect hypersensitivity: A practice parameter update'' is to improve the care for patients with stinging insect hypersensitivity. This parameter is intended to refine guidelines for the use and interpretation of diagnostic methods and for the institution and implementation of measures to manage stinging insect hypersensitivity, with particular emphasis on the appropriate use of immunotherapy.

''Stinging insect hypersensitivity: A practice parameter update'' was developed by the Joint Task Force on Practice Parameters. The 3 major allergy and immunology societies (the American College of Allergy, Asthma and Immunology [ACAAI]; the American Academy of Allergy, Asthma and Immunology [AAAAI]; and the Joint Council of Allergy, Asthma and Immunology) charged the Task Force with the development of practice guidelines for stinging insect hypersensitivity. The document ''Stinging insect hypersensitivity: a practice parameter update'' builds on ''Stinging insect hypersensitivity: a practice parameter'' (Portnoy JM, Moffitt JE, Golden DBK, Bernstein IL, et al. J Allergy Clin Immunol 1999:103;963-80), which was previously published by the Joint Task Force. It follows the same format as that document, with some substantive changes reflecting advancements in scientific knowledge and their effect on management of insect sting allergy. ''Stinging insect hypersensitivity: a practice parameter update'' was written and reviewed by subspecialists in allergy and immunology. The project was exclusively funded by the 3 allergy and immunology societies noted above.

A work group chaired by Dr John Moffitt prepared the initial draft, which was subsequently reviewed by the Joint Task Force. A comprehensive search of the medical literature was conducted with various search engines, including PubMed, and ''immunotherapy,'' ''stinging insect allergy,'' ''anaphylaxis,'' ''venom,'' and related search terms were used. Published clinical studies were rated by category of evidence and used to establish the strength of a clinical recommendation (Table I).

The working draft of ''Stinging insect hypersensitivity: a practice parameter update'' was reviewed by a large number of experts in allergy and immunology. These experts included reviewers appointed by the ACAAI and AAAAI. Copies of the working draft were distributed at the ACAAI annual meeting in the fall of 2002 and the AAAAI annual meeting in the spring of 2003. The authors carefully reviewed and considered additional comments from these reviewers. The revised final document presented here was approved by the sponsoring organizations and represents an evidence-based, broadly accepted consensus parameter.

An annotated algorithm in this document summarizes the key decision points for the appropriate use of allergen immunotherapy (Fig 1). Specific recommendations guide the physician in selecting those patients for whom allergen immunotherapy for insect sting allergy is appropriate.

TABLE I. Classification of evidence and recommendations*

Category of evidence	
Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least 1 randomized controlled trial
IIa	Evidence from at least 1 controlled study without randomization
IIb	Evidence from at least 1 other type of quasiexperimental study
III	Evidence from nonexperimental descriptive studies, such as comparative studies, cor relation studies, and case-controlled studies
IV	Evidence from expert committee reports, opinions or clinical experience of respected authorities, or both
LB	Evidence from laboratory-based studies†
Strength of recommendation	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated from category I evidence
C	Directly based on category III evidence or extrapolated from category I or II evidence
D	Directly based on category IV evidence or extrapolated from category I, II or III evidence
E	Directly based on category LB evidence†
F	Based on consensus of the Joint Task Force on Practice Parameters†

*Printed with permission of the *British Medical Journal* from Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ 1999;318:593-6.
†Added by current authors.

Immunotherapy is recommended for patients with a history of a systemic reaction to Hymenoptera who demonstrate specific IgE antibodies to Hymenoptera venom, as described in the parameter.

Allergen vaccine is the recommended term for the therapeutic agent used in allergen immunotherapy. This term is used in the document when the therapeutic use of the preparation is clear. The terms *allergen extract* or *extract (vaccine)* are used in the text where the nontherapeutic aspects of the allergen preparation are important.

The Joint Task Force on Practice Parameters would like to thank members of the workgroup and Task Force, as listed elsewhere in this document.

EXECUTIVE SUMMARY

Most insect stings produce a transient local reaction that might last up to several days and generally resolves without treatment. Marked local swelling extending from the sting site might be an IgE-mediated late-phase reaction. The risk of a systemic reaction in patients who experience large local reactions is no more than 5% to 10%. More serious anaphylactic sting reactions account

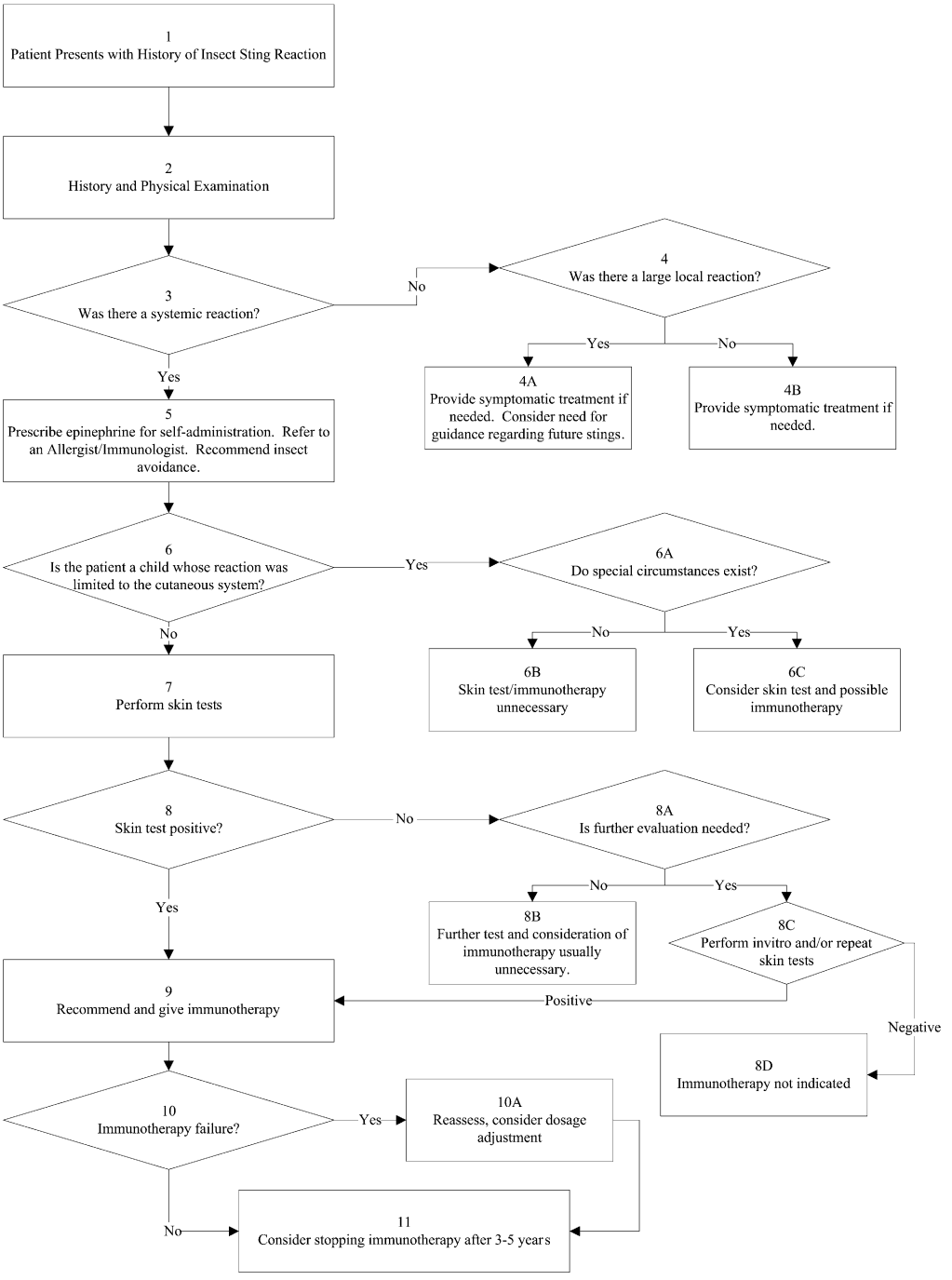

FIG 1. Algorithm: management of stinging insect reactions.

for at least 40 deaths each year in the United States. It is estimated that potentially life-threatening systemic reactions to insect stings occur in 0.4% to 0.8% of children and 3% of adults.

Systemic reactions might be characterized by urticaria and angioedema, bronchospasm, edema of the large airway, hypotension, and other clinical manifestations. The most serious anaphylactic reactions involve the cardiovascular and respiratory systems and are potentially life-threatening. The most common cardiovascular reaction is hypotension. Respiratory symptoms include symptoms of upper or lower airway obstruction. Laryngeal edema is the most common cause of death from anaphylaxis. Patients who have a history of a systemic reaction to an insect sting should (1) be educated in avoidance of stinging insects, (2) carry epinephrine for

emergency self-administration, (3) undergo testing for specific IgE antibodies to stinging insects, (4) be considered for venom immunotherapy (VIT) if test results for specific IgE antibodies are positive, and (5) consider obtaining medical identification of stinging insect hypersensitivity.

Identification of the insect responsible for the sting reaction can be very useful in establishing the diagnosis, prescribing treatment, and educating patients in avoidance measures. For example, yellow jackets generally build their nests in the ground and therefore can be encountered during yard work, farming, and gardening. Hornets are extremely aggressive and build large nests, usually in trees or shrubs, which, despite their size, often go undetected. Wasps build honeycomb nests often in shrubs and under eaves of houses or barns and, like yellow jackets and hornets, are scavengers, increasing the likelihood of their presence at outdoor events where food and drink is being served. Domestic honeybees are found in commercial hives, whereas wild honeybees might build their nests in tree hollows or old logs. Africanized honeybees are hybrids developed from interbreeding of domestic honeybees and African honeybees in South America and are much more aggressive than domestic honeybees, often attacking in swarms. Usually honeybees, and occasionally other stinging insects, leave a barbed stinger and attached venom sack in the skin after they sting. The fire ant, which can be red or black, builds nests in mounds of fresh soil that can be 1 to 2 feet in diameter and elevated at least several inches. These ants are very aggressive, particularly if their nests are disturbed, and often sting multiple times in a circular pattern, producing a sterile pseudopustule that has a distinctive appearance. Education regarding stinging insect avoidance can best be done by an allergist-immunologist who has training and experience in the diagnosis and management of stinging insect hypersensitivity.

Patients who have experienced a systemic reaction to an insect sting should be referred to an allergist-immunologist for skin testing or occasionally *in vitro* testing for specific IgE antibodies to insect venom. Extracts of honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp venom are available for skin testing and VIT. Although there is no venom extract available for commercial use in patients with suspected fire ant hypersensitivity, whole-body extract is available and contains relevant venom allergens, the effectiveness of which is supported by accumulating evidence. It is generally accepted that a positive skin test response to insect venom at a concentration of less than or equal to 1.0 μg/mL demonstrates the presence of specific IgE antibodies. Skin testing with fire ant whole-body extract is considered indicative of specific IgE antibodies if a positive response occurs at a concentration of 1:500 wt/vol or less.

For those patients who have a convincing history of anaphylaxis after an insect sting, especially if they experienced serious symptoms, such as upper airway obstruction or hypotension, it is advisable to consider *in vitro* testing for IgE antibodies or repeat skin testing if the patient has negative skin test responses before concluding that VIT is not indicated. Negative skin test responses within the first few weeks after a reaction to an insect sting might require cautious interpretation. Rarely, patients can have an anaphylactic reaction with a subsequent sting despite negative skin and *in vitro* test responses, possibly because of a non–IgE-mediated mechanism.

Because patients who have experienced an allergic reaction to an insect sting, as defined by history and a positive skin or *in vitro* test response for specific IgE antibodies to insect venom, are at risk for subsequent life-threatening reactions if re-stung, VIT should be considered in such patients. Approximately 30% to 60% of patients with a history of anaphylaxis from an insect sting and venom-specific IgE antibodies detectable by means of skin or *in vitro* testing will experience a systemic reaction when re-stung. As a result, it has been recommended that patients can be better selected for VIT on the basis of the results of an intentional sting challenge. Sting challenges, however, are not consistently reproducible and are associated with considerable risk. The standard management of insect sting hypersensitivity in the United States does not include a sting challenge.

VIT is generally not necessary in children 16 years of age and younger who have experienced isolated cutaneous reactions without systemic manifestations after an insect sting from a wasp, hornet, yellow jacket, or wasp. VIT in adults who have experienced only cutaneous manifestations is controversial but usually recommended. VIT is extremely effective in reducing the risk of a subsequent systemic reaction from an insect sting to less than 5%, and those who experience reactions have milder reactions. VIT is generally not necessary for patients who have had only a large local reaction because the risk of a systemic reaction with a subsequent sting is relatively low. In fact, the vast majority of patients who have had a large local reaction do not need to be tested for specific IgE antibodies to insect venom.

Once initiated, VIT should usually be continued for at least 3 to 5 years. An increasing body of evidence suggests that despite the persistence of a positive skin test response, 80% to 90% of patients will not have a systemic reaction to an insect sting if VIT is stopped after 3 to 5 years. Although most patients can safely discontinue immunotherapy after this period of time, some patients with a history of severe anaphylaxis with shock or loss of consciousness still might be at continued risk for a systemic reaction if VIT is stopped, even after 5 years of immunotherapy. For this reason, some experts recommend continuation of immunotherapy indefinitely in such patients. Other criteria suggested for stopping VIT include a decrease in serum venom-specific IgE to insignificant levels or conversion to a negative skin test response. The optimal duration of fire ant immunotherapy is less well defined. Most allergists consider stopping immunotherapy after a specified period (usually 4-5 years) either empirically or only when skin test responses become negative. Until further data are available, a definitive

recommendation about the duration of immunotherapy for fire ant venom cannot be made.

Less is known about the natural history of fire ant venom hypersensitivity and the effectiveness of immunotherapy than is known about other stinging insects. Fire ant whole-body extract has been shown to contain relevant venom allergens, and evidence continues to accumulate, despite the lack of any placebo-controlled study, to support the effectiveness of immunotherapy with fire ant whole-body extract.

Patients who have experienced more than a local reaction to an insect sting should be prescribed injectable epinephrine (eg, EpiPen and EpiPenJr) and should be advised to carry it with them at all times. Because some patients who experience anaphylaxis might require more than one injection of epinephrine, prescription for more than one EpiPen or EpiPenJr should be considered. Patients and advocates who might be administering epinephrine should be taught how to administer this drug and under what circumstances this should be done. Although patients with coexisting conditions, such as hypertension or cardiac arrhythmias, or concomitant medications, such as β-adrenergic blocking agents, might require special attention, there is no contraindication to the use of epinephrine in a life-threatening situation, such as anaphylaxis. More than one dose of epinephrine might be required with persistence or recurrence of symptoms.

ANNOTATIONS TO FIG 1

Box 1: Patient presents with a history of insect sting reaction

Although insects sting many persons each year, most individuals do not have significant reactions and do not need medical attention. Most who are stung have only local reactions and require only symptomatic, if any, treatment. Persons who have a history of insect stings causing systemic reactions require evaluation and usually treatment. Reactions can range from large local swelling to life-threatening systemic reactions. Delayed or toxic reactions might also occur. Taking a careful history can usually make the diagnosis of insect sting reaction.

Box 2: History and physical examination

Identification of the insect responsible might be helpful in diagnosis and treatment. Patients should be encouraged to bring the offending insect, if available, to the physician for identification.

Factors that might be helpful in identification include the following:

- the patient's activity at the time of the sting (eg, cutting a hedge),
- the location of the person at the time of the sting (eg, close to an insect nest),
- the type of insect activity in the area where the patient was stung, and
- visual identification of the insect.

Young children present special problems with identification of the culprit insect. The presence of a stinger, which is left primarily by honeybees, or the presence of a pustule as a result of a fire ant sting (up to 24 hours later) might help in insect identification.

Box 3: Was there a systemic reaction?

Most insect stings result in local reactions. These include the following:

- redness,
- swelling, and
- itching and pain.

Large local reactions usually include the following features:

- increase in size for 24 to 48 hours,
- swelling to more than 10 cm in diameter,
- possible involvement of more than one joint area, and
  - 5 to 10 days to resolve.

Systemic reactions include a spectrum of manifestations ranging from mild to life-threatening. These include the following:

- cutaneous responses (eg, urticaria and angioedema),
- bronchospasm,
- large airway obstruction (tongue or throat swelling, laryngeal edema), and
- hypotension and shock.

The key feature that distinguishes a systemic reaction from a large local reaction is the nature of the systemic symptoms and involvement of parts of the body not contiguous with the site of the sting.

Box 4, A and B: Provide symptomatic treatment if needed

Most insect stings cause local reactions that are of little serious medical consequence, and no specific treatment is usually required. Some local reactions are manifested by extensive erythematous swelling surrounding the sting site that might persist for several days or more and can be accompanied by itching, pain, or both. Cold compresses might help to reduce local pain and swelling. Oral antihistamines and oral analgesics might also help to reduce the pain or itching associated with cutaneous reactions. Many physicians use oral corticosteroids for large local reactions; several reports support their effectiveness, although definitive proof of efficacy through controlled studies is lacking. Because the swelling is caused by mediator release and not by infection, antibiotics are not indicated unless there is evidence of secondary infection (a common misdiagnosis).

Large local reactions can be IgE mediated but are almost always self-limited and rarely create serious health problems. Patients who have previously experienced large local reactions often have large local reactions to subsequent stings, and up to 10% might eventually have a systemic reaction. Some patients who have had large

local reactions might seek guidance on insect avoidance measures. It is optional but usually not necessary to prescribe an injectable epinephrine kit for use if the patient experiences a systemic reaction in the future. The vast majority of patients with large local reactions need only symptomatic care and are not candidates for testing for venom-specific IgE or VIT. Immunotherapy has, however, been shown to reduce the severity of large local reactions with future stings in a patient with a history of severe local reactions and venom-specific IgE, but a previous report found immunotherapy to be ineffective in preventing reoccurrence of large local reactions.

Box 5: Prescribe epinephrine for self-administration/refer to an allergist-immunologist/recommend insect avoidance

Preventive management includes measures to prevent subsequent stings and to prevent subsequent systemic reactions if the patient is stung. Injectable epinephrine should be provided, and the patient should be instructed on its proper administration and use. Patients should also consider obtaining a medical identification bracelet or necklace. A patient with a history of severe reaction should have injectable epinephrine prescribed because even if the test result for venom-specific IgE is negative, there is a small risk of a systemic reaction. For those patients with very mild or questionable systemic reactions and negative test results for venom-specific IgE, there is no consensus regarding prescription of injectable epinephrine because many physicians believe it is not warranted, whereas others prefer to prescribe it in this situation. Referral to an allergist is appropriate for any patient who has had an allergic reaction and is indicated for any patient who is a potential candidate for immunotherapy, as outlined in Box 6.

Box 6, A, B, and C: Is the patient a child whose reaction was limited to the cutaneous system?

The usual criteria for immunotherapy include a systemic reaction to an insect sting and demonstration of venom-specific IgE by either skin or *in vitro* testing. However, immunotherapy is usually not prescribed for patients 16 years of age and younger who have experienced only cutaneous systemic reactions after an insect sting. They only have about a 10% chance of having a systemic reaction if re-stung, and if a subsequent systemic reaction does occur in these children, it is very unlikely to be worse than the initial isolated cutaneous reaction. Therefore VIT is generally not necessary for patients 16 years of age and younger who have experienced only cutaneous systemic reactions. VIT is still an acceptable option if there are special circumstances, such as lifestyle considerations, that place the child at risk for frequent or multiple stings or if the parents or guardians request venom immunotherapy. Although there is still some controversy in regard to adults who have experienced only cutaneous systemic reactions, there is insufficient evidence to justify withholding VIT for that group of individuals at this time. Although most physicians generally apply the same criteria in selecting patients to receive immunotherapy for fire ant allergy, it is not established that children with only systemic cutaneous reactions are not at risk for serious systemic reactions to subsequent stings. Because the natural history of fire ant hypersensitivity in children who have only cutaneous manifestations has not been well elucidated and there is increased risk of fire ant stings in children who live in areas in which fire ants are prevalent, immunotherapy can be considered for such children.

Box 7: Perform skin testing

Skin tests should be performed on patients for whom venom immunotherapy might be indicated. Skin prick tests with a concentration in the range of 1.0 μg/mL are often performed before intracutaneous tests but are not used by all allergists.

Intracutaneous tests usually start with a concentration in the range of 0.001 to 0.01 μg/mL. If intracutaneous test results at this concentration are negative, the concentration is increased by 10-fold increments until a positive skin test response occurs or a maximum concentration of 1.0 μg/mL is reached. Increasing concentrations of fire ant extract are also used (see text section on fire ants). Positive and negative controls should be placed during skin testing.

Because the insect that caused the sting reaction often cannot be identified, testing is usually done with all of the commercially available venom extracts. However, fire ant is only included under special circumstances (see text). Venoms might contain shared antigenic components. Cross-sensitization and extensive immunologic cross-reactivity have been demonstrated between hornet and yellow jacket venoms (vespids); cross-reactivity is also fairly common, although less extensive, between wasp and other venoms and is uncommon between honeybee and vespid venoms. Fire ant venom has very limited cross-reactivity with other stinging insect venoms.

Box 8: Positive skin test response?

Venom immunotherapy is recommended for patients who have had a systemic insect sting reaction, who have a positive skin test response, and who meet the criteria outlined in the annotation for Box 6. There is no absolute correlation between the skin test reactivity or the level of venom-specific IgE and the severity of the reaction to a sting. Near-fatal and fatal reactions have occurred in patients with barely detectable venom IgE antibodies by means of skin or *in vitro* testing.

Box 8A: Is further testing needed?

Although skin testing has generally been the most reliable diagnostic method used to identify venom-specific IgE and remains the preferred testing modality for most patients, it has been recognized that rare patients might have venom-specific IgE, which is not detected by means of skin testing. Therefore it is recommended that further evaluation for detection of venom-specific IgE be

performed if the skin test result is negative in a patient with a history of a severe systemic reaction. There is no clear scientific evidence that defines the severity of a reaction requiring further evaluation for venom-specific IgE. Patients with a history of wheezing with dyspnea or increased respiratory effort, stridor, or other signs of large airway obstruction; hypotension; shock; or loss of consciousness usually need further evaluation.

Box 8, B, C, and D

For patients who have had a severe systemic reaction, as described in the preceding annotation, to an insect sting and who have negative venom skin test responses, it would be prudent to verify this result with repeat skin testing or *in vitro* testing before concluding that VIT is not necessary. If such test responses are positive, VIT is indicated. If repeat test responses fail to demonstrate the presence of IgE antibodies, there is no indication for venom immunotherapy.

Box 9: Recommend and give VIT

VIT greatly reduces the risk of systemic reactions in stinging insect–sensitive patients with an efficacy of 95% to 97%. Patients who have had a systemic reaction from an insect sting and evidence of venom-specific IgE should therefore be advised to receive VIT. The goal of VIT is primarily to prevent life-threatening reactions. A secondary benefit is that it might alleviate anxiety related to insect stings.

Candidates for VIT should be informed in writing or verbally with documentation in the record about the potential benefits and risks related to the procedure. Patients should receive a description of the procedure and be informed that, although the risk of anaphylaxis is small, they must wait for 20 to 30 minutes after each injection and follow any other specific policies and rules of the provider of the VIT.

In the opinion of some experts, all venoms eliciting positive responses for venom-specific IgE should be included in the immunotherapy vaccine, whereas others contend that if the insect that caused the reaction can be clearly identified, only that venom is needed for VIT, even if skin or *in vitro* test responses for other stinging insects are positive. Depending on the culprit insect, it is likely that other positive skin test or *in vitro* test responses will be obtained. Immunotherapy for patients with fire ant hypersensitivity consists of injections with a whole-body vaccine and should be initiated in patients with a history of a systemic reaction to a fire ant sting who have a positive skin test response with whole-body vaccine or a positive *in vitro* assay result.

VIT injections are generally administered at weekly intervals, beginning with doses no greater than 0.1 to 0.5 μg and increasing to a maintenance dose of up to 100 μg per venom. The dosage schedule for fire ant immunotherapy is less well defined in terms of starting dose and rapidity of buildup. Although most experts recommend a maintenance dose of 0.5 mL of a 1:100 wt/vol dilution, and there is increasing evidence that this dose is protective, a 1:10 wt/vol maintenance concentration has been recommended by some. The interval between maintenance dose injections can be increased to 4-week intervals during the first year of VIT and eventually to every 6 to 8 weeks during subsequent years. Rapid desensitization protocols have been used successfully and safely to treat flying Hymenoptera and fire ant sting allergy.

Patients with insect sting allergy who are taking β-adrenergic blocking agents are at greater risk for more serious anaphylaxis to VIT or a sting. Therefore patients who have stinging insect hypersensitivity should not be prescribed β-adrenergic blocking agents unless absolutely necessary. If the patient who has stinging insect hypersensitivity cannot discontinue the β-adrenergic blocking agent, the decision to administer immunotherapy should be made on an individual basis after analysis of potential risks and benefits. There are some reports that taking angiotensin-converting enzyme inhibitors might also increase risk.

Box 10 and 10A: Immunotherapy failure

VIT at an accepted maintenance dosage is very effective but does not protect all patients. For patients who have allergic reactions to insect stings while receiving maintenance immunotherapy, it is first necessary to identify the culprit insect. If the insect is the same as that causing the initial reaction, an increase in venom dose of up to 200 μg per injection might provide protection.

Box 11: Consider stopping VIT after 3 to 5 years

Guidelines for discontinuation of VIT are evolving. Whereas the package insert for the venom extract product recommends that VIT be continued indefinitely, a decrease in serum venom-specific IgE to insignificant levels or conversion to a negative skin test response have been used as criteria for discontinuing treatment. An increasing body of evidence suggests that despite the persistence of a positive skin test response, approximately 90% of patients will not have a systemic reaction to an insect sting if VIT is stopped after 3 to 5 years, and it is therefore reasonable to consider discontinuation in most patients after therapy of this duration or after losing skin test reactivity. However, there remains a small risk that future sting reactions could occur. In addition, severe reactions have occurred several years after stopping VIT in a small number of patients whose skin test responses became negative while receiving venom immunotherapy. Conversely, although some patients will lose their skin reactivity to stinging insect venom, the persistence of such reactivity does not mean that all such patients are at increased risk of having a systemic reaction if subsequently stung. A decision about the duration of VIT is made individually after discussion between the patient and physician and might involve consideration of lifestyle, occupation, coexistent disease, medications, severity of sting reactions, and other factors. Patients with a history of

severe anaphylaxis (shock or loss of consciousness), even after 5 years of immunotherapy, still might be at continued risk for a systemic reaction if VIT is stopped. For this reason, some recommend that immunotherapy be continued indefinitely in such patients (see text for details).

The optimal duration of imported fire ant immunotherapy has not been clearly established. Skin reactivity appears to be a poor indicator of the risk for a systemic reaction to fire ant venom after fire ant immunotherapy. As a result, there is a great deal of variation in recommendations regarding the duration of immunotherapy for fire ant allergy, with some allergists recommending indefinite treatment. Most allergists recommend stopping immunotherapy after a specific period (usually 4-5 years), either empirically or when skin test responses become negative. Until further data are available, a definitive recommendation about the duration of immunotherapy for fire ants cannot be made.

SUMMARY STATEMENTS

Summary statement 1

Individuals with a history of a systemic reaction to an insect sting are at increased risk for subsequent systemic sting reactions. This risk can be significantly reduced with VIT. **A**

Summary statement 2

Individuals who have a history of systemic reactions to insect stings should:

- be educated in ways to avoid insect stings, **D**
- carry epinephrine for emergency self-treatment, **D**
- undergo specific IgE testing for stinging insect sensitivity and be considered for immunotherapy (testing is optional for those patients who would not be candidates for immunotherapy if test responses were positive), **A**
- consider obtaining a medical identification bracelet or necklace. **D**

Summary statement 3

Immediate hypersensitivity skin tests with stinging insect venoms are indicated for individuals who are candidates for VIT. **A**

Skin tests, rather than *in vitro* assays, should be used for initial measurement of venom-specific IgE, except in special circumstances. If skin test responses are negative and the patient has had a severe allergic reaction, further testing (*in vitro* testing, repeat skin testing, or both) is recommended. **C**

Summary statement 4

VIT is recommended for all patients who have experienced a systemic reaction to an insect sting and who have specific IgE to venom allergens, with the following special considerations:

- VIT is generally not necessary in children 16 years of age and younger who have experienced cutaneous systemic reactions without other systemic manifestations of a reaction after an insect sting from a wasp, hornet, yellow jacket, or bee. **C**
- Adults who have experienced only cutaneous manifestations to an insect sting are generally considered candidates for VIT, although the need for immunotherapy in this group of patients is controversial. **D**
- Because the natural history of fire ant hypersensitivity in children who have only cutaneous manifestations has not been well elucidated and there is increased risk of fire ant stings in children who live in areas where fire ants are prevalent, immunotherapy might be considered for such children. **D**

Summary statement 5

Once begun, VIT should usually be continued for at least 3 to 5 years. Although most patients can then safely discontinue immunotherapy, some patients might need to continue immunotherapy indefinitely. **C**

INTRODUCTION

Most insect stings are associated with transient local reactions characterized by pain, swelling, and redness, which usually last from a few hours to a few days and generally resolve with simple treatment measures. More widespread local reactions extending from the sting site and lasting up to 1 week occur in approximately l0% to 15% of adults. More serious anaphylactic sting reactions account for at least 40 deaths per year in the United States. It is estimated that after insect stings, systemic reactions that are potentially life-threatening occur in 0.4% to 0.8% of children and 3% of adults.[1-4] After a systemic reaction, the diagnosis of stinging insect hypersensitivity should be confirmed, and it is imperative that appropriate treatment be instituted to prevent systemic reactions from subsequent stings. Prompt recognition and treatment of systemic reactions and appropriate allergy management, as described in this practice parameter, can reduce the occurrence of future systemic reactions and fatalities.[5-14] This parameter is an update of the first parameter on insect sting hypersensitivity (Portnoy JM, Moffitt JE, Golden DBK, Bernstein IL, et al. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80). It follows the same format as that document, with some substantive changes reflecting advancements in scientific knowledge and their effect on the management of insect sting allergy. The parameter addresses the management of allergic reactions from yellow jacket, hornet, wasp, honeybee, and imported fire ant stings. Much less is known about allergic reactions to stings and bites of other insects, and they are not the subject of this parameter.

STINGING INSECT IDENTIFICATION

Identification of the insect responsible for an allergic reaction is helpful in diagnosis, treatment, and avoidance education. Patients should be encouraged to bring the captured or killed offending insect to the physician for identification.

Factors that might be helpful in the identification of stinging insects include the following:

- the person's activity at the time of the sting (eg, hedge clipping),
- the location of the person at the time of the sting (eg, near the eaves of a house or near an open garbage can),
- the type of insect activity in the area when the patient was stung,
- visual identification of the insect,
- time of year (yellow jackets are more prevalent in late summer),
- food exposure (food attracts yellow jackets), and
- part of country.

Identification might be particularly difficult in cases involving young children because they are usually not able to specify the insect. The presence of a stinger, which is left usually by honeybees (but occasionally by other insects), or the presence of a pseudopustule as a result of fire ant sting (up to 24 hours later) might help in insect identification.

Yellow jackets are ground-dwelling insects and can be encountered during yard work, farming, or gardening. They can also be found in wall tunnels or crevices and in hollow logs. Yellow jackets are very aggressive and sting with minimal provocation, especially in the presence of food. Patients have been stung in the mouth, oropharynx, or esophagus while drinking a beverage from a container or straw that contained a yellow jacket.

Hornets, which are related to yellow jackets, build large papier-mâché nests that are several feet in diameter and are usually found in trees or shrubs. Hornets are extremely aggressive, particularly in the vicinity of the nest, and have been known to chase individuals for some distance before stinging.

Wasps build honeycomb nests that are several inches or more in diameter and might be seen on the outside of the nest. The nests can be found in shrubs, under the eaves of houses or barns, and occasionally in pipes on playgrounds or under patio furniture.

Yellow jackets, hornets, and wasps are in the vespid family and feed on human foods. They are especially attracted to sweet food. Consequently, they can be found around garbage cans, leftover food, or at outdoor events where food and soft drinks are served.

Domestic honeybees are found in commercial hives. Wild honeybee nests can be found in tree hollows, old logs, or in buildings. Hives usually contain hundreds or thousands of bees.

Honeybees, except for Africanized honeybees, are usually nonaggressive when away from their hives. Africanized honeybees are hybrids that developed from interbreeding of domestic honeybees and African honeybees in South America. Their domain has now expanded northward into portions of the United States. They can now be found in several states, including Texas, New Mexico, Arizona, Nevada, and California. They are far more aggressive than domestic honeybees and more likely to attack in swarms. Their venom is almost identical to domestic honeybee venom.

Honeybees usually leave a barbed stinger with attached venom sac in the skin after they sting, but bumblebees do not usually leave a stinger. Other insects occasionally leave stingers. Consequently, the presence of a stinger is not absolutely diagnostic of a honeybee sting.

The fire ant, which can be red or black, nests in mounds composed of fresh soil that can be at least several inches high and can extend 1 to 2 ft in diameter. Fire ants do not generally denude the area around their nest, and therefore vegetation might be found growing through the mounds. There can be multiple mounds a few feet apart. Fire ant mounds are very common along southeastern roadways and therefore are a danger to traveling motorists. In sandy areas nests are flat. In addition, they are a major problem in residential neighborhoods, back yards, and public places. Their distribution in the United States is depicted in Fig 2. These ants are very aggressive, particularly if their nests are disturbed, and are often responsible for multiple stings. A sterile pseudopustule, which develops at the site of a sting in less than 24 hours, is pathognomonic of a fire ant sting.

STINGING INSECT REACTIONS

Without medical intervention, individuals who have had an allergic reaction from an insect sting might be at risk for further life-threatening allergic reactions if re-stung. Immunotherapy with vaccines of stinging insect venom reduces the risk of subsequent systemic reactions.[13-17] Vaccines of honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp venom are available for skin testing and immunotherapy. Although Africanized honeybees (''killer bees'') are much more aggressive than domestic honeybees, their venom is qualitatively similar to that of domestic honeybees. Imported fire ant (*Solenopsis* species) venom is unavailable for clinical use, but fire ant whole-body vaccine contains relevant venom allergens. Accumulating evidence in the absence of a double-blinded controlled study supports the contention that immunotherapy with fire ant whole-body vaccine is protective.[5-11]

Management of insect sting reactions

Local reactions. Most insect stings cause transient localized reactions that are of little serious medical consequence, and no specific treatment is usually required. Some local reactions consist of extensive erythematous swelling surrounding the sting site that might persist for several days or more and might be accompanied

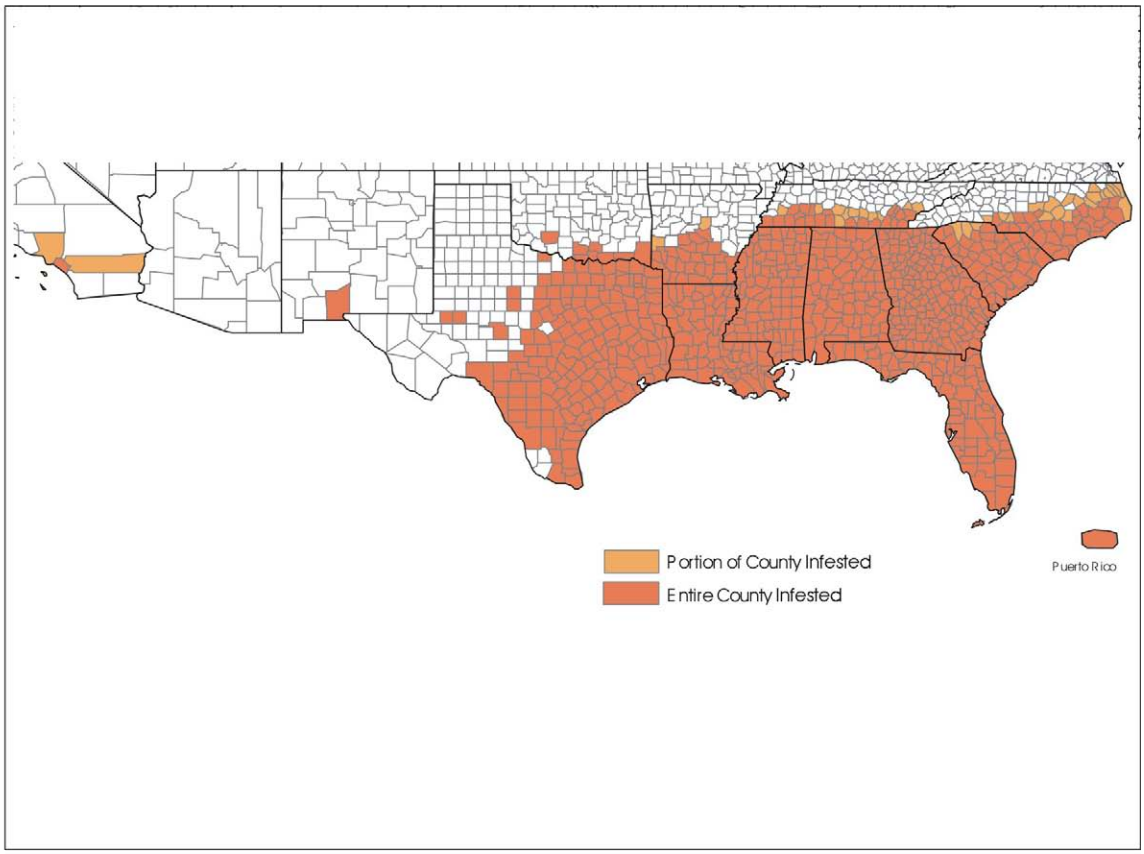

FIG 2. Map depicting current spread of imported fire ants within the United States. Modified from US Department of Agriculture.

by itching, pain, or both. Cold compresses might help to reduce local pain and swelling. Oral antihistamines and analgesics might also help reduce the pain or itching associated with cutaneous reactions. Some physicians use oral corticosteroids for large local reactions. No controlled studies with oral corticosteroids have been performed, but several reports support their efficacy. Because the swelling is caused by mediator release and not by infection, antibiotics are not needed unless secondary infection, which is a rare complication, is present.

Fire ant stings typically cause a sterile pseudopustule 24 hours after the sting. The material in the vesicle is necrotic tissue and is not caused by infection at the site of the sting. The vesicle should be left intact, but if it is accidentally opened, it should be cleansed with soap and water to prevent secondary infection. Although secondary infection is the most common complication of fire ant stings, this is unusual. In the absence of infection, stings are not treated with antibiotics.[9]

Systemic reactions. Systemic reactions include a spectrum of manifestations ranging from cutaneous responses (eg, urticaria and angioedema) to life-threatening reactions manifested by bronchospasm, edema of the upper airway, and shock.

Treatment of anaphylactic reactions caused by insect stings is the same as the treatment of anaphylaxis as a result of other causes. The reader is referred to the practice parameter entitled "The diagnosis and management of anaphylaxis."[12] If a barbed stinger is present, the suspected insect is usually a honeybee. Removal of a stinger within the first 20 to 30 seconds after a sting might prevent injection of additional venom. Removal usually can be accomplished by simply flicking or scraping the stinger away with a fingernail. Grasping the venom sac with the fingers and pulling it out might result in injection of additional venom and should be avoided.

Toxic reactions might occur after multiple simultaneous stings and might be clinically indistinguishable from allergic reactions. Venom components can produce physiologic effects that mimic those produced when mediators are released during the course of allergic reactions. Although unusual, reactions such as serum sickness, vasculitis, neuritis, encephalitis, and nephrosis have been reported after insect stings.[18-20]

INDICATIONS FOR REFERRAL TO AN ALLERGIST-IMMUNOLOGIST

Referral to an allergist-immunologist who has had training and experience in the diagnosis and treatment of, as well as patient education regarding, stinging insect

hypersensitivity should be considered for patients who[13-15]:

- have experienced a systemic reaction to an insect sting,
- have experienced anaphylaxis with an insect sting as a possible cause,
- need education regarding stinging insect avoidance or emergency treatment,
- might be candidates for VIT,
- have a coexisting situation that might complicate treatment of anaphylaxis (eg, taking β-blockers, hypertension, cardiac arrhythmias), or
- request an allergy-immunology consultation.

A diagnosis of stinging insect hypersensitivity is based on a history of a systemic reaction after a sting supported by the demonstration of specific IgE antibodies to insect venom, usually by means of immediate hypersensitivity skin testing initially but occasionally by means of *in vitro* assay.

PREVENTIVE MANAGEMENT

Summary Statement 1: Individuals with a history of a systemic reaction to an insect sting are at increased risk for subsequent systemic sting reactions. This risk can be significantly reduced with VIT.

Summary Statement 2: Individuals who have a history of systemic reactions to insect stings should:

- be educated in ways to avoid insect stings,
- carry epinephrine for emergency self-treatment,
- undergo specific IgE testing for stinging insect sensitivity and be considered for immunotherapy (testing is optional for those patients who would not be candidates for immunotherapy if test responses were positive), and
- consider obtaining a medical identification bracelet or necklace.

Three tenets of treatment for patients at risk of systemic reactions from insect stings are education regarding insect avoidance, availability of emergency medication, and venom immunotherapy. Avoidance measures to reduce the likelihood of insect stings include the following:

- Have known or suspected nests in the immediate vicinity of the patient's home exterminated by trained professionals; periodic surveillance by experts regarding the existence of nests should be considered.
  - Avoid wearing brightly colored clothing or flowery prints and using any strongly scented material that might attract insects.
- Do not walk outside without shoes.
- Wear long pants, long-sleeved shirts, socks, shoes, head covering, and work gloves when working outdoors.
  - Be cautious near bushes, eaves, and attics and avoid garbage containers and picnic areas.
- Keep insecticides approved for use on stinging insects readily available to kill stinging insects from a distance if necessary. Stinging insects are not affected by insect repellants. Fire ants require different specific insecticides.
- Be cautious when eating or drinking outdoors or in situations outdoors where food and beverages are being served or consumed.

IMMEDIATE TREATMENT

Epinephrine is the drug of choice for the treatment of anaphylaxis. Patients allergic to insect venom should carry epinephrine at an appropriate dose for administration in case of a sting. EpiPen (0.30 mg of epinephrine) and EpiPenJr (0.15 mg of epinephrine) are spring-actuated autoinjectors. Patients and parents of children who have experienced a systemic reaction to an insect sting should be taught how to administer epinephrine and under what circumstances to do so. There is no contraindication to the use of epinephrine in a life-threatening situation, such as anaphylaxis. Repeat dosing might be required for persistent and recurrent symptoms. Patients who also have cardiovascular disease should be given epinephrine for use in the event of an allergic reaction, despite concern about epinephrine's cardiac effects because of the potential profound effects of anaphylaxis.

IMMEDIATE HYPERSENSITIVITY TESTING

Summary Statement 3: Immediate hypersensitivity skin tests with stinging insect venoms are indicated for individuals who are candidates for VIT. Skin tests, rather than *in vitro* assays, should be used for the initial measurement of venom-specific IgE, except in special circumstances. If skin test responses are negative and the patient has had a severe allergic reaction, further testing, either *in vitro* testing, repeat skin testing, or both, is recommended.

Skin testing for honeybee, wasps, hornets, and yellow jackets

The presence of venom-specific IgE is usually confirmed by means of intracutaneous skin testing.[16,17,21] Skin prick tests at a concentration in the range of 1.0 μg/mL are often performed before intracutaneous tests but are not used by all allergists. Initial intracutaneous tests generally are done with venom concentrations of no stronger than 0.001 to 0.01 μg/mL. If intracutaneous test responses at these concentrations are negative, the concentration is increased by 10-fold increments until a positive skin test response occurs or a maximum concentration of 1.0 μg/mL is reached. Positive and negative controls also should be done at this time. It is generally accepted that a positive skin test response at

a concentration of less than or equal to 1.0 μg/mL demonstrates the presence of specific IgE antibodies; however, false-positive results from nonspecific responses can occur at higher concentrations (ie, >1.0 μg/mL).[21] An accelerated method for performing venom skin testing has been described.[22] There is no absolute correlation between the degree of skin test reactivity or the levels of serum venom-specific IgE and the severity of clinical symptoms. There are patients who have had severe systemic reactions after an insect sting who have barely detectable venom IgE antibody levels determined by using skin tests or *in vitro* tests. In addition, there are occasional patients who have negative skin test responses but have increased levels of serum venom-specific IgE.[23,24] It is now advisable to consider *in vitro* testing or repeat skin testing for those rare patients who have a convincing history of anaphylaxis after an insect sting and who have negative skin test responses before concluding that VIT is not necessary. Currently, there is no consensus about whether this should be done in all patients with negative skin test responses who would be potential candidates for immunotherapy, but it is recommended for those people who have had serious allergic symptoms, such as respiratory distress, upper airway obstruction, shock, hypotension, or loss of consciousness. Many physicians postpone testing for venom-specific IgE until 3 to 6 weeks after the sting reaction because of concerns about reduced sensitivity of testing modalities within the first few weeks after the reaction. One study found that 79% of patients with insect venom allergy could be identified at 1 week after the sting reaction when patients underwent both skin and *in vitro* tests; the additional 21% of patients whose test responses were negative initially had at least one positive test response when tested again with both methods at 4 to 6 weeks after the reaction.[25] Negative test responses for venom-specific IgE obtained within the first few weeks after a sting reaction might require cautious interpretation. A negative *in vitro* assay in addition to a negative skin test response does not fully exclude the possibility of an anaphylactic reaction to a subsequent sting because rare occurrences have been reported.[23] The pathogenesis of these rare reactions might involve a non-IgE mechanism.

Because the insect that caused the sting often cannot he identified, testing is usually done with all of the commercially available bee and vespid venom vaccines. Venoms might contain shared antigenic components. Cross-sensitization and immunologic cross-reactivity are extensive between hornet and yellow jacket venoms, somewhat less extensive for yellow jacket and hornet with wasp venoms, and less common between honeybee and the other venoms.[26-31]

Skin testing for fire ant hypersensitivity

Imported fire ant whole-body vaccine is the only reagent currently available for diagnostic testing in patients with suspected fire ant hypersensitivity. If screening skin prick test responses are negative, intracutaneous testing should be performed, with initial concentrations of approximately 1×10^{-6} (1:1 million) wt/vol. Intracutaneous skin test concentration should be increased by increments until a positive response is elicited or a maximum concentration of 1×10^{-3} (1:1000) or 2×10^{-3} (1:500) wt/vol is reached.[5,9,11]

Limited cross-reactivity exists between the antigens in fire ant venom and the antigens in venoms of other Hymenoptera.[31,32] If the patient is able to positively identify fire ant as the stinging insect, testing with other stinging insect venoms is not indicated. The presence of a pseudopustule at the sting site at 24 hours after the sting is diagnostic of a fire ant sting. This type of reaction should be looked for carefully in endemic areas if the identity of the culprit insect is uncertain.

In vitro testing. *In vitro* tests can also be used for detection of venom-specific IgE in those individuals who cannot undergo skin testing. This includes patients with dermatographia or severe skin disease. Skin tests are generally the preferred initial testing method. About 20% of people with positive venom skin test responses have undetectable levels of serum venom-specific IgE (negative *in vitro* test). However, recent studies have demonstrated that 10% to 20% of patients with negative skin test responses have positive *in vitro* test responses when using assays capable of detecting low levels of venom-specific IgE.[23,24] Indications for obtaining these studies are discussed in the preceding section on skin tests.

IMMUNOTHERAPY

Summary Statement 4: Venom immunotherapy is recommended for all patients who have experienced a systemic reaction to an insect sting and who have specific IgE to venom allergens with the following special considerations:

- VIT is generally not necessary in children 16 years of age and younger who have experienced cutaneous systemic reactions without other systemic manifestations of a reaction after an insect sting from a wasp, hornet, yellow jacket, or bee.
- Adults who have experienced only cutaneous manifestations to an insect sting are generally considered candidates for VIT, although the need for immunotherapy in this group of patients is controversial.
- Because the natural history of fire ant hypersensitivity in children who have only cutaneous manifestations has not been well elucidated and there is increased risk of fire ant stings in children who live in areas where fire ants are prevalent, immunotherapy might be considered for such children.

Venom immunotherapy for bees, yellow jackets, hornets, and wasps

VIT has proved to be an extremely effective form of treatment for individuals at risk of insect sting anaphylaxis. VIT has been shown to reduce the risk of a sub-

sequent systemic sting reaction to less than 5% compared with the risk of such reactions in untreated patients, for whom the risk might be as high as 60%.[13,14,16,33,34] Moreover, those patients receiving VIT who do experience systemic reactions after an insect sting generally have milder reactions. Candidates for immunotherapy should be informed with documentation in the record about the potential benefits and risks related to the procedure.

Criteria for immunotherapy

Patients who have had a systemic reaction from an insect sting and are found to have venom-specific IgE should generally receive VIT. The goals of VIT are to (1) prevent systemic reactions and (2) alleviate patient anxiety related to insect stings.

Evaluation of patients who have had anaphylactic reactions from insect stings is influenced by reactions that involve more than the cutaneous system and those reactions that are confined to the cutaneous system. The most serious anaphylactic reactions involve the cardiac and respiratory systems and are potentially life-threatening. The most common cardiovascular reaction is hypotension, which is usually associated with tachycardia. More serious reactions include loss of consciousness or shock, airway compromise, and death. Some reactions might be difficult to distinguish from vasovagal reactions. Although bradycardia is a distinguishing aspect of vasovagal reactions, it can occur rarely in anaphylaxis. Paradoxically, hypertension might also occur, presumably from release of endogenous sympathomimetic amines. Respiratory symptoms might include dyspnea, chest tightness, stridor, wheezing, and other symptoms of large or small airway obstruction. Laryngeal edema is the most common cause of death from anaphylaxis. Anaphylaxis can also include symptoms such as dizziness, nausea, vomiting, and diarrhea. Adults and children who have had these reactions are at greatest risk for similar life-threatening reactions after subsequent stings. Therefore VIT is recommended for individuals with a history of these manifestations and the presence of venom-specific IgE.

Cutaneous systemic reactions, such as urticaria, occasional angioedema, or flushing and pruritus, can occur after an insect sting and can be profound. Prospective studies have shown that patients 16 years of age and younger who have experienced cutaneous systemic reactions without other allergic manifestations have approximately a 10% chance of having a systemic reaction if re-stung. If a systemic reaction does occur, it is likely to be limited to the skin.[15] Therefore VIT is generally not necessary for patients 16 years of age and younger who have experienced only cutaneous systemic reactions; VIT is still an acceptable option in such patients if requested by the patients' parents or if the child is likely to experience frequent or multiple stings.

On the other hand, VIT is generally recommended for patients older than 16 years with systemic reactions limited to the skin. Because some studies have suggested that these patients are at low risk of subsequent systemic reactions, some believe that venom immunotherapy is optional in this group of patients.[13,34]

Challenge stings

Approximately 30% to 60% of patients with a history of anaphylaxis from an insect sting and detectable venom-specific IgE by means of skin testing or *in vitro* testing will experience a systemic reaction when re-stung. An intentional sting challenge has been recommended by some to better select those patients who need VIT.[35-37] Patients allergic to honeybees are more likely to have positive sting challenge results than those allergic to yellow jackets. Sting challenges, however, are neither consistently reproducible nor without risk. About 20% of patients who do not react to a sting challenge will react after a second challenge.[36,37] In addition, serious allergic reactions, such as anaphylaxis necessitating intensive care treatment, have occurred from these challenges. The use of sting challenges requires special centers because of the risk of serious reactions and is impractical as a general prerequisite for VIT in the United States.[38]

Large local reactions

Extreme swelling extending from the sting site, usually peaking at 48 to 72 hours after a sting, might be an IgE-mediated late-phase reaction. The risk of a systemic reaction in patients with a history of large local reactions in most studies is no more than 5% to 10%.[39,40] Because the risk of a systemic reaction is relatively low in patients who have previously had large local reactions, VIT is generally not recommended in such patients. Providing injectable epinephrine to patients who have a history of large local reactions for use if a subsequent systemic reaction occurs is optional but usually not necessary. This decision might be influenced by factors such as the potential risk of being stung, personal health issues (eg, the presence of cardiovascular disease), and individual preference.

Although large local reactions can have an allergic cause, as noted, they pose only minimal risk for anaphylaxis from future stings. The vast majority of patients with large local reactions do not need to be tested for the presence of venom-specific IgE and are not candidates for immunotherapy. One report suggests that immunotherapy might reduce the morbidity from severe local reactions to honeybee stings.[41] A previous study found that VIT was not helpful in preventing subsequent large local reactions.[39,41] Most patients with a history of large local reactions will experience similar reactions after subsequent stings.

Selection of venoms for immunotherapy

Identification of the stinging insect responsible for a reaction can be aided by the geographic locality, the circumstances of the sting, and the appearance and location of the insect, nest, or both. Consensus data on

which venoms to include for immunotherapy are not available. In the opinion of some authors, if the insect that caused the reaction can be clearly identified, the vaccine used for VIT need only contain that insect venom, despite positive skin or *in vitro* test responses for other stinging insects.[29,34] Other authors recommend that the vaccine contain venoms from all insects for which positive test responses were obtained.[16,33]

Immunotherapy for fire ant venom hypersensitivity

Compared with other stinging insects, less is known about the natural history of fire ant venom hypersensitivity and the effectiveness of immunotherapy.[8,9,42] Fire ant whole-body vaccine has been shown to contain relevant venom allergens, and evidence continues to accumulate, despite the absence of a placebo-controlled study, to support its efficacy for use as a diagnostic and therapeutic agent.[5-7,10,32,42-45] The current criteria for immunotherapy for fire ant allergy are similar to those for other Hymenoptera (ie, a history of a systemic reaction and demonstration of fire ant antigen–specific IgE antibodies by means of skin or *in vitro* testing). Controversy exists regarding the management of children who have systemic reactions that are confined to the skin. There has been no study that clearly demonstrates the relative risk of a systemic reaction in such a patient after subsequent stings. However, there is a high frequency of fire ant re-stings in endemic areas.[42] The majority of allergists, but not all, in fire ant–endemic areas do not routinely recommend immunotherapy for children who have had only generalized cutaneous reactions.[46] Thus immunotherapy in these children is considered to be optional at the present time. Lifestyle consideration, parental preferences, and other factors can influence this decision.

Dosage schedules for VIT

VIT injections are administered generally at weekly intervals, usually beginning with levels not greater than 0.1 to 0.5 μg and increasing to a maintenance dose of up to 100 μg per insect venom.[33,34,47] More accelerated schedules for VIT have been published and can be used successfully and safely.[48-53] The physician and patient might consider a variety of factors, such as characteristics and circumstances of the sting reaction and patient lifestyle and preferences in choosing a schedule. There is some controversy about the optimum maintenance dose. Initial studies used 100 μg as the maintenance dose.[33] Other authors have used the 50-μg maintenance dose successfully, although some believe that this dose offers a lesser degree of protection.[34,47] Increasing the maintenance dose up to 200 μg per dose has been effective in achieving protection in some patients who have experienced sting reactions while receiving 100 μg of venom immunotherapy maintenance dose.[54]

The interval between maintenance dose injections is usually increased to 4-week intervals during the first year and eventually to every 6 to 8 or even 12 weeks during subsequent years.[55,56]

The dosage schedule for fire ant whole-body vaccine immunotherapy is less well defined in terms of rapidity of buildup. However, most authors recommend a weekly buildup schedule until a maintenance dose is reached, and the interval between doses can then be increased. Two examples of dosage schedules are included in Appendix 1. Successful use of a rush immunotherapy protocol has recently been published.[10] Most reports have recommended a maintenance dose of 0.5 mL of a 1:100 wt/vol vaccine with either *Solenopsis invicta* or a mixture of *Solenopsis invicta* and *Solenopsis richteri* vaccine, although there are some recommendations for a dose as high as 0.5 mL of a 1:10 wt/vol vaccine.[5,6,8-10] A survey of practicing allergists found that 0.5 mL of a 1:100 wt/vol vaccine is the most widely prescribed maintenance dose.[46] Evidence continues to accumulate to support the efficacy of this dosage (0.5 mL of 1:100 wt/vol).[6,10] Special dosing might need to be considered for treatment failures.

Safety considerations related to administration of VIT injections are generally the same as those for other forms of allergen immunotherapy. The major risk of VIT, as with other types of allergen immunotherapy, is anaphylaxis. One study reported that the incidence of systemic reactions from VIT was 12%, although this incidence is higher than that experienced by most allergists.[57] There has been one report of a patient who had serum sickness after venom immunotherapy.[58]

Patients who are taking β-adrenergic blocking agents (see parameter on anaphylaxis) might not respond readily to treatment if they experience an allergic reaction.[12,59,60] Therefore patients who have stinging insect hypersensitivity should not take β-adrenergic blocking agents unless absolutely necessary. If the patient who has stinging insect hypersensitivity cannot discontinue the β-adrenergic blocking agent, VIT should still be given, although with greater caution. In addition, there are data suggesting that patients receiving angiotensin-converting enzyme inhibitors might also be at increased risk of anaphylaxis, but this issue is not fully resolved.[61,62]

Serum sickness has occurred as a sequela to insect stings, usually after an acute systemic reaction.[18-20] Although these patients are subsequently at greater risk of anaphylaxis if re-stung, recurrence of serum sickness has not been observed after initiation of VIT.[20] VIT has been used successfully in this group of patients.

Duration of VIT

Summary Statement 5: Once begun, VIT should usually be continued for at least 3 to 5 years. Although most patients can then safely discontinue immunotherapy, some patients might need to continue immunotherapy indefinitely.

Guidelines for discontinuation of VIT are evolving.[63-65] The package insert for the venom vaccine, which has not changed in more than 20 years, recommends that VIT be continued indefinitely. Criteria suggested for stopping

VIT are a decrease in serum venom-specific IgE to insignificant levels, conversion to a negative skin test response, or a finite period of time (3-5 years). An increasing body of evidence suggests that despite the persistence of a positive skin test response, 80% to 90% of patients will not have a systemic reaction to an insect sting if VIT is stopped after 3 to 5 years and can safely stop immunotherapy after that period of treatment.[13,64-69] The small risk after discontinuation of VIT is a more significant concern for patients who have a history of severe anaphylaxis with shock or loss of consciousness and who maintain persistently positive skin or *in vitro* test responses after receiving immunotherapy for 5 years. The majority of patients, including those with severe anaphylaxis, can safely stop VIT if their skin test responses and specific IgE antibody levels are negative. A few patients who had previously experienced severe anaphylaxis with loss of consciousness and then had negative *in vitro* test responses, skin test responses, or both after several years of immunotherapy have later experienced systemic reactions, several of which were fatal, to subsequent stings after stopping VIT.[68-72] Although this occurrence is rare, some recommend continuation of immunotherapy indefinitely in such patients. The decision to stop immunotherapy can involve consideration of several factors by the patient and physician, including (1) the severity of the initial reaction, (2) the effect of such action on work and leisure activities, (3) the presence of concomitant disease and medications, and (4) patient preferences.

The optimal duration of imported fire ant immunotherapy is less well defined. A survey of allergists indicated a great deal of variation in recommendations regarding the duration of immunotherapy for fire ant allergy.[46] Some allergists recommend indefinite treatment. Most allergists consider stopping immunotherapy after a specified period (usually 4-5 years), either empirically or only when skin test responses become negative. Until further data are available, a definitive recommendation about the duration of immunotherapy for fire ants cannot be made.

We acknowledge the assistance of Susan Grupe of the Joint Council of Allergy, Asthma and Immunology and of Mary Manasco and Vicki Edwards of the University of Mississippi Medical Center in the preparation of the parameter.

REFERENCES

1. Golden DBK. Epidemiology of allergy to insect venoms and stings. Allergy Proc 1989;10:103-7.
2. Settipane G, Boyd G. Prevalence of bee sting allergy in 4,992 Boy Scouts. Acta Allergol 1970;25:292-3.
3. Chaffee F. The prevalence of bee sting allergy in an allergic population. Acta Allergol 1970;25:292-3.
4. Golden DBK, Marsh DG, Kagey-Sobotka A, et al. Epidemiology of insect allergy. JAMA 1989;262:240-4. (LB)
5. Triplett R. Sensitivity to the imported fire ant: successful treatment with immunotherapy. South Med J 1973;66:477-80. (III)
6. Freeman TM, Hylander R, Ortiz A, Martin M. Imported fire ant immunotherapy: effectiveness of whole body extracts. J Allergy Clin Immunol 1992;90:210-5. (IIa)
7. Hoffman D, Jacobson R, Schmidt M, Smith A. Allergens in Hymenoptera venoms, XXIII. Venom content of imported fire ant whole body extracts. Ann Allergy 1991;66:29-31. (LB)
8. Stafford C. Hypersensitivity to fire ant venom. Ann Allergy 1996;77: 87-99.
9. DeShazo R, Butcher B, Banks W. Reactions to stings of the imported fire ant. N Engl J Med 1990;323:462-6.
10. Tankersley MS, Walker RL, Butler WK, Hagan LL, et al. Safety and efficacy of an imported fire ant rush immunotherapy protocol with and without prophylactic treatment. J Allergy Clin Immunol 2002;109: 556-62. (IIa)
11. Kemp SF, deShazo RD, Moffitt JE, et al. Expanding habitat of the imported fire ant *(Solenopsis invicta)*: a public health concern. J Allergy Clin Immunol 2000;105:683-91.
12. Nicklas RA, Bernstein IL, Li JT, Lee RE, Spector SL, Dykewicz MS, et al, editors. The diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998;101(suppl):S465-528.
13. Reisman R. Insect stings. N Engl J Med 1994;331:523-7.
14. Valentine M. Allergy to the stinging insects. Ann Allergy 1993;70: 427-32.
15. Valentine M, Schuberth K, Kagey-Sobotka A. The value of immunotherapy with venom in children with allergy to insect stings. N Engl J Med 1990;323:1601-3.
16. Valentine M. Insect venom allergy: diagnosis and treatment. J Allergy Clin Immunol 1984;73:299-304.
17. Hunt KJ, Valentine MD, Sobotka AK, Lichtenstein L. Diagnosis of allergy to stinging insects by skin testing with Hymenoptera venoms. Ann Intern Med 1976;85:56-9. (IIa)
18. Light W, Reisman R, Shimizu M. Unusual reactions following insect stings. Clinical features and immunologic analysis. J Allergy Clin Immunol 1977;59:391-7. (III)
19. Lichtenstein LM, Golden DBK. The problem patient; postscript to bee stings: delayed serum sickness. Hosp Pract 1983;18:36-46. (IV)
20. Reisman R, Livingston A. Late onset allergic reactions including serum sickness after insect stings. J Allergy Clin Immunol 1989;84: 331-7. (III)
21. Georgitis J, Reisman R. Venom skin tests in insect-allergic and insect-nonallergic populations. J Allergy Clin Immunol 1985;76:803-7. (IIa)
22. Yocum M, Gosselin V, Yunginger J. Safety and efficacy of an accelerated method for venom skin testing. J Allergy Clin Immunol 1996;97:1424-5. (III)
23. Golden DBK, Kagey-Sobotka A, Norman PS, Hamilton RG, et al. Insect sting allergy with negative venom skin test responses. J Allergy Clin Immunol 2001;107:897-901. (III)
24. Reisman RE. Insect sting allergy: The dilemma of the negative skin test reactor. J Allergy Clin Immunol 2001;107:781-2. (IV)
25. Goldberg A, Confino-Cohen R. Timing of venom skin tests and IgE determinations after sting anaphylaxis. J Allergy Clin Immunol 1997; 100:182-4.
26. King TP, Joslyn A, Kochoumian L. Antigenic cross-reactivity of venom proteins from hornets, wasps, and yellow jackets. J Allergy Clin Immunol 1985;75:621-8. (LB)
27. Reisman RE, Mueller U, Wypych J, Elliott W, Arbesman CE. Comparison of the allergenicity and antigenicity of yellow jacket and hornet venoms. J Allergy Clin Immunol 1982;69:268-74. (LB)
28. Reisman RE, Wypych JI, Mueller UR, Grant JA. Comparison of the allergenicity and antigenicity of Polistes venom and other vespid venoms. J Allergy Clin Immunol 1982;70:281-7. (LB)
29. Reisman RE, Mueller U, Wypych JI, Lazell MI. Studies of coexisting honeybee and vespid-venom sensitivity. J Allergy Clin Immunol 1984; 73:246-52. (LB)
30. Hoffman DR. Allergens in Hymenoptera venom. XXV: The amino acid sequences of antigen 5 molecules and the structural basis of antigenic cross-reactivity. J Allergy Clin Immunol 1993;92:707-16. (LB)
31. Hoffman DR, Dove DE, Moffitt JE, Stafford CT. Allergens in Hymenoptera venom XXI. Cross-reactivity and multiple reactivity between fire ant venom and bee and wasp venoms. J Allergy Clin Immunol 1988;82:828-34. (LB)
32. Rhoades RB, Schafer WL, Newman M, Lockey R, Dozier RM, Wubbena PF, et al. Hypersensitivity to the imported fire ant in Florida. Report of 104 cases. J Fla Med Assoc 1977;64:247-54. (III)

33. 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. (IIa)
34. Reisman RE, Livingston A. Venom immunotherapy: 10 years of experience with administration of single venoms and 50 micrograms maintenance doses. J Allergy Clin Immunol 1992;89:1189-95. (III)
35. Blaauw P, Smithuis L. An evaluation of the common diagnostic methods of hypersensitivity for bee and yellow jacket venom by means of an in-hospital sting. J Allergy Clin Immunol 1985;75:556-62. (IIa)
36. Franken HH, Dubois AE, Minkema HJ, van der Heide S, de Monchy JG. 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. (IIa)
37. van der Linden PW, Hack CE, Struyvenberg A, van der Zwan 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. (IIa)
38. Valentine MD. Insect-sting anaphylaxis. Ann Intern Med 1993;118:225-6.
39. 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. (LB)
40. Grant DF, Schuberth KC, Kagey-Sobotka A, Kwiterovich KA, et al. A prospective study of the natural history of large local reactions after Hymenoptera stings in children. J Pediatr 1984;104:664-8.
41. Hamilton RG, Golden DB, Kagey-Sobotka A, Lichenstein LM. Case report of venom immunotherapy for a patient with large local reactions. Ann Allergy Asthma Immunol 2001;87:134-7. (IV)
42. Tracy JM, Demain JG, Quinn JM, Hoffman DR, Goetz DW, Freeman TM. The natural history of exposure to the imported fire ant *(Solenopsis invicta)*. J Allergy Clin Immunol 1995;95:824-8. (IIb)
43. Hannan C, Stafford C, Rhoades R, et al. Seasonal variation in antigens of the imported fire ant. J Allergy Clin Immunol 1986;78:331-6. (LB)
44. Butcher B, deShazo R, Ortiz A, Reed M. RAST-inhibition studies of the imported fire art, *Solenopsis invicta*, with whole body extracts and venom preparations. J Allergy Clin Immunol 1988;81:1096-100. (LB)
45. Strom GB, Boswell R, Jacobs R. In vivo and in vitro comparison of fire ant venom and fire ant whole body extract. J Allergy Clin Immunol 1983;72:46-53. (LB)
46. Moffitt J, Barker J, Stafford C. Management of imported fire ant allergy: results of a survey. Ann Allergy 1997;79:125-30. (III)
47. Golden D, Kagey-Sobotka A, Valentine M. Dose dependence of Hymenoptera venom immunotherapy. J Allergy Clin Immunol 1981;67:370-4. (IIa)
48. Brehler R, Wolf H, Kutting B, Schnitker J, et. Safety of a two-day ultrarush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections. J Allergy Clin Immunol 2000;105:1231-5. (IIb)
49. Golden D, Valentine M, Kagey-Sobotka A, Lichtenstein L. Regimens of Hymenoptera venom immunotherapy. Ann Intern Med 1980;92:620-4. (IIb)
50. Bousquet J, Knani J, Velasquez G, Menardo J, Guilox L, Michel F. Evolution of sensitivity to Hymenoptera venom in 200 allergic patients followed up for up to three years. J Allergy Clin Immunol 1989;84:944-50. (IIa)
51. Bernstein D, Mittman R, Kagen S, Korbee L, Enrione M, Bernstein I. Clinical and immunologic studies of rapid venom immunotherapy in Hymenoptera-sensitive patients. J Allergy Clin Immunol 1989;84:951-9. (IIa)
52. Birnbaum J, Charpin D, Vervloet D. Rapid Hymenoptera venom immunotherapy comparative safety of three protocols. Clin Exp Allergy 1993;23:226-30. (IIb)
53. Rueff F, Przybilla B. Ultrarush immunotherapy in patients with Hymenoptera venom allergy. J Allergy Clin Immunol 2001;107:928-9. (IV)
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. (III)
55. Golden D, Kagey-Sobotka A, Valentine M, Lichtenstein LM. Prolonged maintenance interval in Hymenoptera venom immunotherapy. J Allergy Clin Immunol 1981;67:482-4. (IIa)
56. 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. (IIa)
57. Lockey R, Turkeltaub P, Olive E. The Hymenoptera venom study III. Safety of venom immunotherapy. J Allergy Clin Immunol 1990;86:775-80. (IIa)
58. deBandt M, Atassi-Dumont M, Kahn M. Serum sickness after wasp venom immunotherapy; clinical and biological study. J Rheumatol 1997;24:1195-7. (IV)
59. Hepner M, Ownby D, Anderson J. Risk of severe reactions in patients taking beta blocker drugs receiving allergen immunotherapy injections. J Allergy Clin Immunol 1990;86:407-11. (IIb)
60. Toogood J. Risk of anaphylaxis in patients receiving beta-blocker drug. J Allergy Clin Immunol 1988;81:1-5.
61. Simon P, Potier J, Thebaud HE. Risk factors for acute hypersensitivity reactions in hemodialysis. Nephrologie 1996;17:163-70.
62. Hermann K, Ring J. The renin-angiotensin system in patients with repeated anaphylactic reactions during Hymenoptera venom hyposensitization and sting challenge. Int Arch Allergy Immunol 1997;112:251-6. (LB)
63. Graft DF, Golden DBK, Reisman RE, Valentine MD, Yunginger J. The discontinuation of Hymenoptera venom immunotherapy (a position paper). J Allergy Clin Immunol 1998;101:573-5. (IV)
64. Golden D, Kwiterovich K, Kagey-Sobotka A, Valentine M, et al. Discontinuing venom immunotherapy, outcome after five years. J Allergy Clin Immunol 1996;97:579-87. (IIb)
65. Lerch E, Muller U. Long-term protection after stopping immunotherapy: Results of re stings in 200 patients. J Allergy Clin Immunol 1998;101:606-12. (IIb)
66. Mueller U, Berchfold E, Helbring A. Honeybee venom allergy: results of a sting challenge 1 year after stopping successful immunotherapy in 86 patients. J Allergy Clin Immunol 1991;87:702-9. (IIa)
67. Haugaard L, Norregaard O, Dahl R. In hospital sting challenge in insect venom- allergic patients after stopping venom immunotherapy. J Allergy Clin Immunol 1991;87:699-702. (IIa)
68. Golden DBK, Kwiterovitch KA, Kagey Sobotka A, Lichtenstein LM. Discontinuing venom immunotherapy: extended observations. J Allergy Clin Immunol 1998;101:298-305. (IIb)
69. Golden DBK, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. J Allergy Clin Immunol 2000;105:385-90. (IIb)
70. Light WC. Insect sting fatality 9 years after venom treatment (venom allergy, fatality). J Allergy Clin Immunol 2001;107:925. (IV)
71. Reisman R. Duration of venom immunotherapy: relationship to the severity of symptoms of initial insect sting anaphylaxis. J Allergy Clin Immunol 1993;92:831-6. (IIb)
72. Keating M, Kagey-Sobotka A, Hamilton R, Yunginger J. Clinical and immunological follow-up of patients who stop venom immunotherapy. J Allergy Clin Immunol 1991;88:339-48. (IIb)

APPENDIX 1

Two examples of conventional dosing schedules for fire ant immunotherapy with *Solenopsis invicta* or a mixture of *Solenopsis invicta/Solenopsis richteri* whole-body vaccine have been used successfully. Injections are generally given weekly or, in some cases, 2 times per week. After the maintenance dose of 0.5 mL of 1:100 wt/vol is administered safely several times, the dosage interval can be advanced to every 2 weeks and eventually can be extended to 4 weeks. Schedule 1 is provided by Drs Anne Yates, Sitesh Roy, and John Moffitt of the University of Mississippi Medical Center. Schedule 2 is provided by Dr Ted Freeman.

Schedule 1			Schedule 2		
Dose no.	**Concentration (wt/vol)**	**Volume**	**Dose no.**	**Concentration (wt/vol)**	**Volume**
1	1:100,000	0.05 mL	1	1:100,000	0.05 mL
2	1:100,000	0.10 mL	2	1:100,000	0.15 mL
3	1:100,000	0.20 mL	3	1:100,000	0.25 mL
4	1:100,000	0.30 mL	4	1:100,000	0.50 mL
5	1:100,000	0.40 mL	5	1:10,000	0.05 mL
6	1:100,000	0.50 mL	6	1:10,000	0.10 mL
7	1:10,000	0.05 mL	7	1:10,000	0.20 mL
8	1:10,000	0.10 mL	8	1:10,000	0.30 mL
9	1:10,000	0.20 mL	9	1:10,000	0.40 mL
10	1:10,000	0.30 mL	10	1:10,000	0.50 mL
11	1:10,000	0.40 mL	11	1:1000	0.05 mL
12	1:10,000	0.50 mL	2	1:1000	0.10 mL
13	1:1000	0.05 mL	13	1:1000	0.20 mL
14	1:1000	0.10 mL	14	1:1000	0.30 mL
15	1:1000	0.20 mL	15	1:1000	0.40 mL
16	1:1000	0.30 mL	16	1:1000	0.50 mL
17	1:1000	0.40 mL	17	1:100	0.05 mL
18	1:1000	0.50 mL	18	1:100	0.07 mL
19	1:100	0.05 mL	19	1:100	0.10 mL
20	1:100	0.10 mL	20	1:100	0.15 mL
21	1:100	0.15 mL	21	1:100	0.20 mL
22	1:100	0.20 mL	22	1:100	0.25 mL
23	1:100	0.25 mL	23	1:100	0.30 mL
24	1:100	0.30 mL	24	1:100	0.40 mL
25	1:100	0.35 mL	25	1:100	0.50 mL
26	1:100	0.40 mL			
27	1:100	0.45 mL			
28	1:100	0.50 mL			