CLINICAL PRACTICE

Hypersensitivity to Hymenoptera Stings

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 29-year-old man reported that he was stung by a flying hymenopteran — he does not know what type — outside his door, where he had previously noted a nest. Skin itching, diffuse hives, swelling of his arms and legs, tightness in his throat, dizziness, and difficulty talking developed immediately, and he was taken to a local clinic where he received epinephrine and antihistamines. He was observed for two hours, and all symptoms resolved. How should his case be managed subsequently?

THE CLINICAL PROBLEM

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Insects of the order Hymenoptera, which includes ants, bees, hornets, wasps, and yellow jackets, have a stinging apparatus at the tail end of their abdominal segment and are capable of delivering between 100 ng (fire ants)[1] and 50 μg (bees)[2] of venom (Table 1 and Fig. 1). Although the venoms have various peptide and protein components, some of which are capable of inducing toxic or vasoactive responses, it has been estimated that about 1500 stings would be required to deliver a lethal dose of hymenoptera venom for a nonallergic adult who weighs 70 kg.[5] Despite this estimate, about 40 deaths a year are attributed to hymenoptera stings[6]; these deaths are ascribed to anaphylaxis occurring in persons with a history of prior stings in whom specific IgE antibodies developed to various venom components. Due to the vasoactive components of the venoms, most people experience a local reaction to hymenoptera stings consisting of redness, swelling, tenderness, and pain at the site of the sting. This reaction is self-limited and will resolve within hours. If the sting occurs near or within the oral cavity, there is a potential for respiratory compromise.

Fire-ant venom is composed primarily of a transpiperidine alkaloid that causes tissue necrosis. Most fire-ant stings produce a blister within 24 hours, which often fills with necrotic material, giving the appearance of a pustule (Fig. 2). Despite their appearance, these blisters are not infected and should be left intact.

Occasionally, persons will have swelling from a hymenoptera sting that may involve a large area and persist for up to a week. These large local reactions are not life threatening unless they involve the airway. They may result in considerable morbidity because of a temporary loss of function, such as occurs when the sting involves a foot or hand or is near an eye. Secondary infections can frequently complicate fire-ant stings when the pseudopustule is opened, and they can sometimes complicate other hymenoptera stings. Although it may be difficult in some cases to distinguish a secondary infection from a large local reaction, in the latter event the swelling usually peaks within 48 hours, whereas progression of swelling for more than two days, accompanied by fever or lymphadenitis, suggests secondary infection.

The reactions that lead to anaphylaxis, however, are of more concern than secondary infections. Some anaphylactic events are restricted to cutaneous findings (pruritus, urticaria, and angioedema). Others have a broader effect, with systemic symptoms that

may involve the gastrointestinal tract (metallic taste, nausea, vomiting, diarrhea, and abdominal cramping), genitourinary tract (uterine cramps), or nervous system (sense of impending doom, light-headedness, and dizziness). Reactions that involve the cardiopulmonary system (breathing difficulties, bronchospasm, hypotension, and arrhythmia) pose the greatest risk. Initial subjective symptoms may progress rapidly (in seconds to minutes) to life-threatening cardiopulmonary collapse. The risk of anaphylaxis with any event is dependent on the nature of the most severe previous reaction experienced by a patient (Table 2). Neuropathic and vasculitic responses and reactions that resemble serum sickness have in rare cases been reported after insect stings.[15,16]

STRATEGIES AND EVIDENCE

IMMEDIATE THERAPY

The optimal choice of immediate therapy for insect stings depends on the type of reaction. Strategies are based on anecdotal evidence. Local reactions are best treated symptomatically with nonsteroidal antiinflammatory agents, antihistamines, and cold compresses. Topical antihistamines and corticosteroids may also be used. When large local reactions occur, oral steroids are often added to the therapeutic mix.

The definitive therapy for anaphylaxis is epinephrine by injection (0.01 mg per kilogram of body weight; maximum, 0.3 and 0.5 mg per dose, for children and adults, respectively), and this should be administered to any patient who has more than a cutaneous reaction. Antihistamines are often added to treat cutaneous signs and symptoms. Supplemental oxygen, beta-agonists for bronchospasm, and intravenous fluids for hypotension are sometimes indicated. Occasionally, for a reaction that does not respond to the initial dose of epinephrine, steroids (oral or intravenous) are added, although definitive support for their addition is lacking.

There is a distressing tendency by both patients and physicians to treat anaphylaxis without using epinephrine,[17,18] perhaps because of concern about adverse effects of epinephrine on the heart. However, anaphylaxis itself has been associated with coronary vasospasm.[19-22] The fact that available data suggest that a failure or delay in administering epinephrine increases the chance of a fatal outcome in anaphylaxis[23] underscores the prevailing opinion that epinephrine must be considered the definitive therapy for anaphylaxis.

Epinephrine auto-injectors should be prescribed for any patient who has had an anaphylactic reaction to a hymenoptera sting. The instructions for use are printed on the side of each injector, but these should be reviewed with the patient when prescribing the medication. Patients should be educated to use epinephrine if signs or symptoms beyond a cutaneous reaction develop after a hymenoptera sting, and always to seek additional medical care after using an injector.

LONG-TERM THERAPY

Avoidance

The long-term goal is to prevent future systemic anaphylactic events. The optimal approach to prevent IgE-mediated disease is avoidance of the antigen, but this may not be feasible in practice. Current recommendations for avoidance are summarized in Table 1. The proximity of the habitats of wasps and fire ants to those of humans makes these insects the most likely members of the order to cause anaphylaxis.[24]

Immunotherapy

If avoidance of hymenoptera cannot be ensured, the next step is to minimize the potential for anaphylaxis if a sting should occur. Immunotherapy with hymenoptera venom has been shown to reduce the potential risk of anaphylaxis with subsequent stings significantly[13,14] (Table 2). Although the administration of whole-body extracts is no more effective than placebo therapy for treating the stings of flying hymenoptera,[13] whole-body extracts of fire ants appear to be as useful in preventing future reactions as is venom immunotherapy for flying hymenoptera,[25] perhaps because whole-body extracts of fire ants (in contrast to those of flying hymenoptera) contain adequate amounts of venom.[26] Whole-body extract therapy for fire ants has not been compared directly with fire-ant venom immunotherapy.

Evaluation

The evaluation of patients for whom immunotherapy is considered begins with a review of the history of stings and reactions. The circumstances of the sting may suggest a particular agent (Table 1). The presence of a stinger or a venom sac at the site of a sting suggests, but is not definitive of, a honeybee sting, as occasionally other hymenoptera may leave a stinger in place. Fire ants are usually easy to identify since they do not fly away and will grasp victims with their mandibles and inflict multiple stings if allowed (Fig. 2).

Table 1. Characteristics of Hymenoptera.

Common Name	Taxonomic Classification	Size	Nesting Habits	Feeding Habits	Aggressiveness	Venom Protein per Sting*	Avoidance Techniques
Honeybee	Family Apidae *Apis mellifera*	15–20 mm	Man-made hives	Nectar and pollen	Nonaggressive	50 μg	Avoid flower-print clothing Avoid flowery scents Wear shoes and socks outdoors
Africanized honeybee†	Family Apidae *Apis mellifera scutellata*	15–20 mm	Natural hives	Nectar and pollen	Aggressive	Approximately 50 μg	Avoid flower-print clothing Avoid flowery scents Wear shoes and socks outdoors Remove nests near homes
Fire ant	Family Formicidae *Solenopsis invicta*	4–6 mm	Mounds in disturbed soil	Omnivorous	Aggressive in defense of mounds	10–100 ng	Wear shoes and socks outdoors Wear gloves and pants when gardening Remove mounds near homes
Paper wasp	Family Vespidae Subfamily Polistinae Polistes species	20–25 mm	Single layer hanging from eaves, porches	Nectar and arthropods	Aggressive in defense of nests	NA	Avoid flower-print clothing Avoid flowery scents Remove nests near homes
Yellow jacket	Family Vespidae Subfamily Vespinae Vespula species	15–20 mm	Multilayered, usually underground	Scavengers	Very aggressive	2–20 μg	Avoid open food sources, picnic areas, garbage Remove nests near homes
White-faced or bald-faced hornet	Family Vespidae Subfamily Vespinae Dolichovespula species	25–35 mm	Multilayered, usually in open areas	Nectar and arthropods	Aggressive in defense of nests	NA	Avoid flower-print clothing Avoid flowery scents Remove nests near homes
European hornet	Family Vespidae Subfamily Vespinae Vespa species	25–35 mm	Multilayered, usually in open areas	Nectar and arthropods	Aggressive in defense of nests	NA	Avoid flower-print clothing Avoid flowery scents Remove nests near homes

* NA denotes that data are not available.

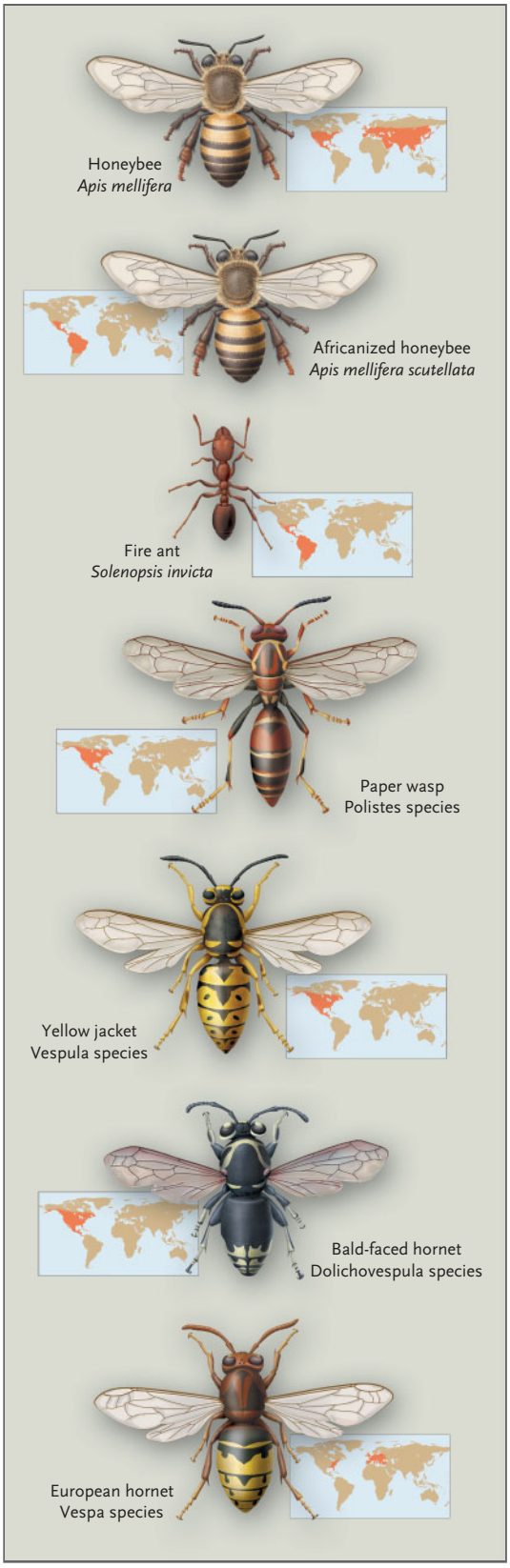
† The subspecies of honeybee called "Africanized" is more aggressive than the parent species and has caused some clinical problems in South and Central America and in south Texas. The venom is similar to honeybee venom, which may therefore be used in testing and treating patients who have had anaphylaxis after being stung by this subspecies.[3,4]

The clinical course is also reviewed to verify the diagnosis of anaphylaxis. It is sometimes difficult to separate anxiety symptoms from true anaphylaxis in the setting of a sting. This is especially true if there are no documented objective findings, such as urticaria, hypotension, or air-flow reduction. However, when patients are concerned enough to seek an evaluation even with an unclear or remote history, it is appropriate to test them for specific IgE antibodies. If the results of these tests are negative, patients can be reassured; if they are positive, immunotherapy should be offered. Age is also important. Studies have shown that in children under the age of 16 years who have cutaneous anaphylaxis (urticaria, angioedema, or both), the risk of systemic (in addition to cutaneous) anaphylaxis in response to future stings is only slightly greater than the risk in the general population[6] (Table 2). It is uncertain whether the same is true in adults.

Subsequent evaluation involves testing for the presence of specific IgE antibodies.[27,28] Initial testing is usually delayed for four to six weeks after the sting event to eliminate the possibility of a false negative result caused by a depletion of mediators in the setting of anaphylaxis. If the particular agent is known, then testing includes only that insect. It is often unclear which insect was the perpetrator, in which case testing of sensitivity to each of the flying hymenoptera is warranted.

Typically, testing involves in vivo skin testing for specific IgE antibodies; this is more sensitive than in vitro methods, which are an alternative. The prick method (a needle pricks the skin through a drop of the antigen) is used as the first step (a dilution of 1:1000 weight/volume [wt/vol] for fire-ant venom; 1 μg per milliliter for venom from other hymenoptera). If the result of this test is negative, testing proceeds with an intradermal method (antigen is injected into the dermis), usually using about 0.001 μg per milliliter (1:1,000,000 wt/vol for fire-ant venom)

Figure 1. Species of Hymenoptera and Their Geographical Distribution.



and increases sequentially by 10 times the previous amount to 1.0 μg per milliliter (1:1000 wt/vol for fire-ant venom); above these concentrations, false positive test results may occur. Testing is stopped when the skin test is positive (the reaction is equivalent to or greater than a histamine control). If the maximal intradermal dose is reached without a positive response, the test result is considered negative. If a false negative result is suspected (on the basis of a history suggestive of anaphylaxis), or for patients who cannot be skin-tested (those who have severe dermatitis or who are receiving medications that suppress the histamine response), in vitro methods are reasonable alternatives. Immunotherapy is then offered to anyone who has both a history consistent with anaphylaxis after a sting and specific IgE antibodies to the potential agent, as demonstrated by positive results on skin testing or in vitro testing.

Whereas there may be extensive cross-reactivity between some venom components, such as antigen 5 (one of the more potent vespid antigens), there are enough highly specific components of the venoms (including differences between molecules common to all the venoms, such as phospholipases)[29] to support the recommendation that all venoms for which skin testing yields positive results should be used in treatment. Treatment with more than one venom can be administered concurrently, but this generally requires multiple injections per visit; an exception is the commercial preparation that is a mixture of venoms from the yellow jacket, white-faced hornet, and yellow hornet (maximal dose, 100 μg of each species' venom).

Therapy

Immunotherapy starts at 0.1 μg per milliliter for most hymenoptera venoms (1:100,000 wt/vol for fire-ant venom). Each subsequent dose increases the amount of venom delivered to the patient, generally until a dose of 100 μg per milliliter for the venom of flying hymenoptera (0.5 ml of 1:100 wt/vol for fire-ant venom) is reached; 100 μg is twice the dose to which a patient would be exposed in a routine sting, and it is the dose used in initial studies showing the effectiveness of venom immunotherapy. Usually the doses are delivered once a week. This

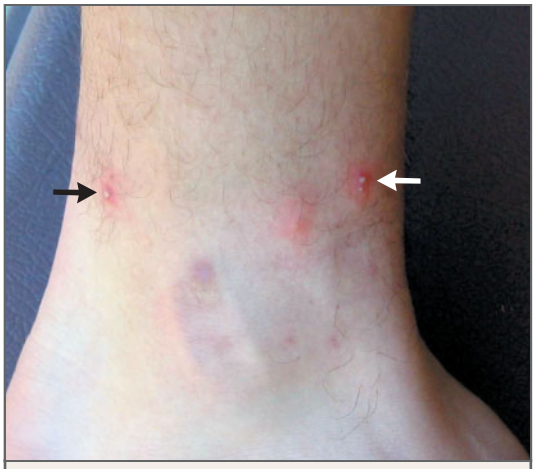


Figure 2. Stings from a Fire Ant on an Ankle, Showing the Pseudopustule.

The clustering of the stings (white arrow) contrasts with the single sting (black arrow) in the photograph, which was taken 24 hours after the event. This pattern is typical of fire-ant stings, as one ant will often inflict multiple stings in a semicircular arc if given time to do so. Also, the pseudopustule is typical of fire-ant stings; it is not a pustule. The stings occurred just above the level of the ankle sock the patient was wearing on the day of the event.

means there is a three-to-six-month period required to reach the maintenance dose. So-called rush protocols have been published,[30-32] in which a shorter dosing interval is used to reach maintenance doses in weeks or even days, and they appear to provide good protection from sting challenges. These are particularly useful when the risk of exposure is high and ongoing, as may occur with patients who must work or play outdoors.[33] These protocols have not been compared directly with standard immunotherapy protocols in randomized controlled trials, but they have been found to give reasonably equivalent protection against direct sting challenges.

When a maintenance level is reached, the interval between injections is often expanded to one month. Some observational data suggest that the interval may be expanded to 8 or even 12 weeks without losing protection.[34,35] The maintenance dose and interval may be adjusted on the basis of clinical criteria. For instance, if a patient receives a sting that results in symptoms while receiving maintenance immunotherapy, the dose interval may be shortened or the dose increased to more than 100 μg.[36]

Protection after a course of immunotherapy appears to last a long time. In a recent report involving a follow-up evaluation of children 10 to 20 years after they had received immunotherapy, only 5 percent of the children with a history of a moderate-to-severe sting reactions who reported a subsequent sting had had a recurrent systemic reaction, as compared with 32 percent of untreated children with a similar history.[37]

The risks associated with hymenoptera immunotherapy are the same as for other allergen immunotherapy. The risk of anaphylaxis after an immunotherapy injection is low (fewer than 1.6 reactions per 100 injections).[13] The majority (88 percent) of patients complete an immunotherapy course without reactions, and most reactions that occur are mild.[38] Rarely, more severe reactions occur, including death (about 1 in 5 million injections for all types of immunotherapy).[39] Therefore, immunotherapy should be administered only in a medical setting by trained personnel capable of recognizing and treating anaphylaxis.

AREAS OF UNCERTAINTY

An important unanswered question relates to the optimal duration of maintenance immunotherapy. The package insert that comes with the venom immunotherapy recommends indefinite use, whereas current clinical guidelines recommend discontinuing immunotherapy after three to five years of the maintenance-level dose,[40,41] especially if the patient no longer has specific IgE antibodies (as evaluated by repeated skin testing).[42,43] However, data from patients who have not received immunotherapy indicate that the loss of these antibodies is no guarantee that anaphylaxis will not occur. In one report, 98 patients (including patients with and patients without a history of anaphylaxis) who had positive tests for specific IgE antibodies at baseline slowly lost their positive responses over time. However, the risk of anaphylaxis was not eliminated; at a mean of four years after initial evaluation, approximately 17 percent of patients (11 of 65) who had subsequent stings had anaphylactic reactions, despite the presumed loss of specific IgE antibodies.[44] Other reports have documented reactions to hymenoptera stings after discontinuing immunotherapy.[37,45] Given these data, some allergists extend venom immunotherapy longer than the suggested three to five years. Consideration of an extended course may be warranted particularly for patients who have had a severe reaction (for such patients, some allergists might continue immunotherapy indefinitely).

Another area that requires additional research is the treatment of patients who have a history of a reaction suggestive of anaphylaxis but in whom testing for specific IgE antibodies yields negative results. One potential explanation is that the earlier reaction was not to hymenoptera; the stings or bites of other insects (mosquitoes, biting flies, and reduvids) and arthropods (spiders, scorpions, and ticks) may also result in anaphylaxis. In rare cases, people with mastocytosis may have an anaphylactoid response to hymenoptera stings without actually having specific IgE antibodies.[46] A more common explanation is the imperfect sensitivity of tests for specific IgE antibodies.[10,47,48] Twenty percent of patients with negative in vitro tests will have positive results on skin testing, and 10 percent of patients whose skin test is negative will have positive results on in vitro testing.[49] In cases in which the suspicion of hymenoptera hypersensitivity is high, and initial tests are negative, it has been recommended that repeated testing be undertaken with both in vivo and in vitro methods.[50,51]

Table 2. Risk of Anaphylactic Reactions to Hymenoptera Stings after an Initial Event.

Patient History*	Approximate Risk of Anaphylaxis (%)†	Immunotherapy If Skin Test or in Vitro Test Is Positive for Antibodies
Unknown history	3	No
Large local reactions	10	No
Cutaneous anaphylaxis in child	10	No
Systemic anaphylaxis in child	50–60	Yes
Anaphylaxis in adult	50–60	Yes
Receiving immunotherapy	2	Not applicable

* The risk in the general population refers to the risk in adults; the risk may be lower in children. Large local reactions are defined as persistent swelling of up to a week's duration; cutaneous anaphylaxis in a child is characterized by pruritus, urticaria, or angioedema. The risk of anaphylaxis for adults with cutaneous reactions only may be as low as it is for children, but this is yet to be determined.

† The data in this table are from Golden,[7] Settipane and Boyd,[8] Chaffee,[9] Golden et al.,[10] Graft et al.,[11] Schuberth et al.,[12] Hunt et al.,[13] and Golden et al.[14]

GUIDELINES

Under the joint auspices of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology, the *Journal of Allergy and Clinical Immunology* will publish the newest set of guidelines for insect hypersensitivity this year.[52] In general, the recommendations presented here are consistent with these guidelines.

SUMMARY AND CONCLUSIONS

For patients with a clear history of anaphylaxis, such as the one described in the vignette, information should be provided on avoidance and on the use of emergency treatment with epinephrine auto-injectors. Patients should be advised to carry an auto-injector and to wear a medical alert bracelet. Referral to an allergist is warranted, and skin testing should be performed for sensitivity to honeybees, wasps, white-faced hornets, yellow hornets, and yellow jackets. Venom immunotherapy should be administered for all venoms for which testing results are positive. The protective benefit is expected from the immunotherapy by the time maintenance dose is reached, usually by three to six months with standard protocols. A rush protocol would be recommended if the patient's risk of being stung again before standard immunotherapy could work were considered high. Although immunotherapy is often administered by allergists, it may be delivered by any practitioner who is willing to observe the patient and to treat anaphylaxis if it should occur.

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