STINGING INSECT HYPERSENSITIVITY: A PRACTICE PARAMETER

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

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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." Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology.

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Practice Parameters for the Diagnosis and Treatment of Asthma. J Allergy Clin Immunol 1995;96:S707-870.

Practice Parameters for Allergy Diagnostic Testing. Ann Allergy 1995:75:543-625.

Practice Parameters for the Diagnosis and Management of Immunodeficiency. Ann Allergy 1996;76:282-294.

Practice Parameters for Allergen Immunotherapy. J Allergy Clin Immunol 1996;98:1001-1011.

Disease Management of Atopic Dermatitis: A Practice Parameter. Ann Allergy 1997;79:197-211.

The Diagnosis and Management of Anaphylaxis. J Allergy Clin Immunol 1998;101:S465-528.

Algorithm for the Diagnosis and Management of Asthma: A Practice Parameter Update. Ann Allergy 1998;81:415-420.

Diagnosis and Management of Rhinitis: Parameter Documents of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Ann Allergy 1998;81:S463-518.

Parameters for the Diagnosis and Management of Sinusitis. J Allergy Clin Immunol 1998;102:S107-49.

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PREFACE

Anaphylaxis from insect stings results in a significant number of fatalities each year. At least 40 deaths occur in the United States yearly from reactions to insect stings, and it is likely that additional deaths are unrecognized and therefore not reported. Data indicating the prevalence of fatalities from insect stings can never adequately reflect the individual tragedy associated with the sudden and unexpected loss of a friend or relative. Although most insect stings produce only local discomfort, potentially life-threatening reactions occur in both children and adults.

Stinging insect hypersensitivity is a complex and challenging condition. With recognition of the importance of venom extracts in the diagnosis and treatment of patients who had experienced reactions to insect stings, a scientifically-based standardized approach to management seemed a reasonable assumption 20 years ago. It has since become clear that there are still important questions that need to be answered, such as the criteria to be used in determining the duration of venom immunotherapy. It is therefore essential that the practicing physician understand basic approaches to the management of stinging insect hypersensitivity so that evaluation and treatment can be appropriately individualized for each patient.

A workgroup of the Joint Task Force on Practice Parameters was responsible for the initial preparation of the "Parameter on the diagnosis and management of stinging insect hypersensitivity." That workgroup, chaired by John E. Moffitt, MD, and consisting of internationally recognized experts in the field of stinging insect allergy, provided the Task Force with the first draft of this parameter, consisting of a text with references, as well as summary statements reflecting the key points to be considered in each section. Jay M. Portnoy, MD, as a member of the Task Force, then accepted responsibility for the initial editing of this document. The Task Force added an algorithm and annotations to support the steps recommended in the algorithm. After evaluation by the entire Task Force, the complete document was then reviewed by selected individuals within the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI).

As is the case with previous parameters produced by the Joint Task Force on Practice Parameters, this document is based on a careful review of the literature and reflects the experience of experts in the area of stinging insect hypersensitivity. When the medical literature did not provide a definitive recommendation on a given issue or there was significant difference of opinion among experts, options were given for the management of patients based on the current state of practice. The result is a concise, focused, evidence-based, consensus practice parameter that will serve as a map for the management of stinging insect hypersensitivity.

The Joint Task Force on Practice Parameters would like to thank those who have so willingly given of their time and expertise in the development of this important parameter. This includes the members of the Workgroup on Stinging Insect Hypersensitivity, as well as reviewers from the AAAAI and the ACAAI. The Task Force would like to acknowledge in particular the support and contributions made by John E. Moffitt, MD, and David B. K. Golden, MD. In addition, the Task Force is indebted to the leadership of both the AAAAI and the ACAAI for their recognition of the importance of developing practice parameters and their support in this endeavor.

EXECUTIVE SUMMARY

Most insect stings produce local reactions, which include redness, swelling, itching, and pain. Systemic reactions include cutaneous manifestations (eg, urticaria, angioedema) bronchospasm, edema of the upper airway, and hypotensive shock, and range from mild to life-threatening.

Stinging insects responsible for such reactions include yellow jackets, hornets, wasps, honeybees, and fire ants. Yellow jackets are ground-dwelling insects. They may be very aggressive and sting with minimum provocation, especially in the presence of food.

Hornets build large nests in trees and shrubs that may not be easily visualized. They are also very aggressive, particularly in the vicinity of the nest.

Wasps build honeycomb nests and may be seen on the outside of the nest, which is often built in dark areas, such as under eaves or porches of homes.

Honeybee hives may be domestic or wild. Nondomestic hives may be found in tree hollows or old logs and may contain hundreds of bees. Honeybees are usually not aggressive away from their hives. When they sting, they leave a barbed stinger with attached venom sac.

Fire ants, which may be red or black, are found in mounds made of fresh soil that may be extremely large. Fire ant mounds are common along southeastern roadways but are becoming increasingly prevalent in residential areas in the south. They are very aggressive if their mounds are disturbed and may sting many times. A sterile pustule usually develops at the site of the sting in less than 24 hours.

Consultation with an allergist/immunologist for evaluation and possible skin or in vitro testing for stinging insect hypersensitivity is appropriate for any patient who has a systemic reaction to an insect sting. Consultation should be considered if the patient (1) has experienced a

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systemic reaction to an insect sting, (2) has experienced anaphylaxis with an insect sting as a possible cause, (3) needs education regarding stinging insect avoidance or emergency treatment, (4) may need venom immunotherapy, (5) has a coexisting condition that may complicate treatment of anaphylaxis (eg, taking β-blockers, hypertension, or a history of cardiac arrhythmias), and/or (6) asks for a consultation.

Avoidance of stinging insects is important in the management of patients with stinging insect hypersensitivity. Avoidance is enhanced by the following: (1) evaluation of the vicinity of the patient's home by trained professionals looking for stinging insect nests and extermination of these nests if found; (2) not wearing brightly colored clothing or strongly scented lotions; (3) walking outside with shoes other than sandals; (4) exercising caution near bushes, eaves, attics, and areas where food is present outside (eg, picnic areas or garbage containers); (5) having insecticides readily available; and (6) wearing long pants, a long-sleeved shirt, socks, shoes, a hat, and work gloves when working outside.

Patient education may be essential in preventing life-threatening reactions and appropriate treatment of such reactions if they occur. This should include the following: (1) identification of stinging insects; (2) knowledge of how to avoid being stung; (3) appropriate treatment of reactions (eg, how and when to self-administer epinephrine); and 4) wearing and/or carrying identification of stinging insect hypersensitivity (eg, Medic Alert bracelet).

Skin testing with stinging insect venom (or, in the case of suspected fire ant hypersensitivity, whole body extract) should be considered for any patient who has experienced a systemic reaction to an insect sting and in whom venom (or, in the case of fire ant hypersensitivity, whole body extract) immunotherapy is being considered. Because the insect that caused the sting often cannot be identified, skin testing is usually done with all of the commercially available venom extracts for stinging insects other than fire ants. Skin testing is usually performed by using prick puncture and intracutaneous techniques. Prick puncture tests are usually performed before intracutaneous tests. Intracutaneous skin testing may initially use a concentration in the range of 0.001 to 0.01 μg/mL, with increasing concentrations being used until a positive skin test response occurs or a concentration of 1.0 μg/mL is reached. There is conflicting data regarding the immunologic specificity, and therefore the clinical significance, of reactions to the 1.0 μg/mL venom concentration. It has been suggested that the 1.0 μg/mL venom concentration may produce an irritant reaction in some patients, and therefore it is recommended that caution be used in attributing a positive skin test response at this concentration to the presence of IgE antibody to venom. On the other hand, there is an increasing amount of data to support the clinical significance of a positive skin test response at this concentration. Interpretation of skin test results always requires correlation with the patient's history. Therefore in patients who have a positive history of stinging insect hypersensitivity, skin tests with a concentration of 1.0 μg/mL are recommended if skin test responses at lower concentrations are negative. There are patients who have severe systemic reactions after an insect sting who have barely detectable venom IgE levels as determined by skin tests or RASTs. A substantial number of such patients may have skin test responses that are negative at 0.1 μg/mL but positive at 1.0 μg/mL. In addition, there may be rare patients who have negative skin test responses at 1.0 μg/mL who have a positive RAST result for venom-specific IgE.

In terms of patients seen with suspected fire ant hypersensitivity, whole body extract is the only reagent currently available for diagnostic testing. Limited cross-reactivity exists between the antigens in fire ant venom and the antigens in venom of other stinging insects. If the patient is able to positively identify fire ant as the stinging insect, skin testing with other stinging insect venoms is not required.

Venom immunotherapy (VIT) has proven to be an extremely effective form of treatment for individuals at risk of insect sting anaphylaxis and has been shown to substantially reduce the risk of subsequent systemic sting reactions. VIT is generally not necessary for patients 16 years of age and younger who have experienced cutaneous systemic reactions without other manifestations. Such patients have only a 10% chance of having a systemic reaction if re-stung, and if a systemic reaction does occur, it is likely to be limited to the skin. VIT is still an acceptable option in such patients if requested by the patient's parents (or guardians) or if the child is likely to experience frequent or multiple stings. The use of sting challenges to better select patients for VIT is controversial and is not considered a prerequisite for VIT in the United States. Guidelines for the duration of VIT are evolving. Although the package insert for the venom extract recommends that VIT be continued indefinitely, a fall in serum venom-specific IgE antibodies to insignificant levels or conversion to a negative skin test response have been used as criteria for discontinuing VIT. However, an increasing amount of data 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. This has lead some experts to advocate discontinuing VIT after 3 to 5 years, regardless of skin test results. However, patients with a history of severe anaphylaxis whose skin test responses remain positive after 3 to 5 years of VIT may still be at increased risk for a systemic reaction if VIT is stopped. For this reason, some experts recommend continuation of VIT indefinitely in such patients, as long as skin test responses remain positive.

Less is know about the natural history of fire ant hypersensitivity and the effectiveness of immunotherapy. Nevertheless, fire ant whole body extract has been shown to contain relevant venom allergens and appears to be effective. The optimal duration of fire ant immunotherapy has not been clearly established because of limited data.

Anaphylaxis from insect stings results in a significant number of fatalities each year. Although most insect stings

produce only local discomfort, potentially life-threatening reactions occur in both children and adults. Stinging insect hypersensitivity is a complex and challenging condition. It is therefore essential that the practicing physician understand the basic approaches to the management of stinging insect hypersensitivity so that evaluation and treatment can be appropriately individualized.

ANNOTATIONS (Fig 1)

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

Although insects sting many people each year, most individuals do not seek medical attention. Most who are stung require only symptomatic treatment. Patients who experience insect stings resulting in systemic reactions require diagnosis and treatment. Taking a careful history can usually make the diagnosis of stinging insect hypersensitivity. Reactions can range from large local reactions to life-threatening systemic reactions. Delayed or toxic reactions may also occur.

Box 2: History and physical examination

Most insect stings occur in the daytime, whereas insect bites (eg, yellow flies, black flies, mosquitoes, and spiders) may occur in the daytime or at night (eg, Triatoma) and therefore may occur while the patient is sleeping. Patients should be encouraged to bring the offending insect, if available, to the physician for identification.

Factors that may 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 patient at the time of the sting (eg, close to an insect nest),
- the location of the sting (eg, face or lower leg),
- the type of insect activity in the area where the patient was stung, and
- visual identification of the insect.

Young children present special problems in diagnosis because they are usually not able to identify the insect. The presence of a stinger, which is left by bees, or the presence of a pustule as a result of a fire ant sting (up to 24 hours later) may help in insect identification.

Box 3: Was there a systemic reaction?

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

- redness,
- swelling,
- itching and pain.

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

- cutaneous responses (eg, urticaria and angioedema),
- bronchospasm,
- obstructive edema of the upper airway,
- hypotension and shock.

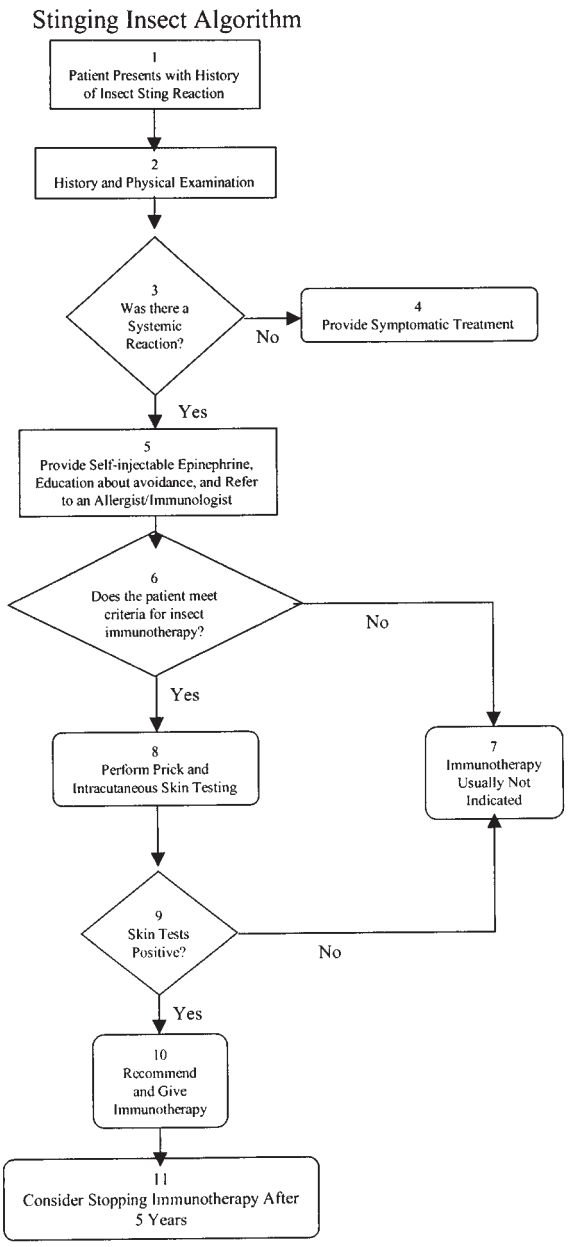

FIG 1.

The key feature that distinguishes a systemic reaction from a large local reaction is that a systemic reaction occurs in a location that is not contiguous with the site of the sting.

Box 4: Provide symptomatic treatment

Most insect stings cause local reactions that are of little serious medical consequence, and no specific treatment is usually required. Some local reactions are manifested by extensive erythematous swelling surrounding the sting site that may persist for several days or more and may be accompanied by itching, pain, or both. Cold compresses may help to reduce local pain and swelling. Local anesthetic cream, oral antihista-

mines, and oral analgesics may also help to reduce the pain or itching associated with cutaneous reactions. Some physicians use topical or oral corticosteroids for particularly severe local symptoms, although this is controversial. Because the swelling is caused by mediator release and not by infection, antibiotics are not required unless there is evidence of secondary infection.

Box 5: Provide self-administered epinephrine and education

Preventive management includes measures to prevent subsequent stings and to prevent systemic reactions if the patient is stung. Injectable epinephrine should be provided, and the patient should be instructed on its proper administration and use. Patients should also be advised to consider obtaining a MedicAlert bracelet or necklace.

Box 6: Does the patient meet criteria for insect immunotherapy?

Patients 16 years of age and younger who have experienced cutaneous systemic reactions, without other manifestations, after an insect sting, other than a fire ant sting, have a 10% chance of having a systemic reaction if restung. If a systemic reaction does occur, it is likely to be limited to the skin. Therefore VIT is not generally necessary for patients 16 years of age and younger who have experienced cutaneous systemic reactions without other manifestations. VIT is still an acceptable option if the child is likely to experience frequent or multiple stings. Although there is some controversy in regard to adults who have experienced cutaneous systemic reactions, there is insufficient evidence to justify withholding VIT for that group of individuals at this time. Immunotherapy may be considered, even in children under 16 years of age, who have had a systemic reaction from a fire ant sting, that is limited to the skin.

Box 7: Immunotherapy is usually not indicated

Patients 16 years of age and younger whose previous reaction consisted of generalized cutaneous signs and symptoms only (eg, pruritus, flushing, urticaria, and angioedema) are at low risk for future anaphylaxis and usually do not require allergy testing or immunotherapy. If the previous reaction included signs and/or symptoms suggesting involvement of other organ systems (eg, wheezing, shortness of breath, dizziness, or loss of consciousness), then allergy skin tests should be performed in this age group, and immunotherapy should be considered. If skin test responses for stinging insects are negative, regardless of the patient's history or age, immunotherapy is usually not indicated.

In rare cases, patients who have experienced severe systemic reactions after an insect sting may have, despite negative skin test responses at a 1.0 μg/mL concentration, a positive in vitro test response for venom-specific IgE. The effectiveness of immunotherapy in these cases is unknown.

Box 8: Perform prick and intracutaneous skin testing

Skin testing should be performed on patients for whom immunotherapy might be indicated. Skin testing is usually performed by using prick puncture tests initially and then intracutaneous tests if necessary. Intracutaneous tests usually start with a concentration in the range of 0.001 to 0.01 μg/mL. If intracutaneous tests at this concentration are nonreactive, the test dose is increased by 10-fold increments until a positive skin test response occurs, up to a maximum concentration of 1.0 μg/mL. Increasing concentrations of fire ant extract are also used (see text section on fire ants). Positive and negative controls should be done at this time.

Because the insect that caused the sting often cannot be identified, testing is usually done with all of the commercially available venom extracts. Venoms may contain shared antigenic components. Cross-sensitization and immunologic cross-reactivity have been demonstrated between hornet and yellow jacket venoms (vespids); however, cross-reactivity is less likely to occur between vespid and wasp venoms and is very unlikely to occur between honeybee and vespid venoms. Fire ant extracts have very limited cross-reactivity with other stinging insect venoms.

Box 9: Positive skin test response?

A positive skin test response at a concentration less than 1.0 μg/mL venom demonstrates the presence of specific IgE antibodies. There is conflicting data regarding the immunologic specificity, and therefore the clinical significance, of reactions to the 1.0 μg/mL venom concentration. It has been suggested that the 1.0 μg/mL venom concentration may produce an irritant reaction in some patients, and it is therefore recommended that caution be used in attributing a positive skin test response at this concentration to the presence of IgE antibody to venom. On the other hand, there is an increasing amount of data to support the clinical significance of a positive skin test response at this concentration. Interpretation of skin test results always requires correlation with the patient's history. Therefore in patients who have a positive history of stinging insect hypersensitivity, skin tests with a concentration of 1.0 μg/mL are recommended if skin test responses at lower concentrations are negative.

Box 10: Recommend and give venom-specific immunotherapy

VIT prevents systemic reactions in stinging insect–sensitive patients 97% of the time. Patients who have had a systemic reaction from an insect sting should therefore be advised to start VIT. The goal of VIT is primarily to prevent life-threatening reactions. A secondary benefit is that it may alleviate anxiety related to insect stings.

Candidates for VIT should be informed about the potential risks and benefits related to the procedure. Patients should receive a description of the procedure and be informed that, because of the risk of anaphylaxis,

they must wait an appropriate time after each injection and follow any other specific policies and rules that the provider of the VIT may have. Appropriate accommodations for language barriers should be made to ensure that proper informed consent is obtained.

In the opinion of some experts, if the insect that caused the reaction can be clearly identified, the extract used for VIT need only contain the venom of that insect, even if skin or in vitro test responses for other stinging insects are positive. On the other hand, other experts recommend that the extract contain venoms of all insects for which a positive skin or in vitro test response was obtained. Immunotherapy for patients with fire ant hypersensitivity uses whole body extract and should be initiated in patients with a history of a systemic reaction to a fire ant sting who have a positive skin test response with whole body extract.

VIT injections are generally administered at weekly intervals beginning with 0.1 to 0.5 μg and increased to a maintenance dose of up to 100 μg per insect. The dosage schedule for fire ant immunotherapy is less well defined in terms of starting dose and rapidity of buildup. Although most experts recommend a maintenance dose of 0.5 mL of a 1:100 wt/vol dilution, a 1:10 wt/vol maintenance level 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. During seasons when stinging insects are likely to be present, rapid desensitization may be considered.

Patients who are taking β-adrenergic blocking agents and possibly patients taking angiotensin-converting enzyme (ACE) inhibitors (see parameters on anaphylaxis) are at greater risk if they experience an allergic reaction, and in the case of ACE inhibitors, may be at greater risk of having an allergic reaction. Therefore patients who have stinging insect hypersensitivity should not be prescribed β-adrenergic blocking agents or ACE inhibitors unless absolutely necessary. If the patient who has stinging insect hypersensitivity cannot discontinue these medications, VIT should still be given, but with greater caution.

Box 11: Consider stopping VIT after 5 years

Guidelines for discontinuation of VIT are evolving. Whereas the package insert for the venom extract product recommends that VIT be continued indefinitely, a fall in serum venom-specific IgE antibodies to insignificant levels or conversion to a negative skin test response have been used as criteria for discontinuing treatment. Most patients will lose their skin reactivity to stinging insect venom; however, the persistence of such reactivity does not mean that they are at increased risk of having a systemic reaction if subsequently stung. 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. Patients with a history of severe anaphylaxis who continue to have positive skin test responses after 3 to 5 years of immunotherapy still may be at increased risk for a systemic reaction if VIT is stopped. For this reason, some experts recommend continuation of immunotherapy indefinitely in such patients, as long as skin test responses remain positive.

The optimal duration of imported fire ant immunotherapy has not been clearly established because of limited data. Skin reactivity appears to be a poor indicator of the risk for a systemic reaction to fire ant venom after fire ant immunotherapy. A recent survey of allergists indicated a great deal of variation in recommendations regarding duration of immunotherapy for fire ants. Some allergists recommend indefinite treatment. Most allergists consider stopping immunotherapy after a specified period (usually 4 to 5 years) either empirically or only when skin tests become negative. Until further data are available, a definitive recommendation about duration of immunotherapy for fire ants cannot be made.

SUMMARY STATEMENTS

1. Individuals with a history of a systemic reaction to an insect sting are at increased risk for subsequent systemic sting reactions. This risk can be significantly reduced with VIT.
2. Individuals who have a history of systemic IgE-mediated reactions to insect stings should:
   - be educated in ways to avoid insect stings,
   - carry epinephrine for emergency self-treatment with them at all times,
   - consider obtaining a MedicAlert bracelet or necklace, and
   - be considered for skin testing for stinging insect sensitivity and VIT if skin test responses are positive, unless medically contraindicated or refused by the patient.
3. Venom immunotherapy is recommended for all patients who have experienced a systemic reaction to an insect sting and who have specific IgE antibodies to venom allergens with the following special considerations:
   - Adults who have experienced only cutaneous manifestations to an insect sting are generally considered candidates for VIT, although the need for immunotherapy in this group of patients is controversial.
   - The natural history of fire ant hypersensitivity in children who have only cutaneous manifestations has not been well elucidated. Because there is increased risk of fire ants stings in children who live in areas where fire ants are prevalent, immunotherapy may be recommended for such children.
   - VIT is generally not necessary in children who have experienced cutaneous systemic reactions without other manifestations after an insect sting from a wasp, hornet, yellow jacket, or bee. Children who experience only cutaneous manifestations after a fire ant sting may be considered candidates for immunotherapy.
4. Immediate hypersensitivity skin testing with stinging

insect venoms is indicated for individuals who are candidates for VIT. Skin testing rather than in vitro assays should be used for measurement of venom-specific IgE antibodies, except in special circumstances.

INTRODUCTION

Hymenoptera insect stings account for at least 40 deaths per year in the United States.[1] Most insect stings are associated with local reactions, including pain, swelling, and redness. These local reactions usually last for only a few days and generally resolve with simple treatment measures. Systemic reactions that can lead to potentially life-threatening manifestations occur in 0.4% to 0.8% of children[2,3] and 3% of adults.[4] Large, more widespread local reactions occur more frequently in approximately 10% to 15% of adults.[4] In such cases it is imperative that a proper diagnosis be made and appropriate treatment be instituted to prevent fatalities from subsequent stings. Prompt recognition and treatment of systemic reactions, as described in the following practice parameter, can be expected to reduce the likelihood of subsequent systemic reactions and fatalities.

STINGING INSECT IDENTIFICATION

Identification and avoidance of the insect responsible for the sting may be helpful in diagnosis, treatment, and avoidance education. Patients should be encouraged to bring the captured and/or killed offending insect, if available, to the physician for identification. Most insect stings occur in the daytime, whereas insect bites (eg, yellow flies, black flies, mosquitoes, and spiders) may occur in the daytime or at night (eg, Triatoma—reduvid or kissing bug) and therefore often when the patient is sleeping.

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

- the patient's activity at the time of the sting (eg, hedge clipping),
- the location of the patient at the time of the sting (eg, close to an insect nest),
- the location of the sting (eg, face or lower leg),
- the type of insect activity in the area when the patient was stung,
- visual identification of the insect.

Young children present special problems in diagnosis because they are usually not able to identify the insect. The presence of a stinger, which is left usually by bees, or the presence of a pustule as a result of fire ant stings (up to 24 hours later) may help in insect identification.

Yellow jackets are ground-dwelling insects and may be encountered during yard work, farming, or gardening. They may also be found in wall tunnels or crevices and in hollow logs. Yellow jackets are very aggressive and sting with minimum provocation, especially in the presence of food. Patients have been stung after drinking a beverage that contained a stinging insect.

Hornets, which are related to yellow jackets, build large papier-mâche nests that are several feet in diameter and are usually found in trees or shrubs.

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

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

Domestic honeybees are found in hives. Wild honeybee nests may be found in tree hollows, old logs, or in buildings. They may contain hundreds or thousands of bees.

Bumblebees and honeybees, except for Africanized honeybees, are usually nonaggressive away from their hives. Honeybees always leave a barbed stinger with attached venom sac when they sting, but bumblebees do not usually leave a stinger. Vespids and stinging ants may occasionally leave stingers. Consequently, the presence of a stinger is not absolutely diagnostic of a honeybee sting.

The fire ant, which may be red or black, is found in mounds composed of fresh soil that may be at least several inches high and may extend 1 to 2 ft in diameter. There may 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 addition, they are a major problem in residential neighborhoods, back yards, and public places. These ants are very aggressive, particularly if their mounds 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 diagnostic of a fire ant sting.

STINGING INSECT REACTIONS

Without medical intervention, individuals sensitive to stinging insect venom are at significant risk for life-threatening allergic reactions if stung. Immunotherapy with extracts of stinging insect venom reduces the risk of subsequent systemic reactions. Extracts of honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp venom are available for skin testing and immunotherapy. Although Africanized honeybees ("killer bees") are much more aggressive than domestic honeybees, their venom is qualitatively similar to that of domestic honeybees. Imported fire ant *(Solenopsis)* venom is unavailable for clinical use, but fire ant whole body extract contains relevant venom allergens, and immunotherapy with this material appears to be protective.[5-9]

Management of insect sting reactions

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

pain, or both. Cold compresses may help to reduce local pain and swelling. Oral antihistamines and oral analgesics may also help reduce the pain or itching associated with cutaneous reactions. Some physicians use topical or oral corticosteroids for particularly severe symptoms, although this is controversial. Because the swelling is caused by mediator release and not by infection, antibiotics are not required unless there is evidence of secondary infection.

Fire ant stings typically cause a pustule 24 hours after the sting. The material in the pustule is necrotic tissue and is not caused by infection at the site of the sting. The vesicle should be left intact, but if it is accidentally opened, it should be cleansed with soap and water to prevent secondary infection. Although secondary infection is the most common complication of fire ant stings, most reactions do not develop secondary infection and, in the absence of infection, do not require antibiotic therapy.[9]

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

Treatment of anaphylactic reactions caused by insect stings is the same as the treatment of anaphylaxis as a result of other causes. The reader is referred to the practice parameter entitled "The Diagnosis and Management of Anaphylaxis."[10] If a stinger is present, the suspected insect is usually a honeybee. The stinger should be removed as quickly as possible. Removal usually can be accomplished by simply flicking or scraping the stinger away with a fingernail. Grasping the venom sac with the fingers and pulling it out may result in injection of additional venom and should be avoided.

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

PREVENTIVE MANAGEMENT

Preventive measures against insect stings should be instituted for individuals allergic to the venom of stinging insects. This requires educating such patients about practical measures for avoidance of insect stings. Avoidance measures to reduce the likelihood of insect stings include the following:

- Have known or suspected nests in the immediate vicinity of the patient's home exterminated by trained professionals; periodic evaluation by experts regarding the existence of nests should be considered.
- Avoid wearing brightly colored clothing or flowery prints, as well as strongly scented lotions that may attract insects.
- Do not walk outside without shoes other than sandals. Walking in socks can be dangerous also.
- Be cautious near bushes, eaves, and attics and avoid garbage containers and picnic areas.
- Keep insecticides readily available that can be used to kill stinging insects from a distance if necessary. Stinging insects are not affected by insect repellants.
- Wear long pants, long-sleeved shirts, socks, shoes, head covering, and work gloves when working outdoors.
- Be cautious when eating or drinking outdoors or in situations outdoors where food and beverages are being served.

IMMEDIATE TREATMENT

Epinephrine is the drug of choice for the treatment of anaphylaxis. Patients allergic to insect venom should carry epinephrine for self-administration in case of a sting. EpiPen (0.30 mg epinephrine) and EpiPen Jr (0.15 mg of epinephrine) are spring-actuated autoinjectors. Ana-Kit and Ana-Guard provide a syringe loaded with 2 doses of 0.3 mg of epinephrine. Although the latter 2 kits require self-injection, they also permit the administration of fractional, as well as multiple, doses. Patients and parents of children who have experienced a systemic reaction to an insect sting should be taught how to self-administer epinephrine and under what circumstances this should be done. Patients allergic to insect venom who are stung and who also have cardiovascular disease should receive epinephrine in the event of a life-threatening sting reaction despite concern about epinephrine's cardiac effects because the benefit clearly outweighs the risk in a life-threatening situation.

CONSULTATION WITH AN ALLERGIST/IMMUNOLOGIST

Consultation with an allergist/immunologist for evaluation and possible skin or in vitro testing for stinging insect hypersensitivity is appropriate for any patient who has had a systemic reaction to an insect sting.[11-13] A diagnosis of stinging insect hypersensitivity is based on a history of a systemic reaction after a sting supported by the demonstration of specific IgE antibodies to insect venom, usually by immediate hypersensitivity skin testing but occasionally by in vitro assay.

Indications for referral to an allergist/immunologist

Referral to an allergist/immunologist who has had training and experience in the diagnosis and treatment of, as well as patient education regarding, stinging insect hypersensitivity should be considered for patients who:

- have experienced a systemic reaction to an insect sting;
- have experienced anaphylaxis, and an insect sting was a possible cause;
- need education regarding stinging insect avoidance or emergency treatment;
- may be candidates for VIT;
- have a coexisting situation that may complicate treat-

ment of anaphylaxis (eg, taking β-blockers, hypertension, cardiac arrhythmias); or
- request an allergy/immunology consultation.

IMMEDIATE HYPERSENSITIVITY TESTING

Skin testing

Skin testing is usually performed by using prick and intracutaneous techniques.[14-16] Prick tests are usually performed before intracutaneous tests. Initial intracutaneous tests use a concentration in the range of 0.001 to 0.01 μg/mL. If intracutaneous test responses at these concentrations are negative, the test dose is increased by 10-fold increments until a positive skin test response occurs up to a maximum concentration of 1.0 μg/mL. Approximately 0.02 to 0.03 mL (amount sufficient to raise a small bleb) is injected very superficially on the upper arm or flexure aspect of the forearm. Positive and negative controls also should be done at this time. It is generally believed that a positive skin test response at a concentration less than 1.0 μg/mL demonstrates the presence of specific IgE antibodies and does not represent a nonspecific irritant reaction. It has been suggested that the 1.0 μg/mL venom concentration may produce an irritant reaction in some patients, and it is therefore recommended that caution be used in attributing a positive skin test response at this concentration to the presence of IgE antibody to venom.[16] On the other hand, there is an increasing amount of data to support the clinical significance of a positive skin test response at this concentration.[14,15] Interpretation of skin test results always requires correlation with the patient's history. Therefore in patients who have a positive history of stinging insect hypersensitivity, skin tests with a concentration of 1.0 μg/mL are recommended if skin test responses at lower concentrations are negative. Other experts recommend that skin testing be performed with a concentration of 1.0 μg/mL if weaker concentrations produce a negative response and believe that a positive skin test response at this concentration demonstrates the presence of venom-specific IgE antibodies.[14,15] There are patients who have severe systemic reactions after an insect sting who have barely detectable venom IgE levels as determined by skin tests or RAST. A substantial number of such patients may have skin test responses that are negative at 0.1 μg/mL but that are positive at 1.0 μg/mL.[4] In addition, there may be patients who have negative skin test responses at 1.0 μg/mL who have a positive RAST result for venom-specific IgE. An accelerated method of performing venom skin testing has been suggested.[17] There have been occasional reports of individuals who have experienced anaphylaxis to an insect sting who have had negative skin test responses for stinging insect venom but positive venom-specific IgE antibodies demonstrated by RAST. Therefore it may be reasonable to consider RAST testing for those rare patients who have a convincing history of anaphylaxis after an insect sting and who have negative skin test responses before concluding that VIT is not necessary. With rare exceptions, in vitro testing for venom-specific IgE is not a substitute for skin testing in making a diagnosis of stinging insect hypersensitivity. In addition, even a negative skin test response does not fully exclude the possibility of an anaphylactic reaction to a sting because such occurrences have been reported. It is not clear in these patients whether a non-IgE mechanism is responsible (eg, mastocytosis) or whether there is simply an inability to detect a trace (but clinically active) level of venom-specific antibodies.

Because the insect that caused the sting often cannot be identified, testing is usually done with all of the commercially available venom extracts. Venoms may contain shared antigenic components. Cross-sensitization and immunologic cross-reactivity have been demonstrated between hornet and yellow jacket venoms (vespids), are less likely to occur between vespid and wasp venoms, and are very unlikely to occur between honeybee and the vespid venoms.[18-23]

Skin testing for fire ant hypersensitivity

Imported fire ant whole body extract is the only reagent currently available for diagnostic testing in patients with suspected fire ant hypersensitivity. If screening prick test responses are negative, intracutaneous testing should be performed, with initial concentrations of approximately 1×10^{-6} wt/vol. Intracutaneous skin test concentration should be increased by increments until a positive response is elicited or a maximum concentration of 1×10^{-3} or 2×10^{-3} wt/vol is reached.[5,9,12]

Limited cross-reactivity exists between the antigens in fire ant venom and the antigens in venoms of other Hymenoptera.[23,24] If the patient is able to positively identify fire ant as the stinging insect, testing with other stinging insect venoms is not required. The presence of a pustule at the sting site at 24 hours after the sting is diagnostic of a fire ant sting. This type of reaction should be looked for carefully, especially if the sting occurred in an area where fire ant mounds have been sighted.

In vitro testing

In vitro testing can also be used for detection of venom-specific IgE antibodies in those individuals who cannot undergo skin testing. This includes patients with dermographism or severe skin disease. Generally, in vitro testing is less sensitive, being positive in only 80% of individuals who have positive venom skin test responses. Skin testing is therefore generally the preferred testing method.

IMMUNOTHERAPY FOR BEES AND VESPIDS

VIT has proven to be an extremely effective form of treatment for individuals at risk of insect sting anaphylaxis. VIT has been shown to reduce the risk of a subsequent systemic sting reaction to less than 3% compared with the risk of such reactions in untreated patients, which may be as high as 60%.[14,25,26] Moreover, those patients receiving VIT who experience systemic reactions after an insect sting generally have milder reactions.

Criteria for immunotherapy

Clinical studies have demonstrated that VIT effectively prevents systemic reactions in patients sensitive to stinging insect venom 97% of the time. Because the incidence of mortality and morbidity from insect stings is unknown, the impact of VIT is impossible to fully document. Even so, patients who have had a systemic reaction from an insect sting and are found to have venom-specific IgE should generally be started on VIT. The goals of VIT are to (1) prevent life-threatening reactions and (2) alleviate anxiety related to insect stings.

Cardiorespiratory reactions

Cardiac and respiratory symptoms of anaphylaxis are of greatest concern and are potentially life-threatening. The most common cardiovascular reaction is hypotension, which is usually associated with tachycardia. Such reactions may be difficult to distinguish from vasovagal reactions. Bradycardia may be a distinguishing aspect of vasovagal reactions but can occur rarely in anaphylaxis. Hypertension may also occur, presumably from release of endogenous sympathomimetic amines. Dyspnea may result from bronchospasm or from upper airway obstruction caused by mucosal edema. Adults and children who have had these reactions are at greatest risk for similar life-threatening reactions after subsequent stings. Therefore VIT is recommended for individuals with a history of these manifestations and the presence of venom-specific IgE.

Cutaneous reactions

Cutaneous systemic reactions consist of urticaria and occasionally angioedema or flushing associated with pruritis, which can be profound. Prospective studies have shown that patients 16 years of age and younger who have experienced cutaneous systemic reactions without other manifestations, have a 10% chance of having a systemic reaction if re-stung. If a systemic reaction does occur, it is likely to be limited to the skin.[13,27] Therefore VIT is not generally necessary for patients 16 years of age and younger who have experienced only cutaneous systemic reactions. VIT is still an acceptable option in such patients if requested by the patient's parents or if the child is likely to experience frequent or multiple stings.

VIT is generally recommended for patients greater than 16 years of age with systemic reactions limited to the skin. Because recent studies have suggested that these patients are at low risk of subsequent systemic reactions, some feel that immunotherapy is optional in this group of patients, whereas others maintain that immunotherapy is indicated.[11,26]

Large local reactions

Extreme swelling extending from the sting site, usually peaking at 48 to 72 hours after a sting, may be an IgE-mediated "late-phase" reaction. VIT is not effective in reducing large local reactions with subsequent stings. The risk of a systemic reaction in patients with a history of large local reactions is approximately 10%.[28] Because the risk of a systemic reaction is relatively low in patients who have previously had large local reactions, VIT is not generally recommended in such patients. Providing injectable epinephrine for use if a subsequent systemic reaction occurs to patients who have a history of local reactions, even if large, is optional. This decision may be influenced by factors such as the potential risk of being stung, personal health issues such as the presence of cardiovascular disease, and individual preference.

Challenge stings

Approximately 30% to 60% of patients with a history of anaphylaxis from an insect sting and a positive skin or in vitro test response for venom-specific IgE antibodies will experience a systemic reaction when re-stung. An intentional sting challenge has been recommended to better select those patients who need VIT.[29,30] Sting challenges, however, are neither reproducible nor without risk. About 20% of patients who do not react to a sting challenge will react after a second challenge. In addition, serious allergic reactions, such as anaphylaxis, have occurred from these challenges, necessitating intensive care treatment.

Thus the use of sting challenges remains controversial and is not considered a prerequisite for VIT in the United States.[31] Patients treated with VIT occasionally request a sting challenge to demonstrate that they are protected against a systemic reaction. If undertaken, a sting challenge should be performed with all the precautions one would use if it were assumed the challenge would result in a life-threatening reaction.

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/or nest. Conclusive data on which venoms to include for immunotherapy is not available. In the opinion of some authors, if the insect that caused the reaction can be clearly identified, the extract used for VIT need only contain that insect venom, despite positive skin or in vitro test responses for other stinging insects.[11,26] Other authors recommend that the extract contain venoms from all insects for which positive test responses were obtained.[14,25]

Immunotherapy for fire ant venom

Compared with other stinging insects, less is known about the natural history of fire ant hypersensitivity and the effectiveness of immunotherapy.[8,9] Fire ant whole body extract has been shown to contain relevant venom allergens and appears to be protective.[5,6,24,32-34] The relative efficacy of fire ant venom and whole body extract in the treatment of fire ant allergy has not been determined. The current criteria for starting immunotherapy for fire ants are similar to those for other Hymenoptera (ie, history of a systemic reaction and demonstration of fire ant antigen–specific IgE antibodies by skin or in vitro testing). Controversy exists regarding the management of

children who have systemic reactions that are confined to the skin. There has been no study that clearly demonstrates the relative risk of a systemic reaction in such a patient after subsequent stings. However, there is a great risk of fire ant re-stings in endemic areas.[35] Nevertheless, although the majority of allergists in fire ant–endemic areas do not routinely recommend immunotherapy for children who have had only generalized cutaneous reactions,[36] many do. Thus immunotherapy in these children is considered to be optional at the present time.

Dosage schedules for VIT

VIT injections are administered generally at weekly intervals, beginning with 0.1 to 0.5 μg and increasing to a maintenance dose of up to 100 μg per insect. There is some controversy about the optimum maintenance dose. The original studies suggested 100 μg as the maintenance dose.[25] Other authors have used the 50-μg dose successfully, whereas some feel that this dose offers a lesser degree of protection.[26,37]

The interval between maintenance dose injections is usually increased to 4-week intervals during the first year and eventually to every 6 to 8 weeks during subsequent years.[38] More accelerated schedules for VIT have been published and may be used successfully.[39-42]

The dosage schedule for fire ant immunotherapy is less well defined in terms of rapidity of buildup. However, most authors recommend a weekly buildup schedule until a maintenance dose is reached, and the interval between doses may then be increased. Most experts have recommended a maintenance dose of 0.5 mL of a 1:100 wt/vol extract, although there are some recommendations for a dose as high as 0.5 mL of a 1:10 wt/vol extract.[5,6,8,9] A recent survey of practicing allergists found that 0.5 mL of a 1:100 wt/vol extract is the most widely prescribed maintenance dose.[36] The use of higher doses for VIT may need to be given on an individual basis.

Safety considerations related to administration of VIT injections are generally the same as those for other forms of allergen immunotherapy. The major risk of VIT, as with other types of allergen immunotherapy, is anaphylaxis. One study reported that the incidence of systemic reactions from VIT was 12%, although this incidence is much higher than the general experience of most allergists.[43]

Patients who are taking β-adrenergic blocking agents and/or ACE inhibitors (see parameters on anaphylaxis) may be at greater risk if they experience an allergic reaction.[44,45] In addition, there are data to indicate that patients receiving ACE inhibitors may be at increased risk for development of anaphylaxis, as well as being more refractory to treatment with epinephrine if anaphylaxis develops.[46,47] Therefore patients who have stinging insect hypersensitivity should not be prescribed β-adrenergic blocking agents or ACE inhibitors unless absolutely necessary. If the patient who has stinging insect hypersensitivity cannot discontinue these medications, VIT should still be given, although with greater caution.

Serum sickness has occurred after insect stings, usually after an acute systemic reaction.[48,49] In such patients recurrence of serum sickness has not been observed after initiation of immunotherapy, although these patients are subsequently at greater risk of anaphylaxis after re-stings.[50] Immunotherapy has been effective in this group of patients.

Duration of VIT

Guidelines for discontinuation of VIT are evolving.[51] Whereas the package insert for the venom extract product recommends that VIT be continued indefinitely, a fall in serum venom-specific IgE antibodies to insignificant levels or conversion to a negative skin test response have been used as criteria for discontinuing treatment. However, 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.[11,52,54] However, patients with a history of severe anaphylaxis who continue to have positive skin test responses after 3 to 5 years of immunotherapy still may be at increased risk for a systemic reaction if VIT is stopped. Furthermore, despite negative RAST and/or skin test responses, some patients will ultimately experience a systemic reaction to a subsequent sting.[55] For these reasons, some experts recommend continuation of immunotherapy indefinitely in such patients as long as skin test responses remain positive.[56,57] Occasionally, because of anxiety, patients whose skin test responses become negative will wish to remain on immunotherapy, although the need for continued treatment is doubtful.

The optimal duration of imported fire ant immunotherapy has not been clearly established because of limited data. In one study of 17 patients, fire ant immunotherapy was discontinued after 2 to 19 years of treatment.[58] All patients were re-tested for specific IgE antibodies before and after being re-stung 3 months later. Thirteen of 17 (76%) had positive skin test responses after being re-stung, although 10 of these 13 had negative skin test responses for specific IgE antibodies at the time of discontinuing immunotherapy. Only 1 of the 17 had a systemic reaction when re-stung. This suggests that skin reactivity is a poor indicator of the risk for a systemic reaction to a fire ant sting after fire ant immunotherapy.

A recent survey of allergists indicated a great deal of variation in recommendations regarding duration of immunotherapy for fire ants.[36] Some allergists recommend indefinite treatment. Most allergists consider stopping immunotherapy after a specified period (usually 4 to 5 years), either empirically or only when skin test responses become negative. Until further data are available, a definitive recommendation about duration of immunotherapy for fire ants cannot be made.

SUMMARY

Stinging insect hypersensitivity is a potentially life-threatening condition. Management should include education related to avoiding subsequent stings, provision of

self-injectable epinephrine, and immunotherapy. Demonstration of venom-specific IgE should be done by skin or in vitro tests, and when test responses are positive, immunotherapy should be considered. VIT (or immunotherapy with whole body extract in the case of fire ants) should be provided to patients 16 years of age and younger who have experienced a systemic reaction involving more than the skin and any patient over 16 years of age who has had a systemic reaction. Once begun, VIT should be continued for at least 3 to 5 years. The appropriate duration of immunotherapy for fire ant hypersensitivity has not been conclusively demonstrated.

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