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Practice Parameter

Stinging insect hypersensitivity
A practice parameter update 2016

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Disclaimer: The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing "Stinging Insect Hypersensitivity: a practice parameter update 2016." 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. 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 ACAAI should be directed to the Executive Offices of the AAAAI or the ACAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

Disclosures: The following is a summary of interests disclosed on Work Group members' Conflict of Interest Disclosure Statements (not including information concerning family member interests). Completed Conflict of Interest Disclosure Statements are available upon request. Conflicts of interest disclosure statements for JTF are available on its website. Dr Golden has served on the speaker's bureau and clinical trials for Genentech, has served on the speaker's bureau for Stallergenes/Greer, has served as an expert witness for & Trifrolis, PC, and is a section editor for UptoDate. Dr Demain is a contributor to UptoDate. Dr Graft is an author for UptoDate. Dr Tracy is a contributor to UptoDate. The other Work Group members have nothing to disclose. The Joint Task Force recognizes that experts in a field are likely to have interests that could come into conflict with development of a completely unbiased and objective practice parameter. To take advantage of that expertise, a process has been developed to prevent potential conflicts from influencing the final document in a negative way. At the workgroup level, members who have a potential conflict of interest either do not participate in discussions concerning topics related to the potential conflict or if they do write a section on that topic, the workgroup completely rewrites it without their involvement to remove potential bias. In addition, the entire document is reviewed by the Joint Task Force and any apparent bias is removed at that level. Finally, the practice parameter is sent for review both by invited reviewers and by anyone with an interest in the topic by posting the document on the web sites of the ACAAI and the AAAAI.

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All published practice parameters are available at http://www.allergyparameters.org/.

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

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Classification of Recommendations and Evidence

Recommendation Rating Scale

Category of Evidence

Ia Evidence from meta-analysis of randomized controlled trials
Ib Evidence from at least one randomized controlled trial
IIa Evidence from at least one controlled study without randomization
IIb Evidence from at least one other type of quasi-experimental study
III Evidence from non-experimental descriptive studies, such as comparative studies
IV Evidence from expert committee reports or 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 Laboratory Based
NR Not rated

How This Practice Parameter Was Developed

The Joint Task Force on Practice Parameters

The Joint Task Force on Practice Parameters (JTF) is a 12-member taskforce consisting of 6 representatives assigned by the American Academy of Allergy, Asthma & Immunology and 6 by the American College of Allergy, Asthma & Immunology. This task force oversees the development of practice parameters, selects the workgroup chair(s), and reviews drafts of the parameters for accuracy, practicality, clarity and broad utility of the recommendations for clinical practice.

The Stinging Insect Hypersensitivity Practice Parameter Workgroup

The Stinging Insect Hypersensitivity Practice Parameter Update 2016 workgroup was commissioned by the JTF to develop practice parameters that address insect stings. The chair, David B. K. Golden, MD, invited workgroup members to participate in the parameter development who are considered experts in the field. Work group members have been vetted for financial conflicts of interest by the JTF, and their conflicts of interest have been listed in this document and are posted on the JTF website at http://www.allergyparameters.org. Where a potential conflicts of interest is present, the potentially conflicted work group member was excluded from discussing relevant issues. The charge to the work group was to use a systematic literature review, in conjunction with consensus expert opinion and workgroup-identified supplementary documents, to develop a Practice Parameter that provides a comprehensive approach for insect hypersensitivity based on the current state of the science.

Protocol for Finding Evidence

A search of the medical literature was performed using a variety of terms that were considered relevant for this practice parameter. Literature searches were performed on PubMed, MEDLINE, Medscape, Google Scholar, and the Cochrane Database of Systematic Reviews. The time frame for most searches was 2011 to 2016, but some topics required searches for an expanded timeframe from 1960 to present. The searches included only English-language articles.

Search terms included *insect venom, Hymenoptera venom, insect sting, venom immunotherapy, venom skin tests, venom diagnostic tests, serum tryptase, mastocytosis, angiotensin-converting enzyme inhibitors* (*ACEIs*), *β-blockers, basophil activation tests, recombinant venom allergens, venom component tests, fire ant, stinging ant, epinephrine, rush immunotherapy, Kounis syndrome*, and *large local reactions*. The search was narrowed by adding the terms *allergy* and *anaphylaxis*. More focused searches were also used (eg, duration of venom immunotherapy [VIT], discontinuing VIT). All reference types were included in the results. Search results were screened for relevance and for the quality of the data and the analysis.

References identified as being relevant were searched for additional references and these also were searched for citable references. In addition, members of the work group were asked for references that were missed by this initial search. Initial search results yielded 1135 references, and additional references were suggested by work group members. Many of the references were excluded because of poor study design or lack of relevance. The 229 references cited in this practice parameter represent the best quality and most relevant evidence for the discussion and recommendations made herein.

Statement	Definition	Implication
Strong recommendation (StrRec)	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B). In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation (Rec)	A recommendation means the benefits exceed the harms (or that the harms clearly exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C). In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option (Opt)	An option means that either the quality of evidence that exists is suspect (Grade D) or that well-done studies (Grade A, B, or C) show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation (NoRec)	No recommendation means there is both a lack of pertinent evidence (Grade D) and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

Although the ideal type of reference would consist of a randomized, double-blind, placebo-controlled study, the topic of this practice parameter is represented by very few such studies. Consequently, it was necessary to use observational studies, case series, basic laboratory reports, and expert review articles to develop a document that addresses most of the issues included in this practice parameter.

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. Particular emphasis is placed on the appropriate use of immunotherapy with venoms (VIT) or imported fire ant whole-body extracts (WBEs).

The document "Stinging Insect Hypersensitivity: A practice Parameter Update 2016" is the fourth iteration of this parameter. The first was published in 1999 (Portnoy JM, Moffitt JE, Golden DB, et al. Stinging insect hypersensitivity: a practice parameter. *J Allergy Clin Immunol*. 1999;103:963–980), and the first update was published in 2004 (Moffitt JE, Golden DB, Reisman RE, et al. Stinging insect hypersensitivity: a practice parameter update. *J Allergy Clin Immunol*. 2004;114:869–886), and there was an update in 2011 highlighting advances in diagnosis and management of insect sting allergy (Golden DBK, Moffitt J, Nicklas RA, AAAAI. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol*. 2011;127:852–854). The working draft of this 2016 update was prepared by a work group 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. On the basis of this process, this parameter represents an evidence-based document.

This document is similar in format to the previous iterations, but it has been considerably reorganized to make it easier for the reader to find the answers to specific questions and the supportive evidence. 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 WBEs unless otherwise stated. The annotated algorithm in this document summarizes the key decision points for the appropriate use of VIT (Fig 1). It has been extensively revised to reflect changes in the recommended evaluation and treatment of insect allergic patients. In this update, we introduce a new section on "What's New and What's Different" in the field. There are some important changes in several areas of this document that address techniques and interpretation of diagnostic tests, selection of patients for VIT, and risk factors for severe anaphylaxis to stings. These new features of the 2016 update are summarized in a new section on "What's New." Because our experience with and understanding of VIT have evolved since it was introduced in 1979, the recommendations made in the product package insert have become out of sync with the published evidence base that is available for clinical guidance. For the attention and consideration of the clinician, these are listed in a new section on "What's Different." There remain important areas of uncertainty that must be addressed in focused practice parameters when the evidence becomes available from future clinical observations and research.

The JTF and the contributing authors wish to thank the ACAAI, the AAAAI, and the Joint Council of Allergy, Asthma and Immunology for their continued and/or past 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 work group and the task force acknowledge the contributions made by Dr Robert E. Reisman (1932–2012) (clinical professor of medicine and pediatrics at University of Buffalo School of Medicine and Biomedical Sciences) and his dedication to this effort over many years, and we dedicate this update to his memory.

What's New and What's Different

What's New?

Every section of this update contains new evidence with references and discussion. Many of these are of great clinical importance, and some of them warrant new sections for comprehensive review. Some of these address new issues and observations, and some of them simply add elements that have been missing from previous documents. Not all these issues have clear-cut answers, but guidance is provided based on the available evidence and the experience of the experts in the field.

1. Discussion of indication for VIT in adults with cutaneous systemic reactions:

   At least 2 prospective studies show less than 2% chance of progression and no severe reactions. There is still the option for VIT when considering high-risk factors and quality-of-life concerns (Table 1).

2. New section on mast cell disorders and measurement of basal serum tryptase:
   - Clinical significance of elevated basal serum tryptase (increased risk of severe anaphylaxis to stings before, during, and after VIT)
   - When to measure tryptase (patients with hypotension or severe anaphylaxis and consider in all patients who are candidates for VIT)
   - What to do with abnormal results (recognize increased risk, monitor for increasing level, consider bone marrow biopsy, give VIT indefinitely)
   - Mastocytosis in adult patients with insect sting allergy (estimated 2% frequency)
   - Insect allergy in patients with mastocytosis (25% frequency; most common cause of anaphylaxis in patients with mastocytosis; can be the presenting sign of indolent systemic mastocytosis)
   - VIT in patients with mast cell disorders (significant benefit but higher than the mean failure rate and more than the mean systemic reactions to VIT)
3. New section on technique and interpretation of venom skin tests:
   - Whether to use the volume of injection (0.02–0.03 mL vs 0.05 mL) or size of bleb (3–4 mm) technique for intradermal skin tests
   - Is a positive test result a wheal diameter of 3 mm or 5 mm?
4. New section on methods and materials for diagnostic tests for insect sting allergy:
   - Recombinant/component resolved diagnosis (increased species specificity; no greater sensitivity than native venom)
   - Basophil activation test (variable methods; may add sensitivity to diagnostic testing; associated with greater severity of

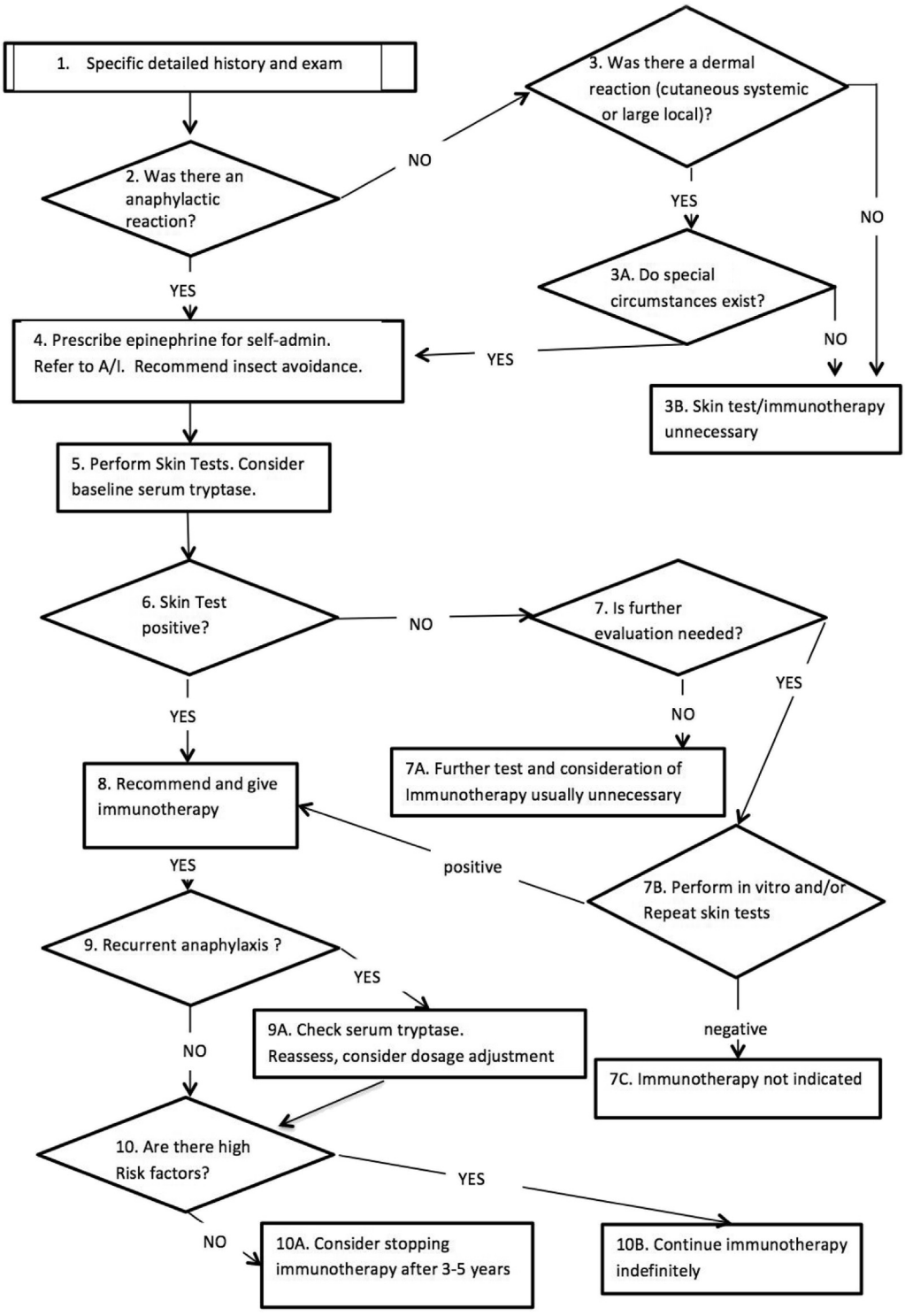

Figure 1. Algorithm for diagnosis and management of patients with a history of allergic reactions to insect stings.

sting reaction, systemic reactions during VIT [to injection or sting], more chance of sting reaction after stopping VIT)

5. New section on risk of cardiovascular medications in insect allergic patients:
   β-blockers:
   - More risk of cardiovascular problems if medication is changed than if continued
   - More risk (of sting reaction) if VIT is stopped than if continued
   - Less risk of reactions to VIT with medications than to stings in untreated patients

   ACEIs:
   - Inconsistent literature but evidence suggests increased severity of reactions to stings
   - Less risk of reactions to VIT with medications than to stings in untreated patients
6. New guidance on assessment and stratification of the risk of anaphylaxis to stings (when considering prescription of

Table 1
Risk Factors for Severe Reactions to Stings

Clinical markers	Laboratory markers
Very severe previous reaction	Venom skin test
Insect species	Venom-specific IgE
No urticaria or angioedema	Basal serum tryptase
Age (>45 years), Sex (male)	Basophil activation test[a]
Multiple or sequential stings	Platelet activating factor–acetylhydrolase[a]
Medications (ACEIs)	ACE

Abbreviations: ACE, angiotensin-converting enzyme; ACEIs, angiotensin-converting enzyme inhibitors.
[a]Not commercially available.

epinephrine injectors or recommendation of venom skin tests or immunotherapy):
- High risk: severe anaphylaxis; elevated basal serum tryptase level; honeybee allergy; frequent exposure; age/medical conditions
- Low risk: patients with cutaneous systemic reactions; large local reactors; asymptomatic sensitization; during VIT; after discontinuing VIT

7. New content on VIT: protocol, procedures, problems, and special circumstances:
   - Starting dose for skin tests and for VIT: reported safe at 1 μg/mL for skin tests, 1 μg for VIT
   - Up-dosing regimens and maintenance doses: semirush and rush are safe, ultrarush associated with more systemic reactions; 50 μg maintenance dose in children, 100 μg in adults)
   - VIT in pregnancy: few data; no known problems; generally safer to continue than stop
   - Maintenance interval gradually increased from 4 weeks to 8 weeks during the initial years (first 1 or 2) of treatment and later up to 12 weeks
   - Management of adverse reactions: minimal adjustment for large local reactions; for repeated systemic reactions, try single venom with pre-medication, consider rush VIT and/or omalizumab
   - Duration: 5 years is better than 3 years; longer treatment recommended in high-risk patients; 3 years may be sufficient in children

What's Different?

There is an increasing number of ways in which the guidance contained in these practice parameters differs from that contained in the US Food and Drug Administration–approved product package insert (Table 2). The clinician should be aware of these differences and the related evidence and rationale. Ultimately, the therapeutic decisions are a matter of professional judgment and should be considered in the context of each individual patient.

Executive Summary

The primary focus of the stinging insect practice parameter over the years has been to provide a working framework for the management of stinging insect hypersensitivity. Every effort has been made to incorporate data-driven recommendations and those based on expert consensus. Since the most recent iteration in 2011, many new, relevant, and practical observations have occurred. This parameter attempts to address many of these observations and includes contemporary recommendations for this potentially lethal condition. Throughout this document, the use of the terms *venom immunotherapy, VIT, venom testing*, and *venom* refers to both venom and imported fire ant WBE unless otherwise stated.

Most insect stings produce a transient local reaction that can last up to several days and generally resolves without treatment.

Table 2
Differences Between Venom Package Insert and the 2016 Practice Parameter

Parameter	Package insert	2016 Practice
Indications for testing	History of systemic reaction	SRs; some LLRs; mastocytosis
ST technique/interpretation		
Prick	1 μg/mL	100 μg/mL (optional)
ID	0.05 mL	0.02–0.05 mL
Wheal	5–10 mm	3–5 mm
Tryptase/mastocytosis	No mention	When to measure, Clinical significance
Cutaneous systemic reactions	VIT	VIT not required (optional) at all ages
Large local reactors	No VIT	VIT not required (optional)
Rush regimens	No mention	Safe and effective
Premedication	No mention	Reduces LLRs (and mild SRs)
Starting dose	0.001–0.01 μg	1.0 μg
Cardiac medications	Standard warnings	Guidance on when to change
Children	Same as adults	Dose, duration may differ
Adverse reactions to VIT	No mention	Premedication, cluster, rush, omalizumab
Maintenance interval	4 weeks	Up to 12 weeks
Duration	Indefinite	5 years, indefinite (if high risk factors)

Abbreviations: ID, intradermal; LLR, large local reaction; SR, systemic reaction; ST, skin test; VIT, venom immunotherapy.

Marked local swelling extending from the sting site is usually an IgE-mediated late-phase reaction. The risk of a systemic reaction in patients who experience large local reactions is 4% to 10%.[1–4] More serious anaphylactic sting reactions account for at least 40 deaths each year in the United States.[5] 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.[6,7]

Systemic reactions are characterized by many different signs and symptoms, including any combination of urticaria and angioedema, bronchospasm, edema of the large airway, hypotension, or other clinical manifestations of anaphylaxis. 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.[8] 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 WBE) if test results for specific IgE antibodies are positive, and (5) consider carrying medical identification for stinging insect hypersensitivity.

Positive serum or skin test results for venom IgE are present in more than 20% of healthy adults, especially in the months after a sting.[7] However, only 5% to 15% of those with such asymptomatic sensitization will have a systemic reaction to a subsequent sting, and most will lose the sensitivity over time.[9,10] In contrast, patients with a history of anaphylaxis to a sting have a mean of almost 50% frequency of systemic reaction to a sting.[11–15] Patients with large local reactions have less than 10% chance of a systemic reaction (and <5% chance of anaphylaxis).[2,3,16] However, no test predicts the severity of a sting reaction (other than basal serum tryptase).

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. Different insects have different nesting and behavioral characteristics that can be distinct and specific. For example, the most common species of yellow jackets in the United States 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 ft in diameter and elevated up to 6 to 12 in or higher. 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 evaluation, including skin testing or 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, WBE is available and contains relevant venom allergens, the effectiveness of which is supported by accumulating evidence.[17,18] 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 reveals the presence of specific IgE antibodies. A survey (by the JTF) of practicing allergists found that there is variation in the reported technique for the performance and interpretation of intradermal skin tests, so the clinician must be consistent in the use of the test. When there is a clear history of sting anaphylaxis and skin test results are negative, then serum IgE antibodies should be measured, and if necessary, skin tests should be repeated after 3 to 6 months. Skin testing with fire ant WBE 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. There are tests in development that may improve the accuracy of diagnosis and treatment of insect sting allergy. Component resolved IgE tests using recombinant venom allergens may improve the specificity of diagnosis and treatment by distinguishing specific from cross-reactive sensitivities (especially between honeybee and vespid venoms).[19] The basophil activation test may improve the sensitivity of diagnostic testing and prediction of which patients are at risk for severe anaphylaxis.[20,21] However, these tests are not clinically available at this time.

Our understanding of the role of mast cell disease and its unique relationship to insect allergy continues to evolve compared with other causes of life-threatening anaphylaxis. An increasing body of evidence reveals that patients with severe insect sting reactions should be evaluated for mast cell disorders.[22,23] Some experts recommend a basal serum tryptase measurement as part of the assessment of all patients with a systemic reaction to insect sting. Basal serum tryptase should be measured when there is a history of severe insect sting anaphylaxis (especially with hypotension or the absence of urticaria) and when skin and serum test results for venom-specific IgE are negative.[24–26] Tryptase measurement should be considered when patients have systemic reactions during VIT and when discontinuing VIT. Patients with mastocytosis should be tested for Hymenoptera venom sensitivity. In individuals with mastocytosis, insect stings are the most common cause of anaphylaxis, and their anaphylactic reactions are more likely to be severe.

There are patients who have negative skin test responses who give a convincing history of anaphylaxis after an insect sting, some of whom experienced serious symptoms, such as upper airway obstruction or hypotension. For such individuals, it is advisable to measure basal serum tryptase and to consider in vitro testing for IgE antibodies and/or repeat skin testing before concluding that immunotherapy is not indicated. Either or both of the serum measurements of specific IgE for insect venom or fire ant WBE 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.[27] Although one might want to wait for this period 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.[28] Some of these patients might have underlying systemic mastocytosis.

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 restung.[11,12,14,15] Therefore, VIT should be considered in such patients. Some investigators suggest that patients can be better selected for immunotherapy on the basis of the results of an intentional sting challenge. Sting challenges, however, are not consistently reproducible and are associated with considerable risk.[11,29] The standard management of stinging insect hypersensitivity in the United States does not include a sting challenge.

VIT is generally not necessary in children (younger than 17 years) who have experienced isolated cutaneous systemic reactions without other systemic manifestations after an insect sting.[30] In a change from previous recommendations, adults who have experienced only cutaneous manifestations of a systemic reaction are also considered to be at low risk for a severe reaction and do not require VIT. VIT is also 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, most patients who have had a large local reaction do not need to be tested for specific IgE antibodies to insect venom. VIT significantly reduces the size and duration of large local reactions and thus might be useful in patients who have unavoidable and/or frequent large local reactions.[31] 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.[32] In patients at low risk for a severe reaction to a sting, such as those with large local or cutaneous systemic reactions, there may be special circumstances that would favor treatment, such as frequent exposure, impaired quality of life, or underlying medical conditions. In these patients, the decision regarding initiation of VIT is based on a risk-benefit discussion with the patient.

Selection of venom and dose schedules are discussed in the main document. Adverse effects are typically minor, although anaphylaxis may occur; therefore, close monitoring is warranted. The full dose of 100 μg must be achieved to ensure optimal clinical protection (50 μg may be considered in children). Large local reactions are most common but can generally be tolerated. Antihistamines help to limit the reaction. If systemic reactions recur, rush VIT (sometimes with omalizumab pretreatment) is usually successful. β-blockers and ACEIs may increase the risk of anaphylaxis to VIT, but the published evidence is inconsistent.[26,33,34] The benefits of VIT clearly outweigh the potential risks associated with β-blockers or ACEIs in those patients with anaphylaxis to stinging insects who also have cardiovascular disease requiring these medications.[35] Once initiated, VIT should usually be continued for at least 3 to 5 years. 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.[36–39] There are no specific tests that can 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.[38,40] Although most patients can safely discontinue immunotherapy after this period, 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. Another group believed to be at increased risk are those who react to maintenance VIT or who have had a systemic reaction to a sting. 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. Some patients have relapsed despite negative venom skin test responses.[37] 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 to stop VIT requires a context-sensitive flexibility based on the available evidence and the preference of the patient.

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. 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. Fire ant WBE contains 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 WBE.[17] Recommendations for immunotherapy with fire ant WBE are generally the same as those for VIT.

Patients who have experienced a systemic reaction to an insect sting should be referred to an allergist and should be given a prescription for an injectable epinephrine device, be instructed in its proper use, and be advised to carry it with them at all times. Some patients who experience anaphylaxis might require more than one injection of epinephrine, so prescription of more than 1 epinephrine injector should be considered. Patients and advocates who might be administering epinephrine should be taught how to administer this drug and under what circumstances this should be done. Although patients with coexisting conditions, such as hypertension or cardiac arrhythmias, or concomitant medications, such as β-adrenergic blocking agents, might require special attention, there is no contraindication to the use of epinephrine in a life-threatening situation, such as anaphylaxis. 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, elevated basal serum tryptase level, underlying medical conditions, or frequent unavoidable exposure.

There remain some unmet needs and unanswered questions in the diagnosis and treatment of insect sting hypersensitivity. Managing the individual with a convincing history of insect-related anaphylaxis but negative or inconclusive diagnostic test results remains a clinical dilemma. Improved diagnostic sensitivity and specificity with better positive predictive value must await studies to validate new tests, such as those using recombinant allergens or epitopes or those designed to detect basophil activation or basophil sensitivity. To better predict which patients will have a systemic reaction to a sting after stopping VIT, there is a need for a test that can identify when permanent tolerance has been achieved. There is a need for a study of discontinuing VIT in low-risk patients after exactly 3 years of VIT (not a range of 3–7 years as in previous studies). An increasing number of patients have been receiving VIT for extended periods because of high-risk factors. Some patients have had systemic reactions up to 13 years after stopping VIT, even some who had negative skin test results. There is a need for a controlled study of discontinuation after 15 to 30 years in high-risk patients with negative skin test responses. One of the greatest concerns is that 50% of fatal sting reactions occur with the first reaction and therefore cannot be prevented by current standards of testing and treating only those who have a history of reaction. Unfortunately, measures of venom-specific IgE (skin or serum tests) have poor positive predictive value, so there is a need for an effective screening test to detect those who are at greatest risk for a severe reaction to a future sting so that VIT can be recommended with greatest efficiency.

Annotations to the Algorithm (Fig 1)

Box 1: Specific detailed history and physical examination

Patient presents with a history of insect sting reaction. Most people of all ages 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 preventive 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.

Identification of the responsible insect might be helpful in 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 sterile pustule caused by an imported fire ant sting (up to 24 hours or longer) might help in insect identification.

Box 2: Was there an anaphylactic reaction?

Most insect stings result in local reactions at the site of the sting. These include the following:

- Redness
- Swelling
- Itching and pain

Large local reactions occur at the site of the sting and 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
- 3 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. Cutaneous systemic reactions are limited to skin manifestations, whereas anaphylaxis includes hypotension or involvement of at least 2 organ systems. These may include the following:

- Cutaneous (eg, urticaria, angioedema, itching, flushing)
- Bronchospasm
- Upper airway obstruction (eg, tongue or throat swelling and laryngeal edema)
- Cardiac (eg, arrhythmias and coronary artery spasm)
- Hypotension and shock
- Gastrointestinal (eg, nausea, vomiting, diarrhea, and abdominal pain)
- Neurologic (eg, seizures)

Box 3, 3A, 3B: Was there a dermal reaction (cutaneous systemic or large local)?

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. Swelling (and even lymphangitis) may be caused by mast cell mediator release and not by infection, so antibiotics are not indicated unless there is clear evidence of secondary infection, such as fever, chills, or sweats.

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. Most patients with large local reactions need only symptomatic care and are not candidates for testing for venom specific IgE or venom immunotherapy (VIT). There is, however, increasing evidence that VIT significantly reduces the size and duration of large local reactions and thus might be useful in affected individuals with a history of frequent unavoidable large local reactions and detectable venom specific IgE. The decision to give VIT for patients with large local reactions must be weighed against the added cost and potential inconvenience.

The usual criteria for VIT 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 required for patients who have experienced only cutaneous systemic reactions after an insect sting. In a prospective field-sting study of children, there was a 10% chance of having a systemic reaction if re-stung (usually milder than their previous sting reactions), and a 3% or less chance of a more severe reaction. Prospective sting challenge studies in adults found a less than 3% chance of a more severe reaction in such people. VIT is still an acceptable option if there are special circumstances, such as frequent exposure, or lifestyle considerations (potential impairment in quality of life) and must be weighed against added cost and potential inconvenience. There is evidence that VIT improves the quality of the patient's life in patients with cutaneous systemic reactions.

The need to carry epinephrine autoinjectors can be determined by the patient or caregiver and physician after discussion of the relative risk of anaphylaxis and the anticipated effect on quality of life. In addition, the cost of autoinjectors and the inconvenience of having to carry them should be considered when recommending that a patient have them available. Although VIT is considered almost completely effective in preventing life-threatening reactions to stings, carrying self-injectable epinephrine might still be desired, even during VIT, particularly for honeybee and fire ant VIT, which are known to offer less complete protection. This decision is subject to discussion between the patient or caregiver and the physician. Although most physicians generally apply the same criteria in selecting patients to receive immunotherapy for fire ant allergy, it has not been established that patients (children or adults) 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 patients who have only cutaneous manifestations has not been elucidated and there is increased risk of fire ant stings in those who live in areas in which fire ants are prevalent, immunotherapy can be considered for such individuals.

Box 4: Prescribe epinephrine for self- administration/refer to an allergist-immunologist/recommend insect avoidance

Patients with a known risk for severe reaction to a future sting should have injectable epinephrine prescribed and 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 because 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 5: Perform skin or in vitro testing and consider measuring basal serum tryptase

Skin or in vitro tests should be performed on patients for whom VIT might be indicated. Skin tests with increasing concentrations of fire ant extract are also used (see text section on fire ants). Positive and negative controls should be included.

Detection of all potentially relevant sensitivities requires testing with all 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 reliably 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 [WBE]) has very limited cross- reactivity with other stinging insect venoms.

Compared with other causes of anaphylaxis, such as foods or medications, the prevalence of mast cell disorders is higher in patients who have had anaphylaxis to an insect sting. Therefore, measurement of basal serum tryptase should be considered in all patients who are candidates for VIT. Elevated basal serum tryptase

is closely correlated with the risk of severe anaphylaxis to stings and is most frequently found in patients with reactions, including hypotensive shock. The frequency of abnormal basal tryptase is much lower in patients with less severe systemic reactions to stings, and the clinical significance in these patients is less clear. There is a cost and burden associated with abnormal results of basal tryptase (eg, bone marrow biopsy, consultation with other specialists, anxiety associated with an abnormal test result). However, an abnormal result is associated with severe anaphylaxis to stings, increased risk of systemic reactions during VIT (to a sting or venom injection), and greater risk of sting anaphylaxis after stopping VIT. With these considerations in mind, measurement of basal serum tryptase is highly recommended in patients who had hypotensive reactions to a sting and should be considered in other patients with systemic reactions to stings. In addition, elevated basal tryptase may indicate the presence of an occult mast cell disorder and also may be present in sting allergic patients with negative venom allergy test results.

Box 6: Positive skin or in vitro test response?

VIT is recommended for patients who have had a systemic insect sting reaction, who have a positive skin or in vitro test response, and who meet the criteria outlined in the annotation for Box 3. 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 7, 7A, 7B, 7C: Is further evaluation 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. This would include serum IgE assays for venom IgE and repeat skin tests and may include new modalities in the future. Patients with a history of systemic reaction but with no detectable venom allergy should be tested for basal serum tryptase (if not already done).

For patients who have had a severe systemic reaction to an insect sting, as described in the preceding annotation, 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, although basal serum tryptase levels should be measured to assess for an underlying mast cell disorder.

Box 8: 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. VIT has been shown to improve the quality of life.

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 may be needed for VIT, even if skin or in vitro test results for other stinging insects are positive. Immunotherapy for patients with fire ant hypersensitivity consists of injections with a WBE 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 WBE 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. Rush immunotherapy 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 angiotensin-converting enzyme inhibitors or β-adrenergic blocking agents are at greater risk for more serious anaphylaxis to a sting. Therefore, patients who have stinging insect hypersensitivity should not be prescribed angiotensin-converting enzyme inhibitors or β-blockers unless absolutely necessary. The risk appears to be less during VIT, so if the patient who has stinging insect hypersensitivity cannot discontinue use of these medications, 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.

Box 9, 9A: Recurrent anaphylaxis

VIT at the 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. Consider measuring basal serum tryptase because failure of VIT can be related to underlying mast cell disorders.

Box 10, 10A, 10B: Are there high risk factors? Consider stopping VIT after 3 to 5 years.

The package insert for the Hymenoptera venom extracts recommends that VIT be continued indefinitely. Research on the discontinuation of treatment has suggested several possible criteria, such as the duration of treatment (3-5 years), a decrease in serum venom specific IgE to insignificant levels, or conversion to a negative skin test response. These studies found that even when skin or serum test results for venom IgE remained positive, approximately 90% of patients did not have a systemic reaction to an insect sting if VIT was stopped after 3 to 5 years and that any reaction to a

subsequent sting was usually less severe than the pre-VIT reaction. Most patients should consider discontinuing VIT after 3 to 5 years, 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, the persistence of skin test 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 when considering discontinuation of VIT. Patients with a history of severe anaphylaxis (severe airway obstruction, shock, or loss of consciousness) still might be at continued risk for a severe 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). There is also a higher chance of relapse in patients with elevated basal serum tryptase levels, those who had systemic reactions during VIT (to an injection or a sting), and those who are more frequently stung.

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.

List of Summary Statements

1. Evaluate patients with a history of a systemic reaction to an insect sting for the presence of venom-specific IgE. If venom IgE is present, these patients are at increased risk for subsequent sting anaphylaxis, which can be prevented by VIT. (Strong Recommendation; A Evidence)
2. Evaluate the patient for details of the history of any reactions to insect stings. (Strong Recommendation; B evidence)
3. Recommend to patients who have a history of systemic reactions to insect stings:
   a. effective measures to avoid insect stings. (Recommendation; D evidence);
   b. the need to always carry an epinephrine autoinjector, to be familiar with its proper use and when to use it or not use it, and to carry medical identification (Strong Recommendation; C evidence); and
   c. referral for evaluation by an allergist/immunologist, the utility of specific IgE testing for stinging insect sensitivity, and the potential advantages of VIT (testing is not necessary for patients in whom VIT is not required) (Strong Recommendation; D evidence).
4. Perform skin tests and/or serum tests for IgE to stinging insect venoms on patients who are candidates for VIT. (Strong Recommendation; A evidence)
5. If initial test results are negative in a patient with a clear history of systemic sting reaction, further testing (in vitro testing, repeat skin testing, or both) should be performed, as well as basal serum tryptase measurement. (Strong Recommendation; C evidence)
6. Physicians and patients should not expect the degree of sensitivity found on skin and serologic tests for venom-specific IgE to reliably predict the severity of a reaction to a sting, but it is a good predictor for the likelihood of any systemic reaction. (Recommendation; B evidence)
7. Consider measuring basal serum tryptase in all patients who are candidates for VIT. (Recommendation; B evidence)
8. Use skin tests as the preferred test for initial demonstration of venom-specific IgE. In vitro measurement of serum IgE should be used as a complementary or alternative test. Test for all 5 venoms, with the possible exception of individual patients in whom a single culprit is definitively known. (Recommendation; C evidence)
9. Consider measuring basal serum tryptase in patients with anaphylaxis to a sting, especially in those with severe or hypotensive reactions, and in all those with negative test results for venom IgE. (Strong Recommendation; B evidence)
10. Counsel patients with elevated basal serum tryptase about the clinical significance of potential underlying mast cell disorders. (Recommendation; B evidence)
11. Consider testing patients with mastocytosis for insect venom sensitivity and identify other high risk factors for severe anaphylaxis to stings (including medications). (Recommendation; D evidence) Discuss with the patient the benefits and risks for testing and for VIT.
12. Advise the patient to treat acute systemic reactions to insect stings like any anaphylactic reaction, with timely
    12a. epinephrine injection (Strong Recommendation; A evidence),
    12b. supportive therapy (Strong Recommendation; A evidence), and
    12c. transport to an emergency department. (Strong Recommendation; C evidence)
13. Treat large local reactions symptomatically, with antihistamines, cold compresses, and analgesics as needed. In severe cases a short course of oral corticosteroids may be useful. Antibiotics are usually not necessary and should be prescribed only if specifically indicated. (Recommendation; D evidence)
14. Recommend and initiate VIT in all patients who have experienced an anaphylactic reaction to an insect sting and who have specific IgE to venom allergens (Strong Recommendation; A evidence), with the following special considerations (summary statements 17, 18, and 19):
15. Avoid VIT based solely on in vivo and in vitro testing for venom IgE, without a history of systemic reaction to a sting. (Strong Recommendation; A evidence)
16. Counsel patients who have experienced only large local reactions to stings that VIT is generally not required but might be considered in those who have frequent unavoidable exposure. (Recommendation; B evidence)
17. In a change from previous recommendations, advise both children and adults who have experienced only cutaneous systemic reactions without other systemic manifestations after an insect sting that VIT is generally not required but may be considered when there are special circumstances. This should be a shared decision with consideration of high-risk factors (frequent exposure, cardiovascular or respiratory conditions, or selected medications) and the effects on quality of life. (Recommendation; C evidence)
18. Discuss with adults with cutaneous systemic reactions who are already receiving VIT the reasons for the change in recommendations, possible special circumstances, and the relative risks and benefits of discontinuing or completing the course of VIT. (Recommendation; D evidence)

19. Include in VIT all venoms for which the patient has demonstrated specific IgE. (Recommendation; C evidence) Treatment with some venoms may not be needed if cross-reactivity can be demonstrated by a radioallergosorbent inhibition test. (Recommendation; C evidence)
20. Begin VIT with initial dose of up to 1 μg and increase to maintenance dose of at least 100 μg of each venom. (Recommendation; B evidence) Children might be effectively treated with a maintenance dose of 50 μg. (Recommendation; C evidence)
21. Choose a buildup dose schedule for optimal safety and convenience. Maintenance dose and protection can be achieved with equal safety using conventional (4 months) or modified rush (8 weeks) regimens. The risk of systemic reaction is similar using rush regimens (2–3 days) but may be slightly greater using ultrarush regimens (4–6 hours). (Strong recommendation; B evidence)
22. Continue the maintenance dose monthly for at least 12 to 18 months, then consider extending the interval to 6 or 8 weeks during several years of treatment. For patients who continue VIT for longer than 4 years, a 12-week interval is safe and effective. (Strong Recommendation; C evidence)
23. Advise patients who start VIT to continue injections for 3 to 5 years (most experts recommend 5 years). (Strong Recommendation; B evidence)
24. Encourage continuation of VIT for an extended time, or indefinitely, in patients with high-risk factors, such as very severe reaction before VIT (syncope, hypotension, severe respiratory distress), systemic reaction during VIT, honeybee allergy, and increased basal serum tryptase levels. (Strong Recommendation; C evidence)
25. Consider continuation of VIT for more than 5 years in patients with other high-risk factors for recurrent or severe sting reactions, such as underlying cardiovascular or respiratory conditions, select antihypertensive medications, frequent exposure, and limitation of activity due to anxiety about unexpected stings. (Strong Recommendation; A evidence)
26. Recommend immunotherapy with imported fire ant WBE to all patients who have experienced a moderate or severe systemic reaction to a fire ant sting and who have positive skin test responses or allergen-specific serologic test results with imported fire ant WBE. (Strong Recommendation; B evidence)
27. Consider WBE immunotherapy in patients who have only cutaneous manifestations to fire ant stings because the natural history of fire ant hypersensitivity 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. (Recommendation; D evidence)
28. Consider continuation of imported fire ant WBE for more than 5 years in patients with imported fire ant allergy because the optimal duration of this therapy has been less well studied and the frequency of exposure is high. (Recommendation; C evidence)

Stinging Insects and Venom Allergens

Classification

Identification of the culprit stinging insect by patients is difficult and unreliable. However, an understanding of its biology, behaviors, and geographic distribution may be very helpful in its identification. Changes in geographic distribution, range, and prevalence have been noted because of climate change, as evidenced by increasing reports of yellow jacket sting reactions in Alaska.[41,42]

Domestic honeybees are found in commercial hives, whereas nondomestic honeybees nest in tree hollows, old logs, or in buildings. Hives usually contain hundreds or thousands of bees. Honeybees, except for Africanized honeybees, are usually nonaggressive away from their hives. Many honeybee stings occur on the feet when going barefoot in grass or clover. Honeybees usually leave a barbed stinger with attached venom sac in the skin after they sting. 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. Bumblebees are very uncommon causes of sting reactions but have been reported to cause anaphylaxis during occupational exposure in greenhouse workers.[43] Related to domestic honeybees, Africanized honeybees are hybrids that developed from interbreeding of domestic honeybees and African honeybees in South America. Their domain has now expanded northward, and they can now be found in several states, including Texas, New Mexico, Arizona, Nevada, and California.[44] They are far more aggressive than domestic honeybees and more likely to attack in swarms. Their venom has the same allergens as domestic honeybee venom.[45]

Yellow jackets, hornets, and wasps are in the vespid family and feed on human foods. They are especially attracted to sweet food, fruit, and grilled food. Consequently, they can be found around garbage cans, leftover food, or at outdoor events where food and sweet drinks are served. Yellow jackets can be encountered during yard work, farming, gardening, or other outdoor activities. They may build large paper-enclosed nests underground and can also be found in wall tunnels or crevices and in hollow logs or landscape ties. Yellow jackets are very aggressive and sting with minimum provocation. People 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 build large paper-enclosed nests that are usually found in shrubs and trees. Wasps build open-faced 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 and are a more common cause of stings in the south Atlantic and Gulf Coast states.

The imported fire ant (IFA) can be red (*Solenopsis invicta*) or black (*Solenopsis richteri*) and nests in mounds composed of freshly disturbed soil that can be 6 to 12 in high and might extend 1 to 2 ft in diameter.[18] 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, backyards, and public places. These ants are very aggressive, particularly if their nests are disturbed, and are often responsible for multiple stings. A sterile pustule, which develops at the site of a sting in less than 24 hours, is pathognomonic of an IFA sting. The distribution of Africanized honeybees and fire ants in the Southern United States is depicted in Figure 2. Other species of stinging ants also cause allergic reactions in Asia, the Middle East, North America, and Australia (jack jumper ants), but none of these cross-react with each other or with IFAs.

Cross-reactivity

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.[46–50] Bumblebee venom contains unique allergens and has variable cross-reactivity with honeybee venom.[51] Limited cross-reactivity

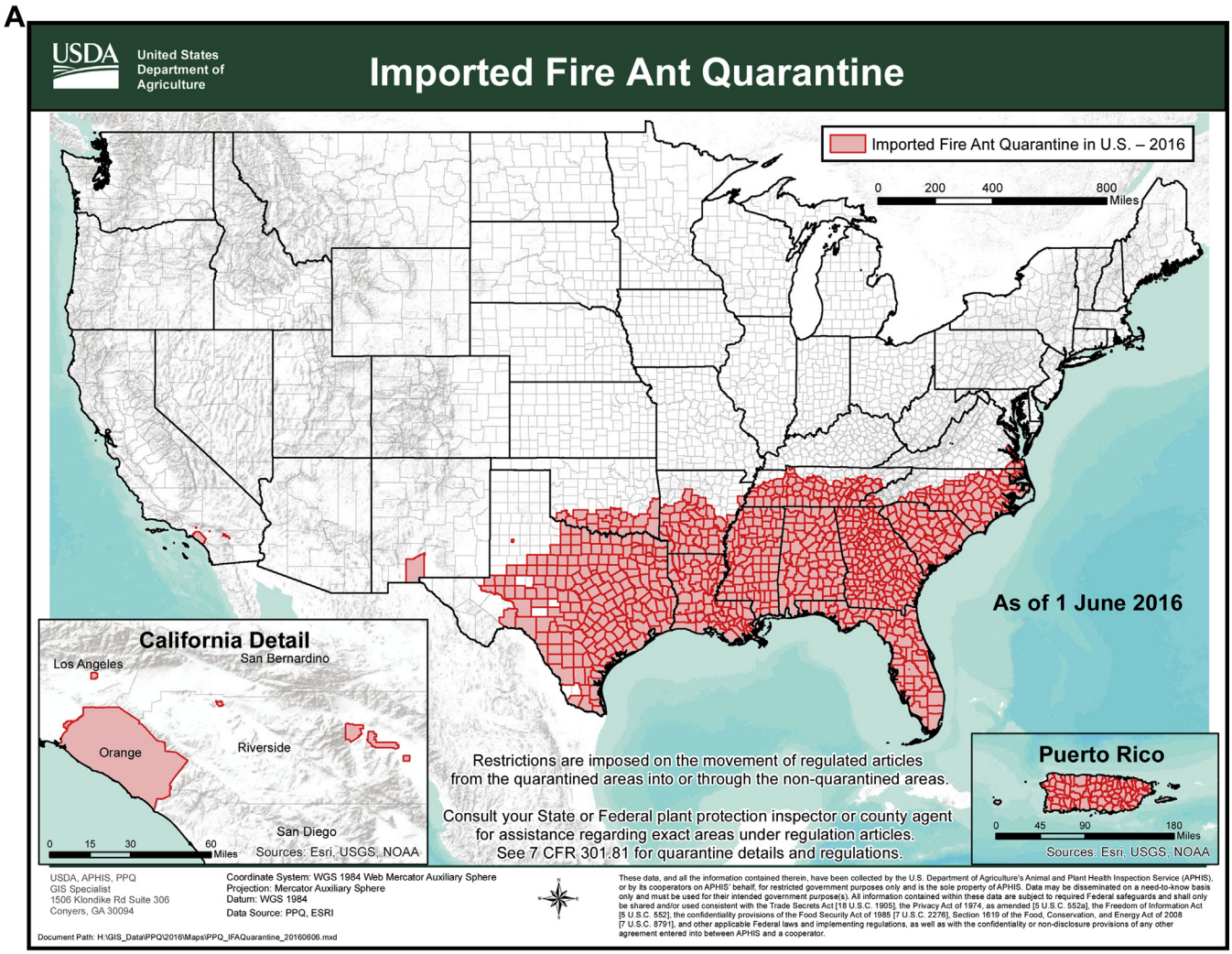

Figure 2. Distribution of imported fire ants (A) and Africanized honeybees (B) in the United States, 2009 (US Department of Agriculture).

exists between the antigens in fire ant venom and the antigens in venoms of other Hymenoptera.[52,53]

The Clinical Spectrum of Venom Allergy

Summary Statement 1: Evaluate patients with a history of a systemic reaction to an insect sting for the presence of venom-specific IgE. If venom IgE is present these patients are at increased risk for subsequent sting anaphylaxis, which can be prevented by VIT. (Strong Recommendation; A Evidence)

Summary Statement 2: Evaluate the patient for details of the history of any reactions to insect stings. (Strong Recommendation; B evidence)

Categories of Adverse Sting Reactions

Most insect stings are associated with normal 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. Adverse reactions to stings may be allergic or nonallergic, with local or systemic manifestations. Some local reactions are IgE mediated, with intense and prolonged local induration and swelling (large local reactions, see below). Systemic allergic reactions can run the full spectrum of signs and symptoms of anaphylaxis, from the mildest (generalized erythema, pruritus, and hives), through mild anaphylaxis, to the most severe anaphylaxis (hypotensive shock or respiratory obstruction and arrest). Cardiac anaphylaxis can cause myocardial ischemia (Kounis syndrome) or arrhythmias.[35,54] Unusual reactions have been reported, including neuropathies, seizures, renal failure (with rhabdomyolysis), serum sickness, and hemorrhagic episodes, including metrorrhagia.[55] These reactions are mostly toxic in nature and delayed in onset, but the mechanism of many of the unusual reactions is not known.

Definitions of Specific Venom Allergy Conditions

Insect stings can trigger a range of immune and clinical responses. It is common for venom-specific IgE antibodies to be induced by an insect sting, although this is more often transient than persistent. Stings also induce production of IgG antibodies.

Large local reactions (LLRs) are abnormally large localized reactions contiguous with the Hymenoptera sting site. Although occasionally rapid in onset, the swelling usually increases 6 to 12 hours after the sting, progresses in 24 to 48 hours, and subsides after 3 to 10 days. There is no universal definition of a LLR, but the induration is often larger than 10 cm in diameter and can involve an entire extremity (crossing joint lines). These reactions represent late-phase IgE-associated inflammatory responses to venom allergens. They do not represent cellulitis even though lymphangitic streaks may be present. They are generally not dangerous but can occasionally cause a compartment syndrome in some anatomically constrained places and could cause airway compromise if the sting occurs in the oropharynx (eg, after drinking from a straw or canned beverage).[31,56]

Systemic reactions (SRs) are typically IgE mediated and may present with a variety of symptoms, involving multiple organ symptoms.[57] Cutaneous symptoms may include pruritus, flushing, urticaria, and angioedema. Respiratory symptoms may include stridor, wheezing, and dyspnea. Gastrointestinal symptoms can include abdominal cramping, nausea, vomiting, and diarrhea. Cardiovascular symptoms and signs are usually related to hypotension and may include lightheadedness, syncope, or cardiovascular shock. Cardiac anaphylaxis can cause arrhythmias or the symptoms and signs of acute coronary insufficiency or myocardial infarction. This is attributable to the high concentration of mast cells near the coronary arteries and cardiac conduction fibers.[35] Kounis syndrome or allergic angina is the occurrence of the symptoms and signs of angina coincident with an acute allergic reaction and has been reported after Hymenoptera sting.[54] Systemic reactions to stings must be differentiated from toxic reactions or anxiety reactions (often subjective symptoms with no objective signs). The pattern and timing of symptoms, the presence of objective signs, and the response to treatment may help clarify the nature of the reaction. Measurement of serum tryptase early in the reaction may provide evidence of anaphylaxis if levels are elevated or significantly increased from basal level.[58,59]

Serum sickness–like reactions to stings have occurred and may be associated with the presence of venom-specific IgE, but the mechanism of the reactions and the risk of anaphylaxis are unknown.[60] Cold urticaria and cold-induced anaphylaxis have been reported after insect stings, generally without anaphylaxis.[61,62]

Prevalence, Natural History, and Prevention

Epidemiology of Venom Allergy

The prevalence of LLRs in the general population is approximately 10%, with estimates ranging from 2.4% to 26.4%, and higher among beekeepers (14%–43%).[56,63] The results of skin testing and/or specific IgE testing are reported to be positive in up to 80% of individuals with LLRs.[16,56]

The prevalence of SRs ranges from 0.5% to 3.3% in US reports and from 0.3% to 7.5% in European reports.[6] The rates of SRs among children are lower, ranging from 0.15% to 0.8%.[63] Fatality from insect sting anaphylaxis accounts for 20% of all cases of any-cause fatal anaphylaxis, with an incidence of 0.03 to 0.48 fatalities per 1 million population.[63] In the United States, there are at least 40 deaths annually due to insect sting anaphylaxis, although this is believed to be underreported.[5,64] Biphasic anaphylactic reactions are associated with the most severe events but may be less frequent in insect sting allergy than other causes of anaphylaxis.

Venom sensitization is common in the general population, estimated to be between 9.3% and 28.7%.[63] In the months after a sting, transient sensitization occurs in up to 40% of adults.[7] This high frequency of asymptomatic sensitization gives the tests a very limited positive predictive value in the absence of a clinical history of allergic reaction to a sting. For this reason, venom testing cannot be used to screen asymptomatic children or adults.[10] Atopy is associated with venom sensitization but not with allergic reactions to stings.

The frequency of insect stings in the general population depends largely on climate and risk of exposure. Between 56% and 94% of the adult population report being stung at least once.[6,63,65] Attack rate is estimated at 10% per year for yellow jackets and up to 50% for IFAs in endemic areas.[66]

Natural History and Factors Influencing the Occurrence of Allergic Reaction

The clinical history is paramount in predicting the chance of future allergic reactions to stings. Asymptomatic sensitization is associated with a relatively low risk of systemic reaction to future stings, estimated at 5% to 15%.[9,10] When systemic reactions occur, they can range from the mildest to the most severe manifestations of anaphylaxis. Unfortunately, there is no test that can distinguish those who will react to future stings and those who will not, and no test other than basal serum tryptase that can predict how severe a reaction might be.

Patients with a history of LLRs have an approximately 7% chance of systemic reaction to a future sting (range, 4%–15%) in both adults and children. Like the other low-risk sensitized individuals, some of these reactions will be severe, and many will be relatively mild (eg, cutaneous).[1–3,16,67]

The frequency of systemic reaction to a future sting in patients with a history of systemic reactions to stings is approximately 50% (range, 25%–75%).[11–13,15] The chance of reaction is in the lower end

of this range for those with a history of mild-moderate systemic reactions and is highest in those with a history of life-threatening anaphylaxis. Children or adults who had only cutaneous systemic reactions have an approximately 10% chance of a future systemic reaction but a less than 3% chance of a more severe reaction.[1,12,15]

Systemic reactions may be more likely in response to multiple stings or sequential stings (within weeks or months). The risk decreases somewhat with time but remains at 20% to 30% for decades.[12–14,63] There is a significantly higher incidence of systemic reactions among beekeepers than the general population.[68] The frequency and/or severity of allergic reactions to stings is also affected by factors other than the clinical history. The level of sensitivity (skin test or serum IgE) is correlated with the frequency but not the severity of the reaction. Sensitized individuals with low total IgE levels (<50 kU/L) had a higher risk for severe reactions.[69] An elevated basal serum tryptase level, the concomitant use of antihypertensive medications, and increasing age are associated with increased risk of more severe anaphylactic reactions to stings.

Prevention of Insect Sting Allergy

Summary Statement 3: Recommend to patients who have a history of systemic reactions to insect stings:

a. effective measures to avoid insect stings. (Recommendation; D evidence);
b. the need to always carry an epinephrine autoinjector, to be familiar with its proper use and when to use it or not use it, and to carry medical identification (Strong Recommendation; C evidence); and
c. referral for evaluation by an allergist/immunologist, the utility of specific IgE testing for stinging insect sensitivity, and the potential advantages of VIT (testing is not necessary for patients in whom VIT is not required) (Strong Recommendation; D evidence).

Three tenets of treatment for patients at risk for systemic reactions to stings are avoidance, availability of emergency medication, and VIT. Table 3 lists some of the effective and ineffective avoidance measures to reduce the likelihood of insect stings, including 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 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).

Table 3
Measures for Avoiding Insect Stings

Effective measures	Ineffective measures
Avoid preparing, grilling, or eating outdoors	Avoiding fragrances
Avoid flowering plants	Avoiding brightly colored or floral clothing
Avoid drinking from straws, cans, or bottles outdoors	Using insect repellants
Remove fallen fruit or pet feces	Running; flailing the arms
Cover trashcans	
Watch for nests in bushes or in the ground when mowing	
Avoid going barefoot outdoors	

Current evidence does not support avoiding particular colors or patterns of clothing because insects do not recognize these as we do.[70]

The prescription of an epinephrine injector generally requires discussion about when and why it should be used (or not used). Although this seems prudent in patients with a potential risk of reaction to a sting, there is also a burden to the patient that accompanies the prescription.[71] Patients may be more fearful of being stung after they have been cautioned about the need to carry an epinephrine injector and can experience a reduction in quality of life compared with similar patients who receive VIT and experience an improvement in quality of life.[72] This contributes to uncertainty about whether there is a need to recommend an epinephrine injector to a patient whose risk of sting anaphylaxis is considered low enough that they do not require VIT. These considerations should be discussed with the patient and considered on an individual basis.

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 their risk of reaction and need stinging insect avoidance or emergency treatment;
- might be candidates for VIT;
- 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, or
- request consultation for more detailed information or specific testing.

Diagnosis of Venom/Sting Allergy, Differential Diagnosis

Diagnosis of IgE-Mediated Venom Allergy

Summary Statement 4: Perform skin tests and/or serum tests for IgE to stinging insect venoms on patients who are candidates for VIT. (Strong Recommendation; A evidence)

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. Even when there has been a sting without a reaction occurring after the systemic reaction, the risk of anaphylaxis can persist.[11,12]

The presence of venom-specific IgE antibodies is usually confirmed by means of intracutaneous skin testing.[67,73,74] Skin prick tests at concentrations up to 100 μg/mL can be performed before intracutaneous tests but are not used by all

allergists. Initial intradermal (ID) tests are commonly initiated with venom concentrations of 0.001 to 0.01 μg/mL. If ID test responses at these concentrations are negative, the concentration is increased by 10-fold increments every 20 minutes until a positive skin test response occurs or a maximum concentration of 1.0 μg/mL is reached. With appropriate positive and negative control tests, a positive skin test response at a concentration less than or equal to 1.0 μg/mL indicates the presence of specific IgE antibodies. False-positive results caused by nonspecific responses have been reported at concentrations greater than 1.0 μg/mL.[73] Several accelerated methods for performing venom skin testing have been described, including a 1-step method using only the 1.0-μg/mL concentration.[75–77] Systemic reactions to venom skin tests are quite rare and are no more frequent with accelerated methods.

There has been some recent concern about what might be considered a positive ID skin test result because there is some inconsistency in the description of the technique and interpretation of venom skin tests. Some of the recommendations that have been used include the following:

- In North America, Europe, and many countries, venom extract sufficient to produce a bleb of 3 mm is injected, which is usually a volume of 0.02 to 0.03 mL. A wheal 3 to 5 mm greater than the negative control, with appropriate surrounding erythema at a concentration of 1 μg/mL or less is considered positive.[78,79]
- In the United Kingdom, 0.03 mL of venom extract is injected to raise a bleb of 3 to 5 mm. A wheal diameter of 3 mm greater than the negative control at 20 minutes is considered positive.[80]
- One manufacturer's package insert suggests the injection of 0.05 mL of venom and defines a positive reaction as 5- to 10-mm wheal and 11- to 20-mm erythema (ALK Prescribing Information: Allergenic Extracts: Hymenoptera Venom/Venom Protein; ALK Abello A/S Horshhol, Denmark Revision C 12.01.2014). This was the method used in the early clinical trials.[74,81]

There are no definitive studies to suggest any specific ID technique to be superior for determining specific IgE for venom. The original studies that validated venom skin tests as a diagnostic technique used an injection sufficient to raise a 3–4 mm bleb, and defined a positive test according to the method of Norman (at least 5 to 10 mm wheal and 11 to 20 mm erythema).[74,81,82]

In a recent survey of 5203 members of the AAAAI and ACAAI carried out by this task force in 2015, there were 540 responses (10.4%). For ID tests, most of the respondents use a volume of injection of 0.02–0.03 ml (48.5%), or sufficient to raise a 3–4 mm bleb in the skin (29.5%). A volume of 0.05 ml was use by 22.8% of the respondents. The result of the ID skin test was considered positive by 65.6% of the respondents if the wheal was 3 mm greater than the negative control accompanied by surrounding erythema. The result was considered positive with a 5–10 mm wheal and >10 mm erythema (20.7% of respondents), with a 3 mm wheal regardless of erythema (8.1%), or with a 5 mm wheal regardless of erythema (5.6%) Currently, there are no data to suggest an inferior method of ID testing or interpretation. Consequently, it is recommended that practitioners use the technique they are most familiar with to determine a positive response.

Detection of all potentially relevant sensitivities requires testing with all 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 preexisting sensitization. Some experts recommend testing with a single venom when the culprit is definitively known, particularly in the case of honeybee or fire ant stings.

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.[46–50] (Table 4). It is therefore common for skin or serum tests for venom IgE to test positive for multiple vespid venoms, and many patients test positive to both honeybee and vespid venoms.

Summary Statement 5: If initial test results are negative in a patient with a clear history of systemic sting reaction, further testing (in vitro testing, repeat skin testing, or both) should be performed, as well as basal serum tryptase measurement. (Strong Recommendation; C evidence)

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.[65] In patients who have a history of an anaphylactic reaction to a sting and have positive diagnostic test results to some venoms and negative results to others, some experts recommend further evaluation for the negative venoms (by serum IgE tests and/or repeat skin tests) to identify all potentially relevant sensitivities before beginning VIT. Even repeat negative in vitro and skin test results do not fully exclude the possibility of an anaphylactic reaction to a subsequent sting because rare occurrences have been reported.[28] The pathogenesis of these rare reactions might involve a non-IgE mechanism, and measurement of basal serum tryptase is recommended in such patients.

Summary Statement 6: Physicians and patients should not expect the degree of sensitivity found on skin and serologic tests for venom-specific IgE to reliably predict the severity of a reaction to a sting, but it is a good predictor for the likelihood of any systemic reaction. (Recommendation; B evidence)

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, although they predict the severity of sting reactions.[12,83] Some patients who have had severe systemic reactions after an insect sting 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.[28,84,85] In vitro venom testing should be performed in patients with negative skin test responses who would otherwise be potential candidates for VIT. 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 they 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.[27] Negative test results for venom-specific IgE obtained within the

Table 4
In Vitro Cross-reactivity of Hymenoptera Venoms[a]

	Honeybee	YJ	Hornet	Wasp	IFA
Honeybee	++++	+	+/−	−	−
YJ	+	++++	+++	++	+/−
Hornet	+/−	+++	++++	++	+/−
Wasp	−	++	++	++++	+/−
IFA	−	+/−	+/−	+/−	++++

Abbreviations: IFA, imported fire ant; YJ, yellow jacket.
[a] ++++ indicates same antigen; +++, extensive; ++, less extensive; +, limited; +/−, infrequent/very limited/less common; and −, no cross-reactivity.

first few weeks after a sting reaction might require cautious interpretation.

Summary Statement 7: Consider measuring basal serum tryptase in all patients who are candidates for VIT. (Recommendation; B evidence)

Basal serum tryptase levels have been found to be increased in some patients with insect sting allergy.[24,86,87] Such patients might require evaluation for mastocytosis or disorders of mast cell function (discussed in more detail below). Some experts recommend measuring basal serum tryptase in all patients who are candidates for VIT because the result is abnormal in approximately 11% of all cases and is an important risk factor for severe reactions before, during, and after VIT.[23–26,87] The likelihood of an elevated basal serum tryptase level is higher, and the test is therefore most useful, in patients with very severe reactions to stings (particularly when there is hypotension or the absence of urticaria) and those with no detectable venom IgE on both skin and serum tests and should be considered in those with systemic reactions during VIT and when considering discontinuation of VIT (see below and Table 5). Full review of the available evidence and recommendations for this test will be the subject of a focused practice parameter in the near future.

Summary Statement 8: Use skin tests as the preferred test for initial demonstration of venom-specific IgE. In vitro measurement of serum IgE should be used as a complementary or alternative test. Test for all 5 venoms, with the possible exception of individual patients in whom a single culprit is definitively known. (Recommendation; C evidence)

In Vitro Testing

In vitro tests can also be used for detection of venom-specific IgE antibodies in patients with insect sting allergy, particularly in those who cannot undergo skin testing or have negative venom skin test results, including patients with dermatographism or severe skin disease. Skin tests are generally the preferred initial testing method. Up to 20% of patients with positive venom skin test responses have undetectable serum levels of specific IgE antibodies (negative in vitro test result). However, studies have found that approximately 10% 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.[28,84,85] Whichever test is performed first, a negative result to any of the venoms may justify repeating a test for that venom with the complementary diagnostic test method. The need for supplemental tests should be assessed for each patient based on the known risk factors for severe reactions and the results of the initial tests for venom IgE. This is also 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.[88,89] Clinicians should also be aware that although technical improvements permit reporting of serum IgE levels between 0.1 and 0.35 kU/L as positive, the clinical significance of these low levels has not been determined.[90] Nevertheless, it remains possible that even very low levels of venom IgE could be clinically significant, particularly in the context of relatively low total serum IgE (ie, high specific to total IgE ratio).

Table 5
When to Measure Basal Serum Tryptase

Recommended:
Severe reaction to a sting
Hypotensive reaction
Lack of urticaria in systemic reaction to a sting
Systemic reaction to a sting with negative venom IgE test results
Consider:
Systemic reaction during VIT (to injection or sting)
Before discontinuing VIT
Any patient who is a candidate for VIT

Abbreviation: VIT, venom immunotherapy.

Skin Testing for Fire Ant Hypersensitivity

IFA WBE 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.[18,91–93] Limited cross-reactivity exists between the antigens in fire ant venom and the antigens in venoms of other Hymenoptera.[52,94] If the patient is able to positively identify fire ant as the stinging insect, testing with other stinging insect venoms may not be necessary. The presence of a sterile pustule at the sting site at 24 hours after the sting is diagnostic of an IFA sting. This type of reaction should be looked for carefully in endemic areas if the identity of the culprit insect is uncertain.

New Diagnostic Methods

One of the issues that remain undefined for Hymenoptera allergy is the lack of a test that is 100% sensitive for assessing specific IgE. Some improvement in sensitivity can be gained with the use of skin tests with less irritating dialyzed venoms that can be used at concentrations up to 10 mg/mL with no irritant response.[95] Dialyzed venom skin test preparations are not commercially available in the United States.

The basophil activation test (BAT) has been offered to address this problem. Because basophils have high-affinity IgE receptors on their surface, they will bind to specific IgE and be activated when exposed to an appropriate antigen. In the BAT, basophils from a patient with suspected Hymenoptera allergy are exposed to defined concentrations of Hymenoptera venom (usually 0.1–1.0 μg/mL), and activation is measured based on the percentage of basophils that express activation markers (CD63) on their surface. BAT may be useful in patients with mastocytosis.[96] In one study, BAT had better sensitivity and specificity than ID testing in those with negative prick and in vitro venom test results.[97] Unfortunately, this and other studies assessing BAT have compared determination of specific IgE to other testing methods and not to a gold standard of a sting challenge. Thus, BAT does not improve diagnostic sensitivity with clinical relevance.

In addition, BAT has been used to determine whether VIT has been successful as determined by sting challenge.[98] Lower values of BAT are associated with fewer systemic reactions after VIT.[99] Higher expression of CD63 on basophils has been associated with a lack of response to VIT.[100] A reduction in BAT has been associated with a protective immune response to honeybee VIT in children.[101]

Finally, there are many technical challenges associated with the use of BAT. Included among these are a short half-life for viable basophils and a variable determination of what is considered a positive test result.[20,21,102] Consequently, routine use of BAT in evaluating Hymenoptera sensitive patients is not currently recommended. If technical issues can be addressed, BAT may be useful in diagnostic evaluation and for monitoring the effectiveness of VIT.

Just as there are multiple components for aeroallergens and food allergens, there are multiple components for each of the Hymenoptera venoms. The clinical significance of diagnostic testing with recombinant venom allergens is not yet clear. Of interest is whether component testing allows better diagnosis than whole venom (ie, sensitivity) and/or more specific assignment of reactivity (ie, specificity).[19] The data available so far are limited in

that most studies are from Europe, which limits applicability in the United States for 2 reasons. First, in northern and central Europe, there are basically only 2 genera of concern (honeybee and yellow jacket). Second, most of the studies looking at sensitivity compare them only to the use of whole venom for the same in vitro IgE test, which makes it impossible to show improved sensitivity over current diagnostic testing.[103,104]

For honeybee, studies show that rApi m 1 has a sensitivity of 57% to 96% when compared with whole honeybee venom.[105–107] For the lowest sensitivity study, use of the natural Api m 1 rather than recombinant led to an improved sensitivity of 91%.[106] Similar studies for yellow jacket have found sensitivities of 84% to 87% using Ves v 5 with an increase to 92% if Ves v 1 was determined as well.[107,108] The use of additional components can increase the sensitivity of the test for both honeybee and vespid allergies.[109] Until studies are performed on patients with known Hymenoptera sensitivity but with negative whole venom in vitro test results, it will be impossible to show an improved sensitivity with component testing.[103,104]

The attribution of specific sensitivity to individual species of Hymenoptera seems more promising. A number of studies have reported the utility of recombinant venom allergens in differentiating honeybee from yellow jacket sensitivity in those with double positivity.[110–112] One study using only Api m 1 and Ves v 1 found these were not sufficient to separate out species-specific sensitivity.[113] Measurement of IgE to multiple recombinant allergens may distinguish *Vespula* and *Polistes* sensitivity.[114] The evaluation of clinical utility in the United States of component testing awaits studies performed with components from all the species found in the United States.

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.[11,14,15,32,115–118] An intentional sting challenge has been recommended by some to better select those patients who need VIT.[15,119] In research studies, sting challenge has been considered the gold standard for determining the risk of reaction (and the predictive value of other tests) in treated and untreated patients. Patients allergic to honeybees are more likely to have positive sting challenge results than those allergic to yellow jackets.[15] Sting challenges, however, are neither consistently reproducible nor without risk. Approximately 20% of patients who do not react to a sting challenge will react after a second challenge.[11] 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.[29,120]

Mast Cell Disorders and Insect Sting Allergy, Basal Serum Tryptase

Summary Statement 9: Consider measuring basal serum tryptase in patients with anaphylaxis to a sting, especially in those with severe or hypotensive reactions, and in all those with negative test results for venom IgE. (Strong Recommendation; B evidence)

Mastocytosis, other mast cell diseases, and serum tryptase have assumed new importance in the management of allergic disease and anaphylaxis in recent years.[22,87,121,122] This has been particularly important with venom allergic patients because mast cell disorders are associated more with sting anaphylaxis than with other common causes of anaphylaxis, including foods and drugs.[122,123] Mastocytosis occurs in approximately 2% of patients with insect sting anaphylaxis, and insect sting anaphylaxis occurs in approximately 25% of patients with mastocytosis.[124] The importance of mast cell disease in venom allergic individuals has been an important factor during initial diagnosis and when assessing high-risk individuals for future severe reactions and may be a consideration in the duration of venom immunotherapy (VIT).[23,86,87,121] (see next section) Diagnostic criteria of systemic mastocytosis are discussed elsewhere.[59] Measurement of serum tryptase, a marker for systemic mast cell disorders, is an important and readily available diagnostic tool for mast cell disorders. In most laboratories, the upper limit of the reference range is 11.4 ng/mL (Phadia AB. ImmunoCAP tryptase. Directions for use. Uppsala, Sweden: Phadia AB, 2008). The refernce range of basal serum tryptase in children may differ from adults.[125]

Management of patients who have a compelling history of insect-induced anaphylaxis yet test negative via both skin and in vitro testing remains a clinical challenge.[84,85,126] Mastocytosis has emerged as a surprising link in this clinical quandary. A significant percentage of patients with severe systemic reactions after insect sting, who have an elevated basal tryptase level, indeed may have mastocytosis or monoclonal mast cell activation syndrome.[24,122,127] In addition, in patients with mastocytosis, the most common cause of anaphylaxis is insect sting.[122,128] Basal serum tryptase should be measured in patients with sting anaphylaxis who have no detectable venom IgE. Clonal mast cell disorders can occur in patients with severe Hymenoptera venom allergy and normal serum tryptase levels.[129]

Summary Statement 10: Counsel patients with elevated basal serum tryptase about the clinical significance of potential underlying mast cell disorders. (Recommendation; B evidence)

Serum tryptase has been described as a predictor of the severity of a systemic reaction to a sting. Rueff et al,[25] in a multicenter retrospective study of Hymenoptera venom–sensitive patients, looked at predictors of severe systemic anaphylaxis after a sting. Of the 962 patients, 202 (26%) had severe anaphylaxis (Mueller grade III or IV) after a field sting. The risk factors for severe anaphylaxis to stings or VIT included basal serum mast cell tryptase levels above 5 ng/mL, use of angiotensin-converting enzyme inhibitors (ACEIs), vespid allergy, older age, and male sex.[130] Bonadonna et al[24] reported a correlation between systemic reaction to Hymenoptera sting and mast cell tryptase. Of 379 patients with a history of systemic insect sting reactions, 11.6% had serum mast cell tryptase levels that exceeded 11.4 ng/mL. Of this group, the rate of systemic (Muller grade IV) anaphylaxis was 70.5%. In patients with hypotensive reactions to stings (grade IV), 25% had elevated basal tryptase levels. Thirty-four of the patients with elevated mast cell tryptase levels underwent bone marrow biopsy; of those, 61.8% were ultimately diagnosed with indolent systemic mastocytosis. Blum et al[131] confirmed these findings in a 5-year retrospective study of 868 patients referred for the evaluation of severe reactions to Hymenoptera stings (758 had both total IgE and basal tryptase levels drawn). Elevated basal tryptase level (>11.4 ng/mL) was associated with severe systemic reactions ($P = .03$). Stoevesandt et al[26] found a strong correlation between severity of sting anaphylaxis and elevated basal serum tryptase level and with the absence of urticaria. Finally, Guenova et al[128] confirmed the correlation between severe systemic reaction to sting and elevated basal tryptase level ($P = .003$) and also found a correlation with increasing age ($P = .001$). Because of the large increase in the severity of sting-related anaphylaxis in patients with mastocytosis, physicians should consider occult mast cell disease in anyone with unexplained anaphylaxis or severe sting-related anaphylaxis.

Rueff et al[130] reported that elevated basal tryptase level correlated with severe reactions occurring during the immunotherapy buildup phase (odds ratio, 1.56; $P < .005$). Generally, VIT in patients with clonal mast cell disorders has reasonable safety and

significantly reduces the chance of sting anaphylaxis.[124,132,133] Honeybee venom allergy correlated with higher risk of systemic reaction than vespid venom allergy. There was also a correlation of severe anaphylaxis to a sting with the use of antihypertensive medications (β-blockers and ACEIs). This has been reported in relation to immunotherapy and anaphylaxis in general. Patients with mastocytosis who are taking these antihypertensive medications should consult their physicians about the possibility of changing to an alternative medication (if it is safe and effective). Fatal anaphylaxis has been reported in patients with mastocytosis who discontinued VIT.[134,135]

When to discontinue VIT remains controversial. However, the historical recommendation of 3- to 5-year VIT may not be optimal for venom allergic patients with mastocytosis. Patients with mastocytosis have lower probability of long-term protection and consequently a greater risk for recurrent severe, even fatal anaphylaxis if they discontinue VIT.[134,135] In a thorough review, Bonadonna et al[136] recommend VIT for life in patients with mastocytosis and venom allergy. Because the efficacy of VIT is less than optimal in patients with mastocytosis, they should continue to carry 2 epinephrine injectors.[124]

Because there appears to be a high correlation with mastocytosis when the basal tryptase level exceeds 11.4 ng/mL, this diagnosis should be entertained (and basal serum tryptase measured) in patients with severe anaphylaxis from Hymenoptera, especially when there was hypotension (and/or the absence of urticaria). The frequency of elevated basal serum tryptase level is 25% in patients with Mueller grade IV sting anaphylaxis but is approximately 5% in patients who had mild-to-moderate systemic reactions to stings (grade I, II, III) in whom the clinical significance is less clear.[24] Some experts suggest that the evaluation of all patients with a history of a systemic reaction to Hymenoptera should include measurement of the basal serum tryptase.[80,136] If clonal mast cell disease is suspected, initial evaluation for venom-specific IgE should begin using in vitro methods, with skin testing in those individuals who test negative using in vitro methods. If the serum tryptase is elevated (>11.4 ng/mL) bone marrow biopsy should be considered. Mastocytosis can occur with normal serum tryptase.[129] There is a cost and burden associated with abnormal results of basal tryptase (eg, bone marrow biopsy, consultation with other specialists, anxiety associated with an abnormal test result). However, an abnormal result is associated with more chance of severe anaphylaxis to stings, greater chance of systemic reactions during VIT (to a sting or venom injection), and increased chance of sting anaphylaxis after stopping VIT. The potential benefits and risks of ordering the test should be considered with each patient.

Summary Statement 11: Consider testing patients with mastocytosis for insect venom sensitivity and identify other high risk factors for severe anaphylaxis to stings (including medications). (Recommendation; D evidence) Discuss with the patient the benefits and risks for testing and for VIT.

Individuals with known mastocytosis may warrant being tested for Hymenoptera venom sensitivity because insect stings are the most common cause of anaphylaxis in such patients. In patients with mastocytosis, sting anaphylaxis is more likely to occur and more likely to be life-threatening, and the risk can be significantly reduced with VIT. The frequency of sting anaphylaxis in patients with mastocytosis and positive skin or serum test results for venom IgE is not known. The positive predictive value of venom-IgE tests in asymptomatic, healthy individuals is poor. Nevertheless, it is the opinion of this work group that, when test results are positive for venom IgE in patients with mastocytosis, the clinician should discuss with the patient the potential benefits and risks of VIT. The presence of other high-risk factors (Table 1) would be likely to further increase the risk of severe anaphylaxis to a sting and would add to the strength of recommendation for VIT. It is not known whether children with mast cell disorders (particularly those with urticaria pigmentosa) have the same risks as adults.

It seems likely that dysregulation of other mediators of anaphylaxis will be found to correlate with the frequency or severity of reactions to stings. It has already been confirmed that levels of platelet-activating factor (PAF) and PAF-acetylhydrolase correlate with the severity of sting anaphylaxis and with fatal anaphylaxis.[137,138]

Management of Venom/Insect Allergy

Treatment of Acute Sting Reactions

Summary Statement 12: Advise the patient to treat acute systemic reactions to insect stings like any anaphylactic reaction, with timely

12a. epinephrine injection (Strong Recommendation; A evidence),
12b. supportive therapy (Strong Recommendation; A evidence), and
12c. transport to an emergency department. (Strong Recommendation; C evidence)

Epinephrine is the drug of choice for the treatment of anaphylaxis.[139,140] 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 will achieve a more rapid and higher plasma concentration than subcutaneous or intramuscular injection in the arm.[141,142] Delayed use of epinephrine might be ineffective.[143] Reports of fatal and near-fatal anaphylaxis reveal that fatal outcome is associated with delay or lack of administration of epinephrine.[144–146] 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. They should be instructed to follow the package inset for managing the device, including protecting it from excess heat. 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, so more than 1 unit should be prescribed, particularly for those with severe reactions or those who live or spend time in locations distant from medical attention. 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 â-blocker medication). Antihistamines and corticosteroids should not be considered substitutes for epinephrine. In patients who have a relatively low risk of anaphylaxis 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 in addition to the cost and burden of having to carry epinephrine. Patients with a low risk of reaction include 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), a history of anaphylaxis to a honeybee sting, increased basal tryptase levels, underlying medical conditions or concomitant medications, or frequent unavoidable exposure to stinging insects.

Summary Statement 13: Treat large local reactions symptomatically, with antihistamines, cold compresses, and analgesics as needed. In severe cases a short course of oral corticosteroids may be useful. Antibiotics are usually not necessary. (Recommendation; D evidence)

Most patients with large local reactions need only symptomatic care and are not candidates for testing for venom-specific IgE or VIT. 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. Swelling (and even lymphangitis) may be caused by mast cell mediator release and not by infection, so antibiotics are not indicated unless there is clear evidence of secondary infection (a common misdiagnosis).

Venom Immunotherapy

Summary Statement 14: Recommend and initiate VIT in all patients who have experienced an anaphylactic reaction to an insect sting and who have specific IgE to venom allergens. (Strong Recommendation; A evidence)

Summary Statement 15: Avoid VIT based solely on in vivo and in vitro testing for venom IgE, without a history of systemic reaction to a sting. (Strong Recommendation; A evidence)

VIT for honeybees, yellow jackets, hornets, and wasps is an extremely effective treatment for individuals at risk of insect sting anaphylaxis. VIT reduces the risk of a subsequent systemic sting reaction to as low as 5% compared with up to 60% in untreated patients.[32,115,117] The same has been shown for jack jumper ant VIT in Australia.[115] Efficacy is somewhat less with honeybee VIT (<85%) than with vespid venoms (>95%).[147] However, those patients receiving VIT who experience systemic reactions after an insect sting generally have milder reactions than the pre-VIT sting reaction. Candidates for immunotherapy should receive informed consent with documentation in the medical record regarding the potential benefits and risks related to the procedure. There are individuals who seek treatment because of a fear of sting reactions but have no history of abnormal reaction to previous stings. A family history of insect sting allergy is also not a reason for testing or VIT because sting anaphylaxis is not statistically correlated with family history of sting allergy.[6,7] Testing for venom IgE is not recommended in children or adults with no history of reaction to stings (except in patients with mastocytosis). This is because venom IgE can be detected in more than 20% of adults who have no history of reaction to stings, and the tests have poor positive predictive value. For the same reasons, VIT is not recommended when there is no history of abnormal reaction to a sting, even if the venom IgE test results are positive.

Criteria for Immunotherapy

History of Sting Anaphylaxis

Patients who have had an anaphylactic reaction from an insect sting and are found to have venom-specific IgE antibodies should receive VIT. The goals of VIT are to (1) prevent systemic reactions and (2) alleviate patients' anxiety related to insect stings (with improved quality of life). 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. VIT is recommended for individuals 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.[35] VIT has also been effective in cases of delayed anaphylaxis after a sting.[148] Some patients are at particularly high risk for severe anaphylactic reactions to future stings. Patients who have experienced a very severe (near-fatal) anaphylactic reaction to a sting are more likely to have a similar event in the future.[14,37,149] Patients with mastocytosis or an increased basal serum tryptase level are also at higher risk for severe reactions to future stings.[25,26,86,87,123,131] Such high-risk patients should have the greatest benefit from VIT.

Summary Statement 16: Counsel patients who have experienced only large local reactions to stings that VIT is generally not required but might be considered in those who have frequent unavoidable exposure. (Recommmendation; B evidence)

History of Large Local Reaction

A large local reaction or extreme swelling extending from the sting site, usually peaking at 48 to 72 hours after a sting and lasting 1 week or more, is generally 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 4% to 10%.[1–3,150] Because of this relatively low risk, diagnostic testing and VIT are generally not required in such patients. Although their risk of anaphylaxis is barely more than that of the general population, large local reactors might be considered for VIT (and therefore diagnostic testing) for quality-of-life reasons and to reduce the morbidity of frequent or unavoidable sting reactions.[31]

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 and/or severe reactions might benefit from VIT.[31,151,152] Beekeepers, on the other hand, often have diminished large local reactions when they receive frequent stings.[153,154]

Summary Statement 17: In a change from previous recommendations, advise both children and adults who have experienced only cutaneous systemic reactions without other systemic manifestations after an insect sting that VIT is generally not required but may be considered when there are special circumstances. This should be a shared decision with consideration of high-risk factors (frequent exposure, cardiovascular or respiratory conditions, or selected medications) and the effects on quality of life. (Recommendation; C evidence)

History of Cutaneous Systemic Reaction

Cutaneous systemic reactions, such as urticaria, angioedema (excluding tongue, throat, larynx), flushing, and pruritus, can occur after an insect sting. Although these can be extensive and intense, they do not affect other systems (throat, breathing, lightheadedness, hypotension). Prospective studies have found that patients 16 years 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 occurs, it is likely to be limited to the skin, with less than a 3% risk of a more severe reaction and less than a 1% risk of life-threatening anaphylaxis.[1,30] Therefore, VIT is generally not necessary for patients 16 years 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. VIT gives improved quality of life in patients with cutaneous systemic reactions.[155]

VIT is generally not required for patients older than 16 years who have experienced only cutaneous systemic reactions. This is a change from the recommendation in the previous updates of this practice parameter. Although VIT has previously been

recommended in the United States for patients older than 16 years with systemic reactions limited to the skin, this is not usually the case in other countries.[80,156] There are no studies comparing outcomes in those patients receiving VIT vs those not receiving VIT to guide this decision. However, sting challenge studies suggest that these patients are very unlikely to have severe anaphylactic reactions to subsequent stings and may not require VIT.[12,15] The risk-benefit ratio for VIT in such patients is uncertain. This should be a shared decision with consideration of potential high-risk factors (eg, concomitant cardiovascular disease or specific medications, for example, ACE inhibitors and β-blockers, elevated basal tryptase level, a high likelihood of future stings, or detrimental effect on quality of life).[80,156–158] It is also possible that younger adults and older adults should not have the same recommendations, especially because deaths from insect stings increase with age (for 1980–1999, US data: 20–29 years old, 41 deaths; 30–39 years old, 112 deaths; 40–49 years old, 196 deaths; 50–59 years old, 217 deaths; 60–69 years old, 207 deaths; older than 70 years, 131 deaths).[5]

Summary Statement 18: Discuss with adults with cutaneous systemic reactions who are already receiving VIT the reasons for the change in recommendations, possible special circumstances, and the relative risks and benefits of discontinuing or completing the course of VIT. (Recommendation; D evidence)

This new recommendation that VIT is not required for adults with cutaneous systemic reactions will raise an important question for such patients who are already undergoing VIT based on prior recommendations. The clinician may discuss with the patient the evidence base for the change of recommendation, the possible mitigating special circumstances (as above), and the option to discontinue VIT. The choice to discontinue VIT should be subject to a review of potential risk factors, as in all patients who are considering discontinuing VIT (systemic reactions during VIT, basal serum tryptase, cardiovascular or respiratory conditions, selected medications, or impairment of quality of life). The frequency of elevated basal serum tryptase levels in patients with cutaneous systemic reactions to stings is relatively low, and the clinical significance in these patients is unknown. The alternative choice, to complete the course of VIT, presents a slight risk (of systemic reaction to injections) and some potential benefit: the long-term outcome in children with cutaneous systemic reactions was better in those who received VIT than those who did not.[27]

Procedures for VIT

Summary Statement 19: Include in VIT all venoms for which the patient has demonstrated specific IgE. (Recommendation; C evidence) Treatment with some venoms may not be needed if cross-reactivity can be demonstrated by a radioallergosorbent inhibition test. (Recommendation; C evidence)

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 and nest. On the other hand, patient identification of stinging insects is notoriously unreliable.[159] 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 if the culprit is definitively known, despite positive skin or in vitro test results for other stinging insects.[50,160] Other authors recommend that the treatment include 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.[161,162]

Both these approaches are valid, and they are not mutually exclusive. In vitro radioallergosorbent inhibition tests (where available) can distinguish those yellow jacket allergic patients who are cross-sensitized to *Polistes* wasp venom from those with true dual sensitivity, which would inform the choice of venoms for VIT.[163] This approach has also been used for honeybee and yellow jacket double positivity. More recently, the use of recombinant venom allergens has resolved dual sensitivity to honeybee and yellow jacket from cross-reactivity that may be due to cross-reacting venom allergens or their cross-reacting carbohydrate determinants.[110–114]

Summary Statement 20: Begin VIT with initial dose of up to 1 μg and increase to maintenance dose of at least 100 μg of each venom. (Recommendation; B evidence) Children might be effectively treated with a maintenance dose of 50 μg. (Recommendation; C evidence)

Summary Statement 21: Choose a buildup dose schedule for optimal safety and convenience. Maintenance dose and protection can be achieved with equal safety using conventional (achieving 100-μg maintenance dose in 4 months) or modified rush (8 weeks) regimens. The risk of systemic reaction is similar using rush regimens (2–3 days) but may be slightly greater using ultrarush regimens (4–8 hours). (Strong recommendation; B evidence)

Dosage Schedules for VIT

The dose schedules approved by the US Food and Drug Administration are given in Appendix 1. VIT injections are usually administered once or twice a week, usually beginning with a dose of 0.01 to 1.0 μg and increasing to a maintenance dose of 100 μg of each insect venom (300 μg of mixed vespid venom).[156,160,164] Treatment can be safely started at a dose of 1 μg with no greater risk of reaction than regimens that begin with lower doses.[34,165] The 100-μg 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 have found variability in venom deposition from honeybee stings, and vespid stings deliver 2 to 20 μg of venom protein per sting.[32,166,167] 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. The 100-μg maintenance dose is achieved in 8 to 16 weeks using the US Food and Drug Administration–approved dose schedules. Safe and effective use of more accelerated schedules for VIT have been reported, and some can be considered routine.[156,168–170] Rush VIT schedules achieve the full dose in a matter of days instead of weeks. Some achieve the full dose in 2 to 3 days and others in 3 to 5 days. Rush regimens are 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, when there have been repeated systemic reactions impeding progress of VIT, and are optional in all cases. Ultrarush VIT is described using a buildup schedule for a period of hours instead of days. However, these regimens, like many rush regimens, do not achieve the maintenance dose until day 2.[170–173] Comparison of the frequency of systemic reactions using rush and ultrarush regimens is difficult because there are different definitions of rush and ultrarush regimens and they use different classification systems for the severity of systemic reactions. There are also different outcomes using honeybee or yellow jacket venoms. Rush regimens have been described giving a maximum dose between 0.4 and 20 μg (cumulative dose, 0.7–58 μg) on day 1. Ultrarush regimens are reported giving a maximum dose of 40 to 50 μg (cumulative dose, 80–111 μg) on day 1. Certain rush regimens are similar to some ultrarush regimens. The frequency of systemic reactions was 5% to 10% in most studies of rush regimens and 0% to 28% (median, 11%) with ultrarush regimens. In a study of jack jumper ant VIT, the reaction

rate was 12% (none severe) using an 8-week schedule and 65% (6% severe) using an ultrarush regimen.[115] 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. It has been noted that clinical protection is established as soon as the maintenance dose is achieved.[174,175]

There has been some controversy about the optimum maintenance dose. Initial studies used 100 μg as the maintenance dose.[32,117] One investigator 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.[160,164] Since the introduction of VIT, the same 100-μg maintenance dose has been recommended to children and adults. In 2 recent studies, children treated with a 50-μg dose had a frequency of systemic reactions to stings during and after VIT that was similar to the experience with the 100-μg dose.[176,177] The children in these studies had a mean (SD) age of 9.5 (3.2) and 8 years (range, 2–14 years), respectively. In one study there was a trend to better protection with 100 μg than with 50 μg. Increasing the maintenance dose up to 200 μg per dose has been effective in achieving protection in patients who had sting reactions while receiving a 100-μg maintenance dose of VIT.[178] If the insect that caused the reaction during VIT 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.

Summary Statement 22: Continue the maintenance dose monthly for at least 12 to 18 months, then consider extending the interval to 6 or 8 weeks during several years of treatment. For patients who continue VIT for longer than 4 years, a 12-week interval is safe and effective. (Strong Recommendation; C evidence)

The interval between maintenance dose injections is usually increased to 4 weeks during the first year and then to every 6 to 8 weeks during subsequent years. 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.[156,179,180] Twelve-week intervals have proven safe and effective for patients who have had several years of VIT at increasing intervals, but there is less evidence of efficacy for a 12-week interval in the first 1 to 2 years of VIT.[181,182] A 6-month interval was not effective.[183]

Problems During VIT (Adverse Effects, Risk Factors for Severe Reactions, Pregnancy, Medications)

Adverse effects and premedication

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.[165,184,185] When a patient has repeated systemic reactions despite adjustment of dose and schedule, a rush regimen with premedication has been safe and effective.[186] When this is not successful, pretreatment with omalizumab has been reported to prevent reactions and enable treatment to the maintenance dose.[187–189]

Large local reactions to VIT are common but do not presage systemic reactions and are generally tolerated if the induration does not exceed 3 to 4 inches in diameter. Premedication with antihistamines during buildup VIT reduces the incidence of local reactions and mild systemic reactions but not anaphylaxis.[190,191] 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.[192] There is also one report of reduced local reactions to VIT with montelukast premedication.[193]

There have been reports of patients who had serum sickness–like reactions from VIT.[194,195] In most of these patients the symptoms subsided and did not prevent maintenance treatment. Serum sickness has occurred as a sequel to insect stings, with or without an acute systemic reaction.[55,60,196] It is not known whether these patients are at greater risk of anaphylaxis if re-stung. VIT has been reported in such patients, with no recurrence of serum sickness from VIT or stings.[196] However, the safety and efficacy of this approach are unknown.

Practitioners have been uncertain about the safe procedure when beginning a new vial of venom or changing from one manufacturer to another. There is no universal answer to these questions and no data on which to base recommendations. Hymenoptera venoms are standardized extracts and should have minimal batch-to-batch variation. When changing to a different lot number, some physicians reduce the dose initially by 20% to 50%, and others make no adjustment. When changing from one manufacturer to another, most physicians reduce the dose initially by 20% to 50%. There are known differences between manufacturers in the species included in the yellow jacket venom mix and the *Polistes* wasp venom mix, so appropriate caution is warranted when changing manufacturers.[197] Fire ant whole-body extracts (WBEs) are not standardized, and each new vial should be started with caution, similar to the procedures for aeroallergen immunotherapy.

Risk factors for systemic reactions during VIT

Systemic reactions to VIT are more frequent in honeybee venom allergic patients, those with previous severe reactions to stings, during rush regimen initial treatment, and with greater time elapsed since the last sting reaction.[130,198] The risk of systemic reactions to VIT injections is also increased in patients with elevated basal serum tryptase levels or mastocytosis.[130,172,198,199]

There is continued concern about the risk of anaphylaxis in patients taking antihypertensive medications. In patients with insect sting allergy, the risk of more severe systemic reactions to insect stings in patients not treated with VIT is increased by β-blockers or ACEIs.[25,200] However, in patients receiving VIT, there is limited and conflicting evidence that these medications increase the risk of anaphylaxis.[33,199,201] The incidence of systemic reactions to VIT is not significantly affected by these medications. The possibility that the severity of such reactions, should they occur, might be increased by the medications is supported by some studies and not by others.[57,202] There is limited evidence that the risk associated with these medications is minimized by withholding the medication for 24 hours before VIT (if medically appropriate).[203,204]

The practice parameter on anaphylaxis states that the benefits of allergen immunotherapy with Hymenoptera venoms clearly outweigh the potential risks associated with β-blockers or ACEIs in those patients with anaphylaxis to stinging insects who also have cardiovascular disease that requires these medications.[108] Currently, the venom product package insert and the practice parameter on the management of anaphylaxis suggest that consideration should be given to the discontinuation of any drug treatment that may worsen an episode of anaphylaxis or complicate its treatment (eg, β-adrenergic blockers, ACEIs, α-adrenergic blockers, some tricyclic antidepressants [e.g., amitriptyline], monoamine oxidase inhibitors, and possibly angiotensin receptor blockers and renin inhibitors).

Systemic reactions to stings during VIT (treatment failure) can occur in less than 5% of patients treated with vespid venoms but are more frequent during treatment with honeybee immunotherapy.[147] There is also more chance of treatment failure in patients with mast

cell disorders, and there is some evidence of increased chance of a severe reaction in patients taking ACEIs or β-blockers. It may be prudent for patients who have an increased chance of reactions during VIT to have epinephrine autoinjectors available.

Pregnancy

There are scant data on VIT in pregnancy.[205] As with other allergen immunotherapy, it is recommended to avoid beginning or building up immunotherapy during pregnancy because of the higher chance of systemic reaction during up-dosing. The risk-benefit ratio must be considered, especially when the pregnancy overlaps the sting season. Strict avoidance of outdoor exposure is not always possible, and the risk of anaphylaxis in pregnancy must be considered. This should be a shared decision that should also consider other risk factors (eg, severity of previous reactions, frequency of exposure, basal serum tryptase level). In addition, like other immunotherapy, maintenance dose treatment can be and probably should be continued during pregnancy.

Duration of VIT

Summary Statement 23: Advise patients who start VIT to continue injections for 5 years. (Strong Recommendation; B evidence)

Summary Statement 24: Encourage continuation of VIT for an extended time, or indefinitely, in patients with high-risk factors, such as very severe reaction before VIT (syncope, hypotension, severe respiratory distress), systemic reaction during VIT, honeybee allergy, and increased basal serum tryptase levels. (Strong Recommendation; C evidence)

Summary Statement 25: Consider continuation of VIT for more than 5 years in patients with other high-risk factors for recurrent or severe sting reactions, such as underlying cardiovascular or respiratory conditions, select antihypertensive medications, frequent exposure, and limitation of activity due to anxiety about unexpected stings. (Strong Recommendation; A evidence)

Guidelines for discontinuation of VIT have evolved since the products were approved in 1979.[37,38,156,206,207] The package insert for the venom extract has always recommended 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 undetectable levels, or conversion to a negative skin test response. Some authors recommend repeat testing every 3 to 5 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. If both skin and serum test results are negative for venom IgE, there would seem to be no justification for continued treatment, although there is inadequate evidence on which to base any recommendation. 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 they can safely stop immunotherapy after that period of treatment.[36–40,208–214] 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 (Table 6). Relapse is less likely with 5 years than with 3 years of VIT.[38,40] Relapse is less likely in younger children than in adolescents or adults.[214] 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 (vs vespid stings), and those who had a systemic reaction during VIT (to a venom injection or a sting).[37–40,147] A few patients who had previously experienced severe anaphylaxis with loss of consciousness and then, after more than 5 years of immunotherapy, had negative in vitro test or skin test responses, have later experienced systemic reactions to subsequent stings after stopping VIT.[37,209,215] Fatal reactions to stings have occurred after stopping VIT in patients with mastocytosis.[134,135] Although this occurrence is rare, some recommend continuation of immunotherapy indefinitely in patients with a history of severe anaphylaxis or with mast cell disorders. 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 basal serum tryptase level, (3) the frequency of exposure, (4) the presence of concomitant disease and medications, (5) the effect of such action on work and leisure activities, and (6) the patient's preferences. This decision requires a context-sensitive flexibility based on the available evidence. A recommendation to carry an epinephrine autoinjector during extended VIT, or after stopping VIT, should also be considered based on the same risk factors, as discussed previously.

Table 6
Factors for Elevated Risk of Relapse After Discontinuing VIT

Proven:
Very severe reaction to previous stings
Elevated basal serum tryptase level
Systemic reaction during VIT (to injection or sting)
Less than 5 years of maintenance VIT
Honeybee anaphylaxis
Frequent exposure
Possible:
No decrease in venom IgE or skin tests
Underlying cardiovascular or respiratory disease
Use of ACEIs or β-blockers

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; VIT, venom immunotherapy.

Fire Ant Immunotherapy

Summary Statement 26: Recommend immunotherapy with imported fire ant WBE to all patients who have experienced a moderate or severe systemic reaction to a fire ant sting and who have positive skin test responses or allergen-specific serologic test results with imported fire ant WBE. (Strong Recommendation; B evidence)

Summary Statement 27: Consider WBE immunotherapy in patients who have only cutaneous manifestations to fire ant stings because the natural history of fire ant hypersensitivity 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. (Recommendation; D evidence)

Compared with other stinging insects, less is known about the natural history of IFA hypersensitivity and the effectiveness of immunotherapy.[17,18,66,91,216,217] IFA WBE contains 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.[17,36,91,93,94,218–222] The current criteria for immunotherapy for IFA allergy are similar to those for other Hymenoptera (ie, a history of a systemic reaction and demonstration of IFA antigen–specific IgE antibodies by means of skin or in vitro testing). There is a high frequency of IFA re-stings in endemic areas, even in patients receiving IFA WBE immunotherapy, who it might be expected would actively practice avoidance techniques.[66,223,224] Given the high frequency of IFA stings, both 1- and 2-day rush immunotherapy schedules have been reported to expedite the achievement of a therapeutic dose.[219,225] Most systemic reactions occur from a single sting, and a systemic reaction to skin testing is a risk factor for a systemic reaction to IFA WBE immunotherapy.[226] For stability, IFA WBE should be delivered alone and not mixed with other allergens.[227,228]

Controversy exists regarding the management of patients 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 IFA in children usually do not progress to more serious reactions.[216] Most allergists, but not all, in IFA endemic areas do not routinely recommend immunotherapy for children who have had only generalized cutaneous reactions.[229] Thus, immunotherapy in these patients is currently optional. Lifestyle consideration, parental preferences, and other factors might influence this decision.

The dosage schedule for fire ant WBE 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 2. Successful use of a rush immunotherapy protocol has been published.[219,225] 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.[17,18,219,229] A survey of practicing allergists found that 0.5 mL of a 1:200 wt/vol extract is the most widely prescribed maintenance dose.[229] Evidence continues to accumulate to support the efficacy of this dose.[17,18,219] Special dosing might need to be considered for treatment failures.

Summary Statement 28: Consider continuation of imported fire ant WBE for more than 5 years in patients with imported fire ant allergy because the optimal duration of this therapy has been less well studied and the frequency of exposure is high. (Recommendation; C evidence)

The optimal duration of IFA 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.[36] A survey of allergists indicated a great deal of variation in recommendations regarding the duration of immunotherapy for fire ant allergy.[44] 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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Appendix 1

Two Examples of Conventional Dosing Schedules for Venom Immunotherapy[a]

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

[a]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 may be advanced from weekly to monthly. Schedule 1 is based on the package insert for HollisterStier venom extracts (Spokane, Washington). Schedule 2 is based on the package insert for ALK-Abello venom extracts (Round Rock, Texas).

Appendix 2

Two Examples of Successful Conventional Dosing Schedules for Fire Ant Immunotherapy With *Solenopsis invicta* or a Mixture of *S invicta* and *Solenopsis richteri* Whole-Body Extract[a]

Schedule 1		
Dose	Concentration, wt/vol	Volume, mL
1	1:100,000	0.05
2	1:100,000	0.10
3	1:100,000	0.20
4	1:100,000	0.30
5	1:100,000	0.40
6	1:100,000	0.50
7	1:10,000	0.05
8	1:10,000	0.10
9	1:10.000	0.20
10	1:10,000	0.30
11	1:10,000	0.40
12	1:10,000	0.50
13	1:1,000	0.05
14	1:1,000	0.10
15	1:1,000	0.20
16	1:1,000	0.30
17	1:1,000	0.40
18	1:1,000	0.50
19	1:100	0.05
20	1:100	0.10
21	1:100	0.15
22	1:100	0.20
23	1:100	0.25
25	1:100	0.35
26	1:100	0.40
27	1:100	0.45
28	1:100	0.50
Schedule 2		
Dose	Concentration, wt/vol	Volume, mL
1	1:100,000	0.05
2	1:100,000	0.15
3	1:100,000	0.25
4	1:100,000	0.50
5	1:10,000	0.05
6	1:10,000	0.10
7	1:10,000	0.20
8	1:10,000	0.30
9	1:10,000	0.40
10	1:10,000	0.50
11	1:1000	0.05
12	1:1000	0.10
13	1:1000	0.20
14	1:1000	0.30
15	1:1000	0.40
16	1:1000	0.50
17	1:100	0.05
18	1:100	0.07
19	1:100	0.10
20	1:100	0.15
21	1:100	0.20
22	1:100	0.25
23	1:100	0.40
25	1:100	0.50

[a]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.