Practice parameter

Stinging insect hypersensitivity: A practice parameter update 2011

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These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology.
The AAAAI and the ACAAI have jointly accepted responsibility for establishing "Stinging insect hypersensitivity: a practice parameter update II." 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. These parameters are not designed for use by pharmaceutical companies in drug promotion. The Joint Task Force understands that the cost of diagnostic tests and therapeutic agents is an important concern that may appropriately influence the work-up and treatment chosen for a given patient. The Joint Task Force recognizes that the emphasis of our primary recommendations regarding a medication may vary, for example, depending on third party payer issues and product patent expiration dates. However, since a given test or agent's cost is so widely variable, and there is a paucity of pharmacoeconomic data, the Joint Task Force generally does not consider cost when formulating Practice Parameter recommendations. In extraordinary circumstances, when the cost benefit of an intervention is prohibitive as supported by pharmacoeconomic data, commentary may be provided. (J Allergy Clin Immunol 2011;127:852-4.)

Key words: *Insect hypersensitivity, anaphylaxis*

To read the Practice Parameter in its entirety, please download the online version of this article from www.jacionline.org. The full document follows the Executive Summary. Please note that all references cited in the Executive Summary can be found in the online document.

Most insect stings produce a transient local reaction that can last up to several days and generally resolves without treatment. Marked local swelling extending from the sting site is usually an IgE-mediated late-phase reaction.[1-4] The risk of a systemic reaction in patients who experience large local reactions is no more than 5% to 10%.[1,3-5] More serious anaphylactic sting reactions account for at least 40 deaths each year in the United States.[6] It is estimated that potentially life-threatening systemic reactions

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AAAAI: American Academy of Allergy, Asthma & Immunology
ACAAI: American College of Allergy, Asthma & Immunology
VIT: Venom immunotherapy

to insect stings occur in 0.4% to 0.8% of children and 3% of adults.[7-10]

Systemic reactions are characterized by symptoms and signs, including any combination of urticaria and angioedema, bronchospasm, edema of the large airway, hypotension, or other clinical manifestations of anaphylaxis.[11] 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 and circulatory failure are the most common causes 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 and be instructed in its appropriate indications and administration, (3) undergo testing for specific IgE antibodies to stinging insects, (4) be considered for immunotherapy (with insect venom or fire ant whole-body extract) if test results for specific IgE antibodies are positive, and (5) consider carrying medical identification for 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. 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.

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 are 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 sac in the skin after they sting. The imported 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 sterile pseudopustules that have a distinctive appearance. 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 insects. Extracts of honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp venom are available for skin testing and venom immunotherapy (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.[12-18] It is generally accepted that a positive intradermal 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.[19-22] Skin testing with fire ant whole-body extract is considered indicative of specific IgE antibodies if a positive response occurs at a concentration of 1:100 wt/vol or less by using the skin prick method or 1:1000 wt/vol or less by using the intradermal method.[13,14,17]

For those patients who have negative skin test responses despite 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 before concluding that immunotherapy is not indicated.[23-25] Either or both of the serum measurements of specific IgE for insect venom or fire ant whole-body extract and the skin test responses might be temporarily nonreactive within the first few weeks after a systemic reaction to an insect sting and might require retesting in 6 weeks.[26] Although one might want to wait for this period of time before initial testing, it might be important to skin test patients without waiting, especially if rapid initiation of VIT is required. Rarely (<1% of patients with a convincing history of systemic reaction to a sting), patients can have an anaphylactic reaction from a subsequent sting despite negative skin and *in vitro* test results.[23,27] Some of these patients might have underlying systemic mastocytosis.

Because patients who have a history of an allergic reaction to an insect sting and have a positive skin or *in vitro* test result for specific IgE antibodies to insects might be at risk for subsequent life-threatening reactions if re-stung, immunotherapy should be considered in such patients. Approximately 30% to 60% of patients with a history of systemic allergic reactions from an insect sting who have specific IgE antibodies detectable by means of skin or in vitro testing will experience a systemic reaction when re-stung.[27-34] As a result, it has been suggested that patients can be better selected for immunotherapy on the basis of the results of an intentional sting challenge.[27,35] Sting challenges, however, are not consistently reproducible and are associated with considerable risk.[29,36] The standard management of insect sting hypersensitivity in the United States does not include a sting challenge.[37] A recent study of severe and recurrent anaphylaxis highlights that patients with severe insect sting reactions should also be evaluated for mast cell disorders. Work-up for mast cell disorders might include baseline serum tryptase measurement and bone marrow biopsy.

Throughout this document, the use of the terms *venom immunotherapy*, *VIT*, *venom testing*, and *venom* refers to both venom and imported fire ant whole-body extracts unless otherwise stated. VIT is generally not necessary in children 16 years of age and younger who have experienced isolated cutaneous systemic reactions without other systemic manifestations after an insect sting.[38,39] VIT in adults who have experienced only cutaneous manifestations of a systemic reaction 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 sting reactions that occur during VIT are usually milder than those experienced before VIT.[28,31,32] VIT is generally not necessary for patients who have had only a large local reaction because the risk of a systemic reaction to 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. There is growing evidence that VIT significantly reduces the size and duration of large local reactions and thus might be useful in subjects who have unavoidable, frequent, or both large local reactions.[5,40,41]

Once initiated, VIT should usually be continued for at least 3 to 5 years.[42,43] 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.[44-52] There are no specific tests to distinguish which patients will relapse after stopping VIT, but there is a higher risk in some patients than others. Relapse is less likely with 5 years than with 3 years of VIT.[50,53] 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.[46,47,52] For this reason, some experts recommend an extended duration of immunotherapy, possibly 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.[54] Some patients have relapsed despite negative venom skin test responses. Repeat skin (or venom-specific IgE serum) testing is not required for consideration of discontinuing VIT. Measurements of venom-specific IgG antibodies have no predictive value when discontinuing VIT. The decision on stopping VIT requires a context-sensitive flexibility based on the available evidence.

The optimal duration of fire ant immunotherapy is less well defined. Most allergists consider stopping fire ant immunotherapy after a specified period (usually 3-5 years) either empirically or only when skin test or *in vitro* test results become negative.[55] Until further data are available, a definitive recommendation about the duration of immunotherapy for fire ant sting allergy 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.[4,13,15,56-58] 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.[12,15-18,44,59] Recommendations for immunotherapy with fire ant whole-body extract are generally the same as those for VIT.[14]

Patients who have experienced a systemic reaction to an insect sting should be given a prescription for an injectable epinephrine device and be advised to carry it with them at all times. Because some patients who experience anaphylaxis might require more than 1 injection of epinephrine, a prescription for more than 1 epinephrine injector should be considered.[60,61] Patients and advocates who might be administering epinephrine should be taught how to administer this drug and under what circumstances this should be done.[62] 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. In patients who have a relatively low risk of a severe anaphylactic reaction from a sting, the decision whether to carry injectable epinephrine can be determined by discussion between the patient and physician. Patients with a low risk of reaction are those with a history of only large local reactions to stings or of strictly cutaneous systemic reactions, those receiving maintenance VIT, and those who have discontinued VIT after more than 5 years of treatment. Factors associated with a higher risk include a history of extreme or near-fatal reactions to stings, systemic reactions during VIT (to an injection or a sting), severe honeybee allergy, underlying medical conditions, or frequent unavoidable exposure.

There remain some unmet needs in the diagnosis and treatment of insect sting hypersensitivity. Improved diagnostic accuracy with better positive predictive value might await studies to validate new tests, such as those using recombinant allergens or epitopes or those designed to detect basophil activation or basophil sensitivity. Similarly, there is a need for a better predictor of relapse after stopping VIT, a study of discontinuation after just 3 years of VIT (not a range of 3-7 years as in most studies), a study of discontinuation after 12 to 15 years in "high-risk" patients with negative skin test responses, and, perhaps most of all, an effective screening test to detect the 50% of fatal sting reactors who die on their first reaction (and therefore cannot be prevented by current standards of testing and treating only those who have a history of reactions).

The entire document is available online, and the reader is referred to that portion of the document for more detailed discussion of the comments made in the printed version.

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

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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

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
IV Evidence from expert committee reports, opinions or clinical experience of respected authorities, or both

Strength of recommendation

A Directly based on category I evidence
B Directly based on category II evidence or extrapolated recommendation from category I evidence
C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
LB (Lab based)

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 with venoms (venom immunotherapy [VIT]) or whole-body extracts.

The document "Stinging insect hypersensitivity: a practice parameter update 2011" is the third iteration of this parameter. The first was published in 1999 (Portnoy JM, Moffitt JE, Golden DB, Bernstein IL, Dykewicz MS, Fineman SM, et al. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999;103:963-80), and the first update was published in 2004 (Moffitt JE, Golden DB, Reisman RE, Lee R, Nicklas R, Freeman T, et al. Stinging insect hypersensitivity: a practice parameter update. J Allergy Clin Immunol 2004;114:869-86). Using the 2004 publication as a starting point, the working draft of this updated parameter was prepared by a workgroup chaired by David B. K. Golden, MD, and was revised and edited by the Joint Task Force on Practice Parameters. Preparation of this draft includes a review of the recent medical literature using a variety of search engines, such as PubMed and Ovid. Published clinical studies were rated as defined in the preamble by category of evidence and used to establish the strength of the recommendations in the summary statements. It was then reviewed by experts on insect sting allergy selected by the sponsoring organizations of the AAAAI and the ACAAI, as well as being placed online for comments from the entire membership of both organizations. Based on this process, this parameter represents an evidence-based document.

This document follows the same format as the previous iterations. It should be noted that with respect to diagnosis and treatment, the use of the terms *venom immunotherapy*, *VIT*, *venom testing*, and *venom* refers to both venom and imported fire ant whole-body extracts unless otherwise stated. Some substantive changes in content were made to reflect advancements in scientific knowledge and their effect on management of insect sting allergy. Particular developments and modifications of note are the following:

1. Studies in emergency departments show the need for better recognition and prevention of insect sting–induced anaphylaxis. Patients treated for allergic reactions to stings need better counseling on avoidance, use of epinephrine injectors, and the need for allergy evaluation and treatment.
2. Bumblebees are an important cause of sting reactions in some settings. Bumblebee venom allergy is usually distinct from honeybee venom allergy and requires specific testing.
3. More guidance is provided on when not to perform diagnostic tests. Although the negative predictive value is very high, the positive predictive value is much lower. There are quality-of-life concerns regarding the effect of positive test results in patients with relatively low risk of reactions.
4. Conversely, venom testing and treatment might not be required in some low-risk patients but might be warranted for quality-of-life reasons in some subjects. This explains the change in wording from "not recommended" to "not required" for large local reactors and children with cutaneous systemic reactions.
5. Emphasis is made not only on the low-risk patients with insect sting allergy but also on the high-risk patients who benefit the most from treatment.
6. There is a growing evidence base for imported fire ant evaluation and management, as well as more demographic data on the scope and distribution of the problem.
7. Measurement of baseline serum tryptase is recognized as an important predictor of the severity of sting reactions, the frequency of systemic reactions during VIT, the chance of VIT failure, and the risk of relapse if VIT is stopped.
8. More discussion and guidance are provided on the issues surrounding the prescription of epinephrine injectors and the instructions on when or when not to use them.
9. New evidence is presented for the application of VIT for large local reactors.
10. New evidence and expert review is presented on the relative risk of β-blocker medications or angiotensin-converting enzyme inhibitors in patients with insect sting allergy or receiving VIT.
11. There is more emphasis on the growing evidence that one of the most important predictors of the outcome of a sting is the pattern and severity of previous reactions.
12. There is increasing evidence that patients taking antihistamine medication before venom injections have fewer adverse effects and might have improved outcomes from treatment.
13. Updated recommendations for rush VIT suggest that there are regimens that are safe alternatives to the standard protocols and might be suitable for routine use.
14. More specific information is given on the recommended maintenance dose of VIT and intervals and the possible need for dose increases in some patients.
15. Evidence is updated for the recommendations on discontinuing VIT.

An annotated algorithm in this document summarizes the key decision points for the appropriate use of VIT (Fig E1). Specific recommendations guide the physician in selecting those patients for whom VIT is appropriate. The Joint Task Force on Practice Parameters and the contributing authors wish to thank the ACAAI, the AAAAI, and Joint Council of Allergy, Asthma and Immunology for their continued support of parameter development. The Task Force would also like to thank the contributors to this parameter who have been so generous with their time and effort. The members of the workgroup and the Task Force acknowledge the contributions made by and the dedication of Dr John Moffitt to this effort over many years, and we dedicate this update to his memory.

EXECUTIVE SUMMARY

Most insect stings produce a transient local reaction that can last up to several days and generally resolves without treatment. Marked local swelling extending from the sting site is usually an IgE-mediated late-phase reaction.[1-4] The risk of a systemic reaction in patients who experience large local reactions is no more than 5% to 10%.[1,3-5] More serious anaphylactic sting reactions account for at least 40 deaths each year in the United States.[6] 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.[7-10]

Systemic reactions are characterized by symptoms and signs, including any combination of urticaria and angioedema, bronchospasm, edema of the large airway, hypotension, or other clinical manifestations of anaphylaxis.[11] 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 and circulatory failure are the most common causes 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 and be instructed in its appropriate indications and administration, (3) undergo testing for specific IgE antibodies to stinging insects, (4) be considered for immunotherapy (with insect venom or fire ant whole-body extract) if test results for specific IgE antibodies are positive, and (5) consider carrying medical identification for 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. 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.

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 are 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 sac in the skin after they sting. The imported 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 sterile pseudopustules that have a distinctive appearance.

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 insects. 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.[12-18] It is generally accepted that a positive intradermal 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.[19-22] Skin testing with fire ant whole-body extract is considered indicative of specific IgE antibodies if a positive response occurs at a concentration of 1:100 wt/vol or less by using the skin prick method or 1:1,000 wt/vol or less by using the intradermal method.[13,14,17]

For those patients who have negative skin test responses despite 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 before concluding that immunotherapy is not indicated.[23-25] Either or both of the serum measurements of specific IgE for insect venom or fire ant whole-body extract and the skin test response might be temporarily nonreactive within the first few weeks after a systemic reaction to an insect sting and might require retesting in 6 weeks.[26] Although one might want to wait for this period of time before initial testing, it could be important to skin test patients without waiting, especially if rapid initiation of VIT is required. Rarely (<1% of patients with a convincing history of systemic reaction to a sting), patients can have an anaphylactic reaction from a subsequent sting despite negative skin and *in vitro* test results.[23,27] Some of these patients might have underlying systemic mastocytosis.

Because patients who have a history of an allergic reaction to an insect sting and have a positive skin or *in vitro* test result for specific IgE antibodies to insects might be at risk for subsequent life-threatening reactions if re-stung, immunotherapy should be considered in such patients. Approximately 30% to 60% of patients with a history of systemic allergic reaction to an insect sting who have specific IgE antibodies detectable by means of skin or *in vitro* testing will experience a systemic reaction when re-stung.[27-34] As a result, it has been suggested that patients can be better selected for immunotherapy on the basis of the results of an intentional sting challenge.[27,35] Sting challenges, however, are not consistently reproducible and are associated with considerable risk.[29,36] The standard management of insect sting hypersensitivity in the United States does not include a sting challenge.[37] A recent study of severe and recurrent anaphylaxis highlights that patients with severe insect sting reactions should also be evaluated for mast cell disorders. Work-up for mast cell disorders might include baseline serum tryptase measurement and bone marrow biopsy.

Throughout this document, the use of the terms *venom immunotherapy*, *VIT*, *venom testing*, and *venom* refers to both venom and imported fire ant whole-body extracts unless otherwise stated. VIT is generally not necessary in children 16 years of age and younger who have experienced isolated cutaneous systemic reactions without other systemic manifestations after an insect sting.[38,39] VIT in adults who have experienced only cutaneous manifestations of a systemic reaction 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 sting reactions that occur during VIT are usually milder than those experienced before VIT.[28,31,32] VIT is generally not necessary for patients who have had only a large local reaction because the risk of a systemic reaction to 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. There is growing evidence that VIT significantly reduces the size and duration of large local reactions and thus might be useful in subjects who have unavoidable, frequent, or both large local reactions.[5,40,41]

Once initiated, VIT should usually be continued for at least 3 to 5 years.[42,43] 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.[44-52] There are no specific tests to distinguish which patients will relapse after stopping VIT, but there is a higher risk in some patients than in others. Relapse is less likely with 5 years than with 3 years of VIT.[50,53] 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.[46,47,52] For this reason, some experts recommend an extended duration of immunotherapy, possibly 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.[54] Some patients have relapsed despite negative venom skin test responses. Repeat skin (or venom-specific IgE serum) testing is not required for consideration of discontinuing VIT. Measurements of venom-specific IgG antibodies have no predictive value when discontinuing VIT. The decision on stopping VIT requires a context-sensitive flexibility based on the available evidence.

The optimal duration of fire ant immunotherapy is less well defined. Most allergists consider stopping fire ant immunotherapy after a specified period (usually 3-5 years) either empirically or only when skin or *in vitro* test results become negative.[55] Until further data are available, a definitive recommendation about the duration of immunotherapy for fire ant sting allergy 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.[4,13,15,56-58] 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.[12,15-18,44,59]

Recommendations for immunotherapy with fire ant whole-body extract are generally the same as those for VIT.[14]

Patients who have experienced a systemic reaction to an insect sting should be given a prescription for an injectable epinephrine device and be advised to carry it with them at all times. Because some patients who experience anaphylaxis might require more than 1 injection of epinephrine, prescription of more than 1 epinephrine injector should be considered.[60,61] Patients and advocates who might be administering epinephrine should be taught how to administer this drug and under what circumstances this should be done.[62] 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. In patients who have a relatively low risk of a severe anaphylactic reaction from a sting, the decision on whether to carry injectable epinephrine can be determined by discussion between the patient and physician. Patients with a low risk of reaction are those with a history of only large local reactions to stings or of strictly cutaneous systemic reactions, those receiving maintenance VIT, and those who have discontinued VIT after more than 5 years of treatment. Factors associated with a higher risk include a history of extreme or near-fatal reactions to stings, systemic reactions during VIT (to an injection or a sting), severe honeybee allergy, underlying medical conditions, or frequent unavoidable exposure.

There remain some unmet needs in the diagnosis and treatment of insect sting hypersensitivity. Improved diagnostic accuracy with better positive predictive value might await studies to validate new tests, such as those using recombinant allergens or epitopes or those designed to detect basophil activation or basophil sensitivity. Similarly, there is a need for a better predictor of relapse after stopping VIT, a study of discontinuation after just 3 years of VIT (not a range of 3-7 years as in most studies), a study of discontinuation after 12 to 15 years in "high-risk" patients with negative skin test responses, and, perhaps most of all, an effective screening test to detect the 50% of fatal sting reactors who die on their first reaction (and therefore cannot be prevented by current standards of testing and treating only those who have a history of reaction).

ALGORITHM

Annotations to Fig E1

Box 1: Patient presents with a history of insect sting reaction. Although insects sting many persons each year, most subjects do not have abnormal 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 preventative treatment. Reactions can range from large local swelling to life-threatening systemic reactions. Delayed or toxic reactions can also occur. Obtaining a careful history is important in making the diagnosis of insect sting reaction.

Box 2: History and physical examination

Identification of the responsible insect might be helpful in the diagnosis and treatment. Patients should be encouraged to bring the offending insect, when available, to the physician for identification. The physician should determine whether the patient was stung once or multiple times.

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 nesting places for stinging insects),
- the type of insect activity in the area where the patient was stung, and
- visual identification of the insect.

Identification of stinging insects by patients is not always reliable. The presence of a stinger, which is left most commonly by honeybees, or the presence of a pustule as a result of an imported fire ant sting (up to 24 hours or longer) 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 contiguous to the site of the sting, and
- 5 to 10 days to resolve.

Systemic reactions can include a spectrum of manifestations not contiguous with the site of the sting, ranging from mild to life-threatening. These include the following:

- cutaneous (eg, urticaria and angioedema),
- respiratory,
- bronchospasm,
- upper airway obstruction (eg, tongue or throat swelling and laryngeal edema),
- cardiovascular,
- cardiac (eg, arrhythmias and coronary artery spasm),
- hypotension and shock,
- gastrointestinal (eg, nausea, vomiting, diarrhea, and abdominal pain), and
- neurological (eg, seizures).

Box 4: Provide symptomatic treatment if needed

Most insect stings cause mild local reactions for which no specific treatment is usually required. Some local reactions are manifested by extensive swelling surrounding the sting site that can persist for several days or more and might 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, although definitive proof of efficacy through controlled studies is lacking. Because the swelling (and even lymphangitis) 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 are usually 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 seek guidance on insect avoidance measures. In patients who have had large local reactions, it is optional to prescribe injectable epinephrine 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 for VIT. There is, however, growing evidence that VIT significantly reduces the size and duration of large local reactions and thus might be useful in affected subjects with a history of unavoidable, frequent, or both large local reactions and detectable venom-specific IgE.

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

Injectable epinephrine should be provided, and the patient should be instructed in its proper administration and use. Patients should also consider obtaining and carrying 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 another systemic reaction. 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. Preventive management includes measures to prevent subsequent stings and to prevent subsequent systemic reactions if the patient is stung.

Box 6: Is the patient a child whose reaction was limited to the cutaneous system?

The usual criteria for immunotherapy include a history of a systemic reaction to an insect sting and demonstration of venom-specific IgE by means of 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, it is 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 VIT for improved quality of life. 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 subjects at this time. There is evidence that VIT improves the quality of the patient's life. The need to carry injectable epinephrine can be determined by the patient/caregiver and physician after discussion of the relative risk of reaction and the anticipated effect on quality of life. Although VIT is considered to be almost completely effective in preventing life-threatening reactions to stings, carrying self-injectable epinephrine might still be desired, even during VIT, and is subject to discussion between the patient/caregiver and the physician. 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 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 VIT might be indicated. Skin prick tests with a concentration in the range of 1.0 to 100 μg/mL can be performed before intracutaneous tests.

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.

Detection of all potentially relevant sensitivities requires testing with all of the commercially available bee and vespid venoms and might include fire ant extracts when the patient has exposure to fire ant stings. The insect that caused the sting often cannot be identified, but even if it is clearly identified, the possibility exists of future reactions to other venoms to which there is existing sensitization. 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 less extensive between *Polistes* wasp and other vespid venoms and is infrequent between honeybee and vespid venoms. Fire ant venom (and therefore fire ant whole-body extract) has very limited cross-reactivity with other stinging insect venoms.

Box 8: Positive skin test response?

VIT 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?

Patients might have venom-specific IgE not detected by skin testing, even though skin testing is the most reliable and preferred diagnostic method to identify venom-specific IgE. Therefore it is recommended that further evaluation for detection of venom-specific IgE be performed if the skin test response is negative. Patients usually need further evaluation if there is a history of a sting reaction including 1 or more of the following: wheezing with dyspnea or increased respiratory effort, stridor, or other signs of large airway obstruction; hypotension; shock; or loss of consciousness.

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 and *in vitro* testing before concluding that VIT is not necessary. If the response of either such test is positive, VIT is indicated. If repeat test responses fail to demonstrate the presence of IgE antibodies, there is no indication for VIT, but baseline serum tryptase levels can be measured to determine whether there is an underlying mast cell disorder.

Box 9: Recommend and give VIT

VIT greatly reduces the risk of systemic reactions in stinging insect–sensitive patients with an efficacy of up to 98%. 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 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 regimen, whereas others contend that with knowledge of venom cross-reactivity and insect identification, only a single venom is needed for VIT, even if skin or *in vitro* test results for other stinging insects are positive. Depending on the culprit insect, it is likely that other positive skin or *in vitro* test results will be obtained. Immunotherapy for patients with fire ant hypersensitivity consists of injections with a whole-body extract 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 to whole-body extract or a positive *in vitro* assay result.

VIT injections are generally administered once a week, beginning with doses no greater than 0.1 to 1.0 μg and increasing to a maintenance dose of 100 μg of each venom (eg, 1 mL of an extract containing 100 μg/mL of 1 venom or 300 μg of mixed vespid venom). The dosing interval and increments can be adjusted at the discretion of the prescribing physician to accommodate the preferences of the physician and the tolerance of the patient. 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 concentration—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 VIT protocols have been used successfully and safely to treat flying Hymenoptera and fire ant sting allergy and can be considered for routine use.

Patients with insect venom 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. In patients who have had life-threatening reactions to stings and take β-adrenergic blocking medications, the risk of VIT has been judged to be less than the risk of a life-threatening reaction to a future sting. In a retrospective study of patients experiencing anaphylaxis from Hymenoptera venom, angiotensin-converting enzyme inhibitor exposure was associated with a statistically significant increase in the risk for more severe anaphylaxis (odds ratio, 2.27; 95% CI, 1.13-4.56; $P = .019$). For patients who require an angiotensin-converting enzyme inhibitor for an indication for which there is no equally effective alternative available, a management decision by the physician prescribing VIT should be approached cautiously on an individualized risk/benefit basis.

Box 10: 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. If the culprit is unknown, further testing might be needed to determine whether there is a new or untreated venom sensitivity before considering an increase in the venom dose.

Box 11: Consider stopping VIT after 3 to 5 years

Guidelines for discontinuation of VIT are evolving. Whereas the package insert for the Hymenoptera venom extract recommends that VIT be continued indefinitely, treatment for a finite length of time (3-5 years), 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. When both skin and *in vitro* test results are negative, VIT has been discontinued with no severe reactions to subsequent stings. 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 that any reaction to a future sting is usually less severe than the reaction before VIT. It is therefore reasonable to consider discontinuation in most patients after therapy of this duration, except in certain high-risk patients described in the text. However, there always remains a small risk that future systemic 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 VIT (although most still had positive *in vitro* test results). 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. There are no specific tests to distinguish which patients will relapse after stopping VIT, but there is a higher risk in some patients than in others. 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. Repeat skin (or venom-specific IgE serum) testing is not required for consideration of discontinuing VIT. Patients with a history of severe anaphylaxis (severe airway obstruction, shock, or loss of consciousness), still might be at continued risk for a systemic reaction if VIT is stopped even after 5 years of treatment. 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 3-5 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

Subjects 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

Management of acute reactions to stings is symptomatic, with the following considerations:

- Acute systemic reactions to insect stings should be treated like any anaphylactic reaction, with epinephrine injection, supportive therapy, and transport to an emergency department. (A)
- In patients with a history of only cutaneous systemic reactions, initial treatment of cutaneous systemic symptoms might include antihistamines and close observation. (D)
- Fatal sting reactions have been associated with delay in administration of epinephrine. (B)
- Treatment of large local reactions can include antihistamines, cold compresses, and in severe cases a brief course of oral corticosteroids. Antibiotics are usually not necessary. (D)

Summary statement 3

Referral to an allergist-immunologist is recommended for patients who have had a suspected systemic reaction from an insect sting, especially those who:

- need education about (1) their risk of another reaction if they are stung, (2) options for emergency and preventative treatment, and (3) insect avoidance (B);
- have a coexisting condition or medication that might complicate a potential reaction to a sting (B); or
- request consultation for more detailed information or specific testing. (D)

Summary statement 4

Subjects 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 and be familiar with proper use and indications (D);
- undergo specific IgE testing for stinging insect sensitivity and be considered for immunotherapy (A); and
- consider obtaining and carrying a medical identification bracelet or necklace. (D)

Summary statement 5

Immediate hypersensitivity skin tests with stinging insect venoms are indicated for subjects who are candidates for VIT. (A)

Special considerations include the following:

- Skin tests, rather than *in vitro* assays, should be used for initial measurement of venom-specific IgE, except in special circumstances. (C)
- If skin test responses are negative when done at least 6 weeks after the sting reaction and the patient has had a severe allergic reaction, further testing (*in vitro* testing, repeat skin testing, or both) is recommended, as well as baseline serum tryptase measurement. (C)
- The degree of sensitivity found on skin and serologic tests for venom-specific IgE does not correlate consistently with the severity of a reaction to a sting. (C)
- Skin testing for imported fire ant sensitivity is performed with whole-body extracts. (B)

Summary statement 6

VIT is recommended for all patients who have experienced a systemic reaction to an insect sting and who have specific IgE to venom allergens (A), 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 after an insect sting. (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)
- VIT is generally not necessary in patients who have experienced only large local reactions to stings but might be considered in those who have frequent unavoidable exposure. (B)

Summary statement 7

Immunotherapy with imported fire ant whole-body extracts is recommended for all patients who have experienced a systemic reaction to a fire ant sting and who have positive skin test responses or allergen-specific serologic test results with imported fire ant whole-body extract, (B) with the following special consideration:

- 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 8

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 for an extended period of time or indefinitely. (C)

Special considerations include the following:

- high-risk factors (near-fatal reaction before VIT, systemic reaction during VIT, honeybee allergy, increased baseline

serum tryptase levels, underlying medical conditions and concomitant medications, and frequent exposure) (B);
- quality of life (eg, limitation of activity, anxiety about unexpected stings) (A); and
- the fact that optimal duration of immunotherapy with imported fire ant whole-body extracts has been less well studied. (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 extensive local reactions are usually IgE mediated and cause swelling extending from the sting site, peaking in 24 to 48 hours, and lasting 1 week or more. The frequency of large local reactions is estimated at 5% to 15% but is uncertain because of the variable definition of large local reactions (ranging from 5-8 cm to 4-6 inches in diameter). After insect stings, systemic reactions that are potentially life-threatening occur in 0.4% to 0.8% of children and up to 3% of adults.[7,9,10,63] A review of national mortality data in the United States from 1980 to 1999 found that at least 40 deaths per year are a result of sting-induced anaphylaxis, with the likelihood of additional sting-related deaths in persons reported to have died of cardiovascular causes or "unknown cause."[6,64] These numbers might be understated based on International Classification of Diseases–ninth revision coding in emergency departments.[62,65,66] The diagnosis of stinging insect hypersensitivity should be confirmed after a systemic reaction, and it is imperative that appropriate treatment be instituted to prevent serious reactions from subsequent stings, including a prescription for and instructions on how to use self-administered epinephrine. 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.[14,15,31,32,56,59,67,68] This 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 of other insects, and they are not the subject of this parameter. It should be noted that with respect to diagnosis and treatment, the use of the terms *venom immunotherapy*, *VIT*, *venom testing*, and *venom* in this document refers to both venom and imported fire ant whole-body extracts unless otherwise stated.

STINGING INSECT IDENTIFICATION

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

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

- the person's activity at the time of the sting (eg, hedge clipping or lawn mowing might disturb yellow jacket or hornet nests),
- the location of the person at the time of the sting (eg, near the eaves of a house where Polistes wasps nest or near an open garbage can that attracts yellow jackets),
- the type of insect activity in the area when the patient was stung,
- visual identification of the insect (color, shape, and size might distinguish yellow jackets from wasps or honeybees),
- time of year (yellow jackets are more prevalent in late summer and wasps and hornets in the spring and early summer),
- food exposure (food attracts yellow jackets), and
- part of country (wasps are more prevalent in Texas and Louisiana and fire ants are more prevalent in states located along the Gulf Coast and in the southeastern states).

Identification by patients of the insect that caused a sting is difficult and unreliable. A stinger that is left in the skin is usually associated with a honeybee (but occasionally also with other insects), or the presence of a pseudopustule from an imported fire ant sting (up to 24 hours later) might help in insect identification. Climate change might affect the distribution, range, and prevalence of stinging insects, as evidenced by increasing reports of yellow jacket sting reactions in Alaska.[69,70]

Yellow jackets are ground-dwelling insects and can be encountered during yard work, farming, gardening, or other outdoor activities. They also can be found in wall tunnels or crevices and in hollow logs. Yellow jackets are very aggressive and sting with minimum provocation, especially in the presence of food. Subjects have been stung in the mouth, oropharynx, or esophagus while drinking a beverage from a container that contained a yellow jacket. There are many species of yellow jackets in North America, and they are the most common cause of sting reactions in most areas (see below).

Hornets, which are related to yellow jackets, build large papier-mâché nests that can be 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 subjects for some distance before stinging.

Wasps build honeycomb nests that are several inches or more in diameter and are often visible 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. *Polistes* species wasps are prevalent throughout North America, but are more common causes of stings in Florida, Texas, and Louisiana.

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 non-aggressive away from their hives. Many honeybee stings occur on the feet when going barefoot in grass or clover. Bumblebees are very uncommon causes of sting reactions but are reported to cause anaphylaxis in greenhouse workers.[71] 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.[72] 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 (and are considerably larger than honeybees). Other insects, particularly ground-nesting yellow jackets, also

can leave stingers in the skin. 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 freshly disturbed soil that can be at least several inches high and might extend 1 to 2 feet 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 fire ant nests are flat. In addition, they are a major problem in residential neighborhoods, back yards, and public places. 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 an imported fire ant sting. The distribution of Africanized honeybees and fire ants in the Southern United States is depicted in Fig E2.

STINGING INSECT REACTIONS

Summary statement 1

Subjects 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)

Most people have transient pain and swelling from a sting, but allergic reactions can cause extreme and prolonged local swelling or any of the manifestations of anaphylaxis. Allergic reactions to stings can occur even after many uneventful stings and at any age. Beekeepers can sustain many stings each year, which increases the chance of sensitization. A sufficient number of honeybee stings each year (estimated to be 100-150) results in tolerance of stings (despite sensitization), but allergic reactions can still occur in the spring after the first sting exposures of the season.[73,74] Those who have had systemic allergic reactions to an insect sting are at increased risk for anaphylaxis to a future sting. The chance of a systemic reaction to a future sting in such patients ranges from 25% to 70%, depending on the nature of the previous reactions.[27-34] This risk can be almost completely eliminated by VIT, when indicated.[14,31,32,39,67] Consultation with an allergist is recommended to determine the degree of risk and the most suitable approach to prevent a systemic reaction in each patient.

Summary statement 2

Management of acute reactions to stings is symptomatic, with the following considerations:

- **Acute systemic reactions to insect stings should be treated like any anaphylactic reaction, with injectable epinephrine, supportive therapy, and transport to an emergency department. (A)**
- **In patients with a history of only cutaneous systemic reactions, initial treatment of cutaneous systemic symptoms might include antihistamines and close observation. (D)**
- **Fatal sting reactions have been associated with delay in administration of epinephrine. (B)**
- **Treatment of large local reactions can include antihistamines, cold compresses, and in severe cases a short course of oral corticosteroids. Antibiotics are usually not necessary. (D)**

Local reactions. Most insect stings cause transient localized reactions that are of little serious medical consequence. No treatment usually is required. Some local reactions are more severe and present with extensive erythema and swelling surrounding the sting site that can persist for several days or more and is accompanied by pruritus, pain, or both. Cold compresses might help to reduce local pain and swelling. Oral antihistamines and analgesics help reduce the itching or pain associated with cutaneous reactions. Although there are no controlled studies, prompt use of oral corticosteroids is effective treatment to limit swelling in patients with a history of large local reactions. This large swelling, which usually occurs in the first 24 to 48 hours, is caused by allergic inflammation and not by infection and therefore does not require antibiotic therapy.

Fire ant stings typically cause a sterile pseudopustule within 24 hours after a sting. The vesicle is caused by necrotic tissue and is not infected. The vesicle should be left intact and kept clean to prevent secondary infection. Secondary infection is a complication of fire ant stings, although it is unusual.

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. Reactions can be biphasic or protracted.[75-77] Severe anaphylaxis can result in a biphasic reaction, but the frequency of biphasic reactions to stings is uncertain because very few such cases have been included in the literature.[78] The slower the time of onset of signs and the symptoms of anaphylaxis, the less likely the reaction will progress to a life-threatening event.[79]

Treatment of anaphylactic reactions caused by insect stings is the same as the treatment of anaphylaxis from other causes. The reader is reminded that systemic reactions in children that are limited to the skin are not considered to be anaphylactic reactions. The reader is referred to the Practice Parameter entitled "The diagnosis and management of anaphylaxis" and other guidelines for more detail.[60,77,80,81] If a barbed stinger is present in the skin, removing the stinger within the first 10 to 20 seconds might prevent injection of additional venom.[82] Removal can be accomplished by simply flicking or scraping the stinger away with a fingernail. Grasping the venom sac and pulling it out can result in injection of additional venom and should be avoided. Epinephrine is the drug of choice for the treatment of anaphylaxis.[60,77] The recommended dose is 0.01 mg/kg in children (up to 0.3 mg) and 0.3 to 0.5 mg in adults, depending on the severity of the reaction. Intramuscular injection in the anterolateral thigh might achieve a more rapid and higher plasma concentration than subcutaneous or intramuscular injection in the arm.[83,84] Delayed use of epinephrine can be associated with more serious anaphylaxis or can eventually be ineffective,[85] as reports of fatal and near-fatal anaphylaxis demonstrate.[86-88] Patients allergic to insect venom should carry appropriate doses of autoinjectable epinephrine (see parameter on anaphylaxis). Patients and caregivers of children who have experienced a systemic reaction to an insect sting should be taught how to administer epinephrine and under what circumstances. There is no contraindication to the use of epinephrine in a life-threatening situation, such as anaphylaxis. Repeat dosing might be required for persistent or recurrent symptoms. Patients with cardiovascular disease with anaphylaxis should be given epinephrine. Antihistamines and corticosteroids are not a substitute for epinephrine.

Toxic reactions can occur after a large number of simultaneous stings because of massive envenomation. The number of stings that can cause severe toxic reactions is estimated to be greater

than 100, but some patients report constitutional (nonallergic) symptoms from many fewer stings.[89,90] Although multiple stings are common with imported fire ants, reports of toxic reactions are rare. Toxic reactions 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 an allergic reaction. Although unusual, reactions such as serum sickness, vasculitis, neuritis, encephalitis, and nephrosis have been reported after insect stings and have been extensively reviewed elsewhere.[91-93]

INDICATIONS FOR REFERRAL TO AN ALLERGIST-IMMUNOLOGIST

Summary statement 3

Referral to an allergist-immunologist is recommended for patients who have had a suspected systemic reaction from an insect sting, especially those who:

- **need education about (1) their risk of another reaction if they are stung, (2) options for emergency and prevention treatment, and (3) insect avoidance (B);**
- **have a coexisting condition or medication that might complicate a potential reaction to a sting (B); or**
- **request consultation for more detailed information or specific testing. (D)**

Referral to an allergist-immunologist is recommended for patients who:

- have experienced a systemic allergic reaction to an insect sting;
- have experienced a systemic allergic reaction in which an insect sting could be the cause;
- need education regarding stinging insect avoidance or emergency treatment;
- might be candidates for VIT; or
- have a coexisting situation that might complicate treatment of anaphylaxis by making epinephrine injection less effective or more hazardous (eg, taking β-blockers, hypertension, and cardiac arrhythmias) or might be unable to self-administer epinephrine.

A diagnosis of stinging insect hypersensitivity can be made based on a detailed history of the sting reaction and corroborated by measurement 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 4

Subjects 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 and be familiar with proper use and indications (D);**
- **undergo specific IgE testing for stinging insect sensitivity and be considered for immunotherapy (testing is optional for patients in whom VIT is not required; A); and**
- **consider obtaining and carrying a medical identification bracelet or necklace. (D)**

Three tenets of treatment for patients at risk of systemic reactions from insect stings are education regarding insect avoidance, availability of emergency medication, and VIT. 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 removed by trained professionals (periodic inspection 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;
- avoid walking outside barefoot or with open shoes (sandals);
- 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, and fire ants require different specific insecticides); and
- avoid eating or drinking outdoors and be cautious in situations outdoors in which food and beverages are being served (special care should be taken when drinking from opaque containers and straws).

IMMEDIATE TREATMENT

Epinephrine is the drug of choice for the treatment of anaphylaxis.[60,77] The recommended dose is 0.01 mg/kg, up to 0.3 mg in children, and 0.3 to 0.5 mg in adults, depending on the severity of the reaction. Intramuscular injection in the anterolateral thigh might achieve a more rapid and higher plasma concentration than subcutaneous or intramuscular injection in the arm.[83,84] Delayed use of epinephrine might be ineffective.[85] Reports of fatal and near-fatal anaphylaxis show that fatal outcome is associated with delay or lack of administration of epinephrine.[86-88]

Patients allergic to insect venom should carry epinephrine at an appropriate dosage for administration in case of a sting. Patients and caregivers 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 or 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 the risk of a life-threatening anaphylactic reaction is judged to exceed the risk of administering epinephrine in such patients (even in those using a β-blocker medication). Antihistamines and corticosteroids should not be considered to be substitutes for epinephrine.

In patients who have a relatively low risk of a severe anaphylactic reaction from a sting, the need to carry injectable epinephrine can be determined by the patient and physician after discussion of the relative risk of reaction. Patients with a low risk of reaction are those with a history of only large local reactions to stings or of strictly cutaneous systemic reactions, those receiving maintenance VIT, and those who have discontinued VIT after more than 5 years of treatment. Factors associated with a higher risk include a history of extreme or near-fatal reactions to stings, systemic reactions during VIT (to an injection

or a sting), severe honeybee allergy, increased baseline tryptase levels, underlying medical conditions or concomitant medications, or frequent unavoidable exposure to stinging insects.

DIAGNOSTIC TESTING

Summary statement 5

Immediate hypersensitivity skin tests with stinging insect venoms are indicated for subjects who are candidates for VIT. (A)

Special considerations include the following:

- **Skin tests, rather than *in vitro* assays, should be used for initial measurement of venom-specific IgE, except in special circumstances. (C)**
- **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, as well as baseline serum tryptase measurement. (C)**
- **The degree of sensitivity found on skin and serologic tests for venom-specific IgE does not correlate consistently with the severity of a reaction to a sting. (C)**
- **Skin testing for imported fire ant sensitivity is performed with whole-body extracts. (B)**

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

Diagnostic testing should be performed when the history is consistent with the indications for VIT (see below). Before ordering venom skin tests or venom-specific IgE level measurement, the clinician should discuss with the patient the likely recommendation depending on whether the test results are positive or negative and whether the potential benefit might exceed the potential harm (eg, anxiety, altered lifestyle, and decreased quality of life) from the results of diagnostic evaluation. Diagnostic testing is recommended based on the clinical history, even when the systemic reaction was many years or decades earlier, because the risk of reaction can persist for long periods of time. Even when there has been a sting without a reaction occurring after the systemic reaction, the risk of anaphylaxis can persist.[29,94]

The presence of venom-specific IgE antibodies is usually confirmed by means of intracutaneous skin testing.[95-97] Skin prick tests at concentrations up to 100 μg/mL can be performed before intracutaneous tests but are not used by all allergists. Initial intracutaneous tests generally are done with venom concentrations 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. By using appropriate positive and negative control tests, a positive skin test response at a concentration less than or equal to 1.0 μg/mL demonstrates the presence of specific IgE antibodies. False-positive results caused by nonspecific responses have been reported at concentrations greater than 1.0 μg/ml.[96] An accelerated method for performing venom skin testing has been described.[98] There is no absolute correlation between the degree of skin test reactivity or levels of serum venom-specific IgE antibodies 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 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 antibodies.[23,25] It is appropriate to perform *in vitro* venom testing in selected patients who have negative skin test responses before concluding that VIT is not necessary. Currently, there is no consensus about whether *in vitro* testing should be done in all patients with negative skin test responses who would be potential candidates for VIT (see previous discussion in the annotation of Box 3). Skin tests with less irritating dialyzed venoms might be more sensitive in detecting venom sensitivity in such patients and can be used at concentrations up to 10 μg/mL with no irritant response.[99] Dialyzed venom skin test preparations are not commercially available in the United States. 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 results were negative initially had at least 1 positive test result when tested again with both methods at 4 to 6 weeks after the reaction.[26] Negative test results for venom-specific IgE obtained within the first few weeks after a sting reaction might require cautious interpretation. A negative *in vitro* assay result 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. Baseline serum tryptase levels have been found to be increased, particularly in patients who had severe anaphylactic shock reactions to insect stings and in some affected patients with negative skin test responses and no detectable serum IgE to venoms.[100-102] Such patients might require evaluation for mastocytosis or disorders of mast cell function.

Detection of all potentially relevant sensitivities requires testing with all of the commercially available bee and vespid venoms and might include fire ant extracts when the patient has exposure to fire ant stings. The insect that caused the sting often cannot be identified, but even if it is clearly identified, the possibility exists of future reactions to other venoms to which there is existing sensitization. In states in which fire ants are prevalent, skin testing to fire ant venom alone might be adequate based on the history. Venoms contain some 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.[103-107] Bumblebee venom contains unique allergens and has variable cross-reactivity with honeybee venom. The diagnostic ability to detect all venoms to which each patient is sensitized might be limited by inherent variability in venom IgE test results in some patients, such that any one of the venoms tested could be negative on one occasion and positive at 1.0 μg/mL on a later visit. In patients who have a history of a systemic allergic reaction to a sting and have positive diagnostic test results to some venoms and negative results to others, some experts recommend further evaluation to identify all potentially relevant sensitivities before beginning VIT.[108]

Skin testing for fire ant hypersensitivity

Imported fire ant whole-body extract 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. The intracutaneous skin test concentration should be increased by increments until a positive response is elicited or a maximum concentration of 1×10^{-3} (1:1,000) or 2×10^{-3} (1:500) wt/vol is reached.[13,68,109]

Limited cross-reactivity exists between the antigens in fire ant venom and the antigens in venoms of other Hymenoptera.[57,110] 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 an imported 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 antibodies in those subjects who cannot undergo skin testing. This includes patients with dermatographism or severe skin disease. Skin tests are generally the preferred initial testing method. Up to 20% of subjects with positive venom skin test responses have undetectable serum levels of specific IgE antibodies (negative *in vitro* test result). However, recent studies have demonstrated that 10% to 20% of patients with negative skin test responses have positive *in vitro* test results when using assays capable of detecting low levels of venom-specific IgE antibodies.[23,25] Indications for obtaining these studies are discussed in the preceding section on skin tests. The utility of laboratory methods is also dependent on the reliability of the methods used by clinical laboratories; the clinician is advised to become familiar with differences in results by using different assays and different laboratories.[111,112]

IMMUNOTHERAPY

Summary statement 6

VIT is recommended for all patients who have experienced a systemic reaction to an insect sting and who have specific IgE to venom allergens (A), 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 after an insect sting. (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)**
- **VIT is generally not necessary in patients who have experienced only large local reactions to stings but might be considered in those who have frequent unavoidable exposure. (B)**

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

VIT is an extremely effective form of treatment for subjects at risk of insect sting anaphylaxis. VIT reduces the risk of a subsequent systemic sting reaction to as low as 5% compared with the risk of such reactions in untreated patients, for whom the risk might be as high as 60%.[28,31,32] Moreover, those patients receiving VIT who do experience systemic reactions after an insect sting generally have milder reactions. Candidates for immunotherapy should receive informed consent with documentation in the medical record regarding 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 antibodies should generally receive VIT. The goals of VIT are to (1) prevent systemic reactions and (2) alleviate patients' anxiety related to insect stings.

An estimate of the risk (frequency and severity) of a recurrent sting-induced systemic reaction guides the selection of patients for VIT. 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, shock, airway compromise, and death. Some reactions might be difficult to distinguish from vasovagal reactions. Although bradycardia is a distinguishing aspect of vasopressor reactions, it can also occur in some cases of anaphylaxis.[11] Paradoxically, hypertension might also occur in anaphylaxis, 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 Hymenoptera-induced anaphylaxis. Adults and children who have had these reactions are at the greatest risk for similar life-threatening reactions after subsequent stings. Therefore VIT is recommended for subjects with a history of these manifestations and the presence of venom-specific IgE antibodies. VIT is recommended as safe and effective, even in patients who have had cardiac anaphylaxis.[113] VIT has also been effective in cases of delayed anaphylaxis after a sting.[114]

Cutaneous systemic reactions, such as urticaria, angioedema, or flushing and pruritus, can occur after an insect sting and can be severe. 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, with less than a 5% risk of a more severe reaction and less than a 1% risk of life-threatening anaphylaxis.[38,39] 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 patient's 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 severe systemic reactions, some believe that VIT is optional in this group of patients.[67,115] Patients with a history of solely severe large local reactions to stings are also at low risk for anaphylaxis to future stings and do not require VIT. Although their risk of anaphylaxis is barely more than that of the general population, large local reactors might be considered for VIT (and therefore testing) for quality-of-life reasons and to reduce the morbidity of frequent or unavoidable reactions.[5]

Some patients are at particularly high risk for severe anaphylactic reactions to future stings. Subjects who have experienced a

very severe (near-fatal) anaphylactic reaction to a sting are more likely to have a similar event in the future.[33,47,116] Patients with mastocytosis, or an increased baseline serum tryptase level, are also at higher risk for severe reactions to future stings.[100-102] Such high-risk patients should have the greatest benefit from VIT.

Challenge stings

Approximately 25% to 70% of patients with a history of anaphylaxis from an insect sting and detectable venom-specific IgE antibodies by means of skin or *in vitro* testing will experience a systemic reaction when re-stung.[27-34] An intentional sting challenge has been recommended by some to better select those patients who need VIT.[27,35] Patients allergic to honeybees are more likely to have positive sting challenge results than those allergic to yellow jackets.[27] 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.[29] 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.[36,37]

Large local reactions

Extreme swelling extending from the sting site, usually peaking at 48 to 72 hours after a sting and lasting 1 week or more, is usually the result of 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%.[1,3,38] Because the risk of a systemic reaction is relatively low in patients who have previously had large local reactions, diagnostic testing and VIT are generally not required in such patients. However, testing and VIT might be considered in special circumstances because VIT has been shown to reduce large local reactions to subsequent stings.[5] Providing injectable epinephrine to patients who have a history of large local reactions for use if a subsequent systemic reaction occurs is usually not necessary but might be considered if it provides reassurance to the patient (with instructions on when or when not to use it). This decision and the physician's judgment might be influenced by factors such as the potential risk of being stung, personal health issues (eg, the presence of cardiovascular disease), and the individual patient's preference.

There have been few studies examining the efficacy of VIT in preventing large local reactions to subsequent stings. Most patients with a history of large local reactions will experience similar reactions after subsequent stings, and those with frequent unavoidable exposure might benefit from VIT.[5,40,41] Beekeepers, on the other hand, often have diminished large local reactions when they receive frequent stings.[73,74]

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, applying a knowledge of venom cross-reactivity and insect identification, the extract used for VIT need only contain a single venom, despite positive skin or *in vitro* test results for other stinging insects.[106,117] Other authors recommend that the extract contain venoms from all insects for which positive test results were obtained because of the potential for reaction to any venoms to which the patient is sensitized.[31,37,63,118]

Immunotherapy for fire ant hypersensitivity

Summary statement 7. Immunotherapy with imported fire ant whole-body extracts is recommended for all patients who have experienced a systemic reaction to a fire ant sting and who have positive skin test responses or allergen-specific serologic test results with imported fire ant whole-body extract, (B) with the following special consideration:

- **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)**

Compared with other stinging insects, less is known about the natural history of fire ant hypersensitivity and the effectiveness of immunotherapy.[4,13,15,56-58] Fire ant whole-body extract 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.[12,13,15,16,18,44,57,59,68] 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 prospective study, but one retrospective survey suggests that cutaneous-only systemic reactions from fire ants in children usually do not progress to more serious reactions.[4] However, there is a high frequency of fire ant re-stings in endemic areas.[58,119] 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.[55] Thus immunotherapy in these children is considered to be optional at the present time. Lifestyle consideration, parental preferences, and other factors might influence this decision.

Dosage schedules for VIT

The dose schedules approved by the US Food and Drug Administration are shown in Appendix E1. VIT injections are usually administered once or twice a week, usually beginning with a dose of 0.1 to 1.0 μg and increasing to a maintenance dose of 100 μg of each insect venom (300 μg of mixed vespid venom).[42,117,120] This maintenance dose was selected in the early clinical trials because it was thought to be equivalent to 2 honeybee stings (50 μg per sting). Subsequent studies showed variability in venom deposition from honeybee stings,[82] and vespid stings have been shown to deliver 2 to 20 μg of venom protein per sting.[31,121] The dosing interval and increments might be adjusted at the discretion of the prescribing physician to accommodate the preferences of the physician and the patient. Safe and effective use of more accelerated schedules for VIT have been reported and are no longer considered experimental.[42,122-126] Modified rush schedules, achieving the full dose in 2 to 3 days, have been shown to be as safe as weekly schedules and are used routinely in situations in which patients do not have ready access to

specialists for treatment (in the US armed services and in most European countries). Such rush VIT schedules can be used when there is an urgent need for protection and when there have been systemic reactions to VIT and are optional in all cases. The physician and patient might consider a variety of factors, such as the characteristics and circumstances of the sting reaction and the patient's 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.[31,32] One investigator has used the 50-μg maintenance dose in patients with yellow jacket venom allergy successfully, although some believe that this dose offers a lesser degree of protection.[117,120] Increasing the maintenance dose up to 200 μg per dose has been effective in achieving protection in some patients who have had sting reactions while receiving a 100-μg maintenance dose of VIT.[127] If the insect is unknown, further testing might be needed to determine whether there is a new or untreated venom sensitivity before considering an increase in the venom dose.

The interval between maintenance dose injections is usually increased to 4 weeks during the first year and possibly to every 6 to 8 weeks during subsequent years.[42,128] A maintenance interval of 4 weeks is recommended for indefinite treatment in the US Food and Drug Administration–approved product package inserts. Experts in the field support the regimen of a 4-week maintenance interval for 12 to 18 months followed by a 6-week interval for 12 to 18 months and then 8-week intervals. There have been reports from 1 investigator that a 12-week interval might be safe and effective, particularly after uneventful maintenance VIT at 4- to 8-week intervals for several years, whereas a 6-month interval was not effective.[128-131]

The dosage schedule for fire ant whole-body extract immunotherapy is less well defined in terms of rapidity of buildup. However, most authors recommend a once- or twice-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 E2. Successful use of a rush immunotherapy protocol has been published.[59] Most reports have recommended a maintenance dose of 0.5 mL of a 1:100 wt/vol vaccine/extract with either *Solenopsis invicta* or a mixture of *S invicta* and *Solenopsis richteri* extract, although there are some recommendations for a dose as high as 0.5 mL of a 1:10 wt/vol extract.[13-15,55,56,59,68] A survey of practicing allergists found that 0.5 mL of a 1:200 wt/vol extract is the most widely prescribed maintenance dose.[55] Evidence continues to accumulate to support the efficacy of this dose.[14,15,59] 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. Early reports of the incidence of systemic reactions from VIT were in the range of 12% to 16%, although this incidence is higher than that experienced by most allergists.[126,132] There have been reports of patients who had serum sickness–like reactions from VIT.[133,134] Premedication with antihistamines during build-up VIT has been shown to reduce the incidence of local reactions and mild systemic reactions.[135,136] For appropriate interpretation of reactions, consistency in use or avoidance of antihistamines is suggested. There is evidence that antihistamine premedication can also improve the efficacy of VIT.[137] There is also one report of reduced local reactions to VIT with montelukast premedication.[138]

Patients who are taking β-adrenergic blocking agents might not respond readily to epinephrine treatment if they experience an allergic reaction (see also the practice parameter on anaphylaxis).[12,54,55,139,140] This increases the risk of systemic reaction to stings and VIT injections. Therefore patients who have stinging insect hypersensitivity should not be taking 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.[113,141] In a retrospective study of patients experiencing anaphylaxis from Hymenoptera venom, angiotensin-converting enzyme inhibitor exposure was associated with a statistically significant increase in risk for more severe anaphylaxis (odds ratio, 2.27; 95% CI, 1.13-4.56; $P = .019$).[142] Previous smaller studies found no increased risk with these drugs. For patients who require an angiotensin-converting enzyme inhibitor for an indication for which there is no equally effective alternative available, a management decision by the physician prescribing VIT should be approached cautiously on an individualized risk/benefit basis.

Serum sickness has occurred as a sequel to insect stings, often after an acute systemic reaction.[90,91,93] 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.[93] VIT has been used successfully in this group of patients, but the safety and efficacy of this approach is unknown.

Duration of VIT

Summary statement 8. VIT should usually be continued for at least 3 to 5 years. Although most patients can then safely discontinue VIT, some patients might need to continue VIT for an extended period of time or indefinitely. (C)

Special considerations include:

- **high risk factors (near-fatal reaction before VIT, systemic reaction during VIT, honeybee allergy, increased baseline serum tryptase levels, underlying medical conditions and concomitant medications, and frequent exposure; B);**
- **quality of life (eg, limitation of activity and anxiety about unexpected stings). (A); and**
- **the fact that the optimal duration of immunotherapy with imported fire ant whole-body extracts has been less well studied. (C)**

Guidelines for discontinuation of VIT are evolving.[42,43,47,50] The package insert for the venom extract, which has not changed in more than 30 years, recommends that VIT be continued indefinitely. Criteria that have been suggested for stopping VIT include treatment for a finite length of time (3-5 years), a decrease in serum venom-specific IgE antibodies to insignificant levels, or conversion to a negative skin test response. 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.[44-51,117] There are no specific tests to distinguish which patients will relapse after stopping VIT, but there is a higher risk in some patients than in others. Relapse is less likely with 5 years than with 3 years of VIT.[50,53] 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, those who are

allergic to honeybee stings (versus vespid stings), and those who had a systemic reaction during VIT (to a venom injection or a sting). A few patients who had previously experienced severe anaphylaxis with loss of consciousness and then, after several years of immunotherapy, had negative *in vitro* test or skin test responses have later experienced systemic reactions, several of which were fatal, to subsequent stings after stopping VIT.[46,47,50,52,53,143-145] Although this occurrence is rare, some recommend continuation of immunotherapy indefinitely in such patients. When both skin and *in vitro* test results are negative, VIT has been discontinued with no systemic reactions to subsequent stings.[146] Some authors recommend repeat testing every 2 to 3 years, although negative results are uncommon until 5 years or longer. Repeat skin (or venom-specific IgE serum) testing is not required for consideration of discontinuing VIT. 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) the patient's preferences. This decision requires a context-sensitive flexibility based on the available evidence.

The optimal duration of imported fire ant immunotherapy is less well defined. One retrospective survey suggests an equal risk of a sting reaction whether a patient received more than 3 years of immunotherapy or less than 3 years of immunotherapy, although the numbers were small.[44] A survey of allergists indicated a great deal of variation in recommendations regarding the duration of immunotherapy for fire ant allergy.[72] 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.

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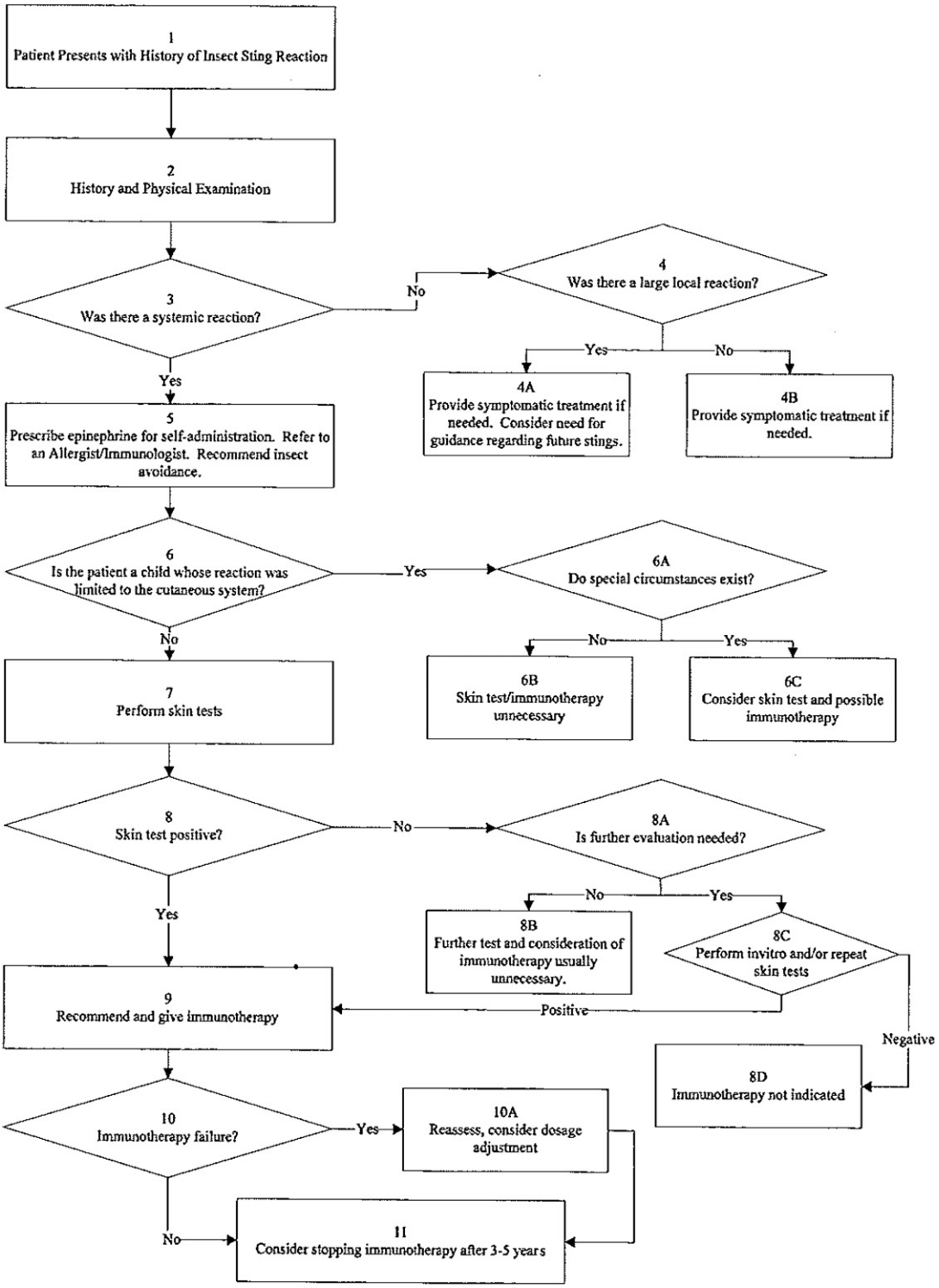

FIG E1. Algorithm: management of stinging insect reactions.

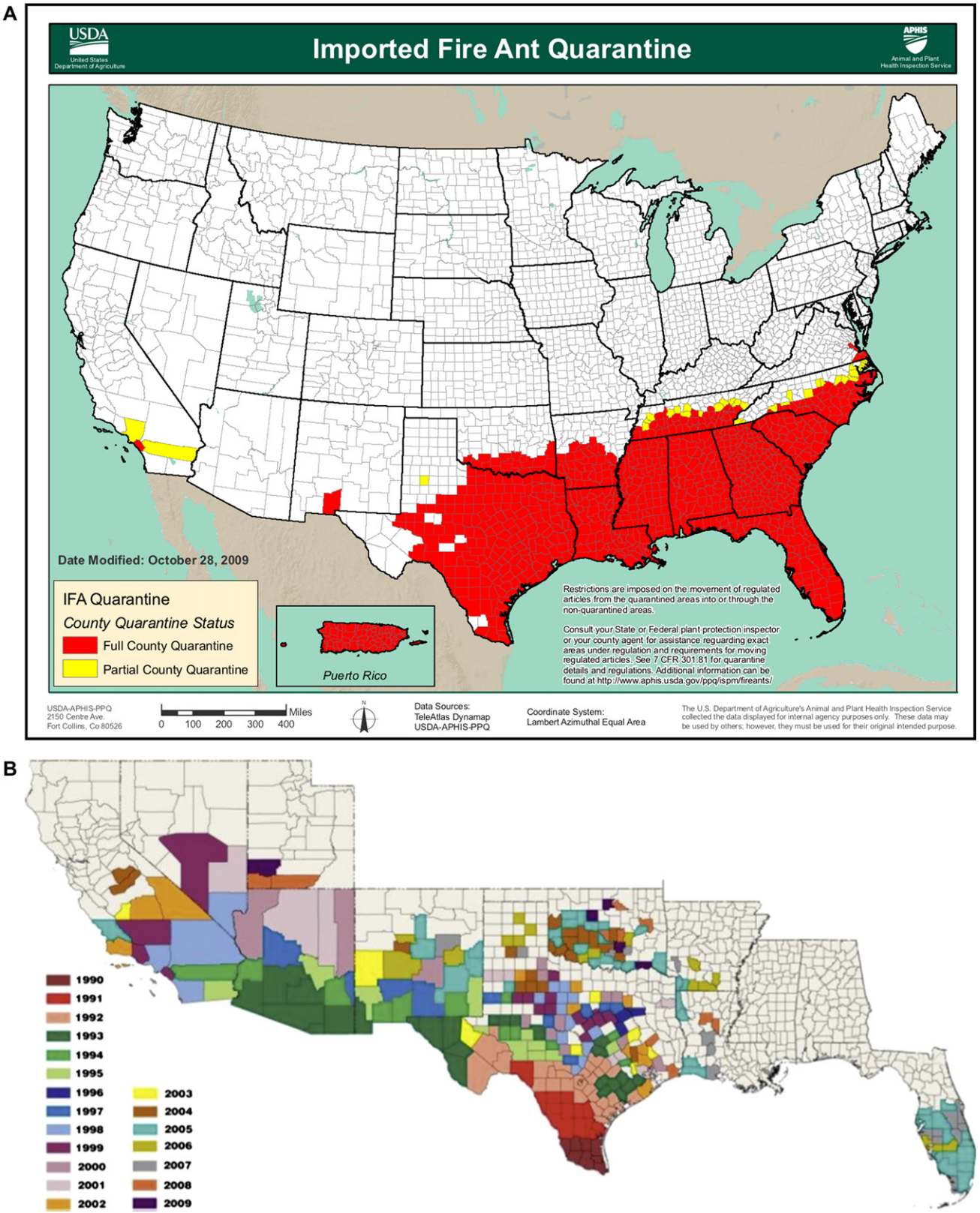

FIG E2. Distribution of imported fire ants **(A)** and Africanized honeybees **(B)** in the United States in 2009 (US Department of Agriculture).

APPENDIX E1. Two examples of conventional dosing schedules for venom immunotherapy

Schedule 1			Schedule 2		
Week	Concentration (μg/mL)	Volume	Week	Concentration (μg/mL)	Volume
1	1.0	0.05 mL	1a	0.01	0.1 mL
			1b	0.1	0.1 mL
			1c	1.0	0.1 mL
2	1.0	0.1 mL	2a	1.0	0.1 mL
			2b	1.0	0.5 mL
			2c	10	0.1 mL
3	1.0	0.2 mL	3a	10	0.1 mL
			3b	10	0.5 mL
			3c	10	1.0 mL
4	1.0	0.4 mL	4a	100	0.1 mL
			4b	100	0.2 mL
5	10	0.05 mL	5a	100	0.2 mL
			5b	100	0.3 mL
6	10	0.1 mL	6a	100	0.3 mL
			6b	100	0.3 mL
7	10	0.2 mL	7a	100	0.4 mL
			7b	100	0.4 mL
8	10	0.4 mL	8a	100	0.5 mL
			8b	100	0.5 mL
9	100	0.05 mL	9	100	1.0 mL
10	100	0.1 mL	Monthly	100	1.0 mL
11	100	0.2 mL			
12	100	0.4 mL			
13	100	0.6 mL			
14	100	0.8 mL			
15	100	1.0 mL			
16	100	1.0 mL			
18	100	1.0 mL			
21	100	1.0 mL			
Monthly	100	1.0 mL			

Injections are generally given weekly. Schedule 2 gives 2 to 3 doses at 30-minute intervals for the first 8 weeks. When the maintenance dose is achieved, the interval can be advanced from weekly to monthly. Schedule 1 is based on the package insert for Hollister-Stier venom extracts (Spokane, Wash). Schedule 2 is based on the package insert for ALK-Abelló venom extracts (Round Rock, Tex).

APPENDIX E2. Two examples of conventional dosing schedules for fire ant immunotherapy with *Solenopsis invicta* or a mixture of *S invicta*/*Solenopsis richteri* whole-body extract have been used successfully

Schedule 1			Schedule 2		
Dose	Concentration (wt/vol)	Volume	Dose	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	1:1,000	0.05 mL
12	1:10,000	0.50 mL	12	1:1,000	0.10 mL
13	1:1,000	0.05 mL	13	1:1,000	0.20 mL
14	1:1,000	0.10 mL	14	1:1,000	0.30 mL
15	1:1,000	0.20 mL	15	1:1,000	0.40 mL
16	1:1,000	0.30 mL	16	1:1,000	0.50 mL
17	1:1,000	0.40 mL	17	1:100	0.05 mL
18	1:1,000	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	0.40 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			

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.