

Stinging insect allergy and venom immunotherapy

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ABSTRACT

The Hymenoptera order is divided into three families: Apidae, Vespidae, and Formicidae. Apidae include the honeybee, bumblebee, and sweat bee, which are all docile and tend to sting mostly on provocation. The Africanized killer bee, a product of interbreeding between the domestic and African honeybee, is very aggressive and is mostly found in Mexico, Central America, Arizona, and California. The yellow jacket, yellow hornet, white (bald) faced hornet, and paper wasp all belong to the Vespidae family. The Formicidae family includes the harvester ant and the fire ant. When a "bee" sting results in a large local reaction, defined as >10 cm induration and lasting > 24 hours, the likelihood of anaphylaxis from a future sting is approximately 5%. For comparison, when there is a history of anaphylaxis from a previous Hymenoptera sting and the patient has positive skin test results to venom, at least 60% of adults and 20–32% of children will develop anaphylaxis with a future sting. Both patient groups should be instructed about avoidance measures and about carrying and knowing when to self-inject epinephrine, but immunotherapy with Hymenoptera venom is indicated for those patients with a history of anaphylaxis from the index sting and not for patients who have experienced a large local reaction. Immunotherapy is highly effective in that, by 4 years of injections, the incidence of subsequent sting-induced reactions is 3%. This incidence may increase modestly after discontinuation of injections but has not been reported to be > 10% in follow up.

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An anaphylactic (systemic) reaction to a stinging insect occurs in 0.5–3.3% of the general population in the United States. Most reactions occur in subjects who are <20 years of age, but fatalities tend to occur in adults, with increasing fatalities as age increases.^{1,2} Insect sting anaphylaxis accounts for at least 40 deaths per year in the United States.¹ The most common trigger of allergic reactions is the yellow jacket.

CLASSIFICATION

There are nine flying insects in the Hymenoptera order that are known to cause anaphylactic reactions. They are divided into three families: Apidae, Vespidae, and Formicidae. The Apidae include the honeybee, bumblebee, and sweat bee, which are all docile and tend to sting mostly on provocation. The Africanized killer bee (found mostly in Mexico, Central America, Brazil south to northern Argentina, Texas, Oklahoma, New Mexico, Arizona, southern Nevada, southern California, western Louisiana, and central and southern Florida) is a product of interbreeding between the domestic and African honeybee, and is very aggressive.

An Africanized honey bee can chase a person for up to 400 m. The yellow jacket, yellow hornet, white (bald) faced hornet, and paper wasp all belong to the Vespidae family. Yellow jacket nests are located in the ground or in rock gardens, and yellow jackets tend to be attracted to garbage, open soda cans, punch bowls, and picnic tables. The hornets are commonly found in shrubs, whereas paper wasps nest in the eaves of homes or inside of walls. The Formicidae family includes the harvester ant and the fire ant. They are found in the southeast and southwestern United States, and are capable of causing systemic allergic reactions. The sting causes a painful, erythematous reaction, followed by a wheal. Within 4 hours, a clear pustule forms. The pustule can last 3–10 days. The pustule is often mistaken for cellulitis, although secondary infections may occur. Immunotherapy (IT) is indicated in patients who have a positive skin test result to fire ant whole-body extract.

TYPES OF REACTIONS

There are five types of sting reactions: normal, local, rare, toxic, and anaphylactic. A normal reaction is characterized by erythema (<5 cm in diameter), swelling, and pain. It is transient in nature and limited to the area of the sting. Treatment consists of cold compresses and analgesics. A large local reaction (induration > 10 cm) and that lasts > 24 hours has as high as a 7–17% incidence in the general population. Local reactions are characterized by extensive erythema and swelling, and can last from 1 to 10 days.^{1,3} It is important to distinguish large local re-

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actions from an anaphylactic reaction. A large local reaction is contiguous along a joint line (*i.e.*, entire arm swelling), whereas an anaphylactic reaction skips contiguous joint lines (*i.e.*, sting on the hand and hive on the lip).¹ The treatment for large local reactions is ice, elevation if feasible, analgesics, and, at times, a course of an oral corticosteroid (not evidence based). When there is a Hymenoptera sting on the forehead, the massive swelling of the face, scalp, and eyelids can cause a disfiguring appearance.

In the absence of evidence for anaphylaxis, this reaction is categorized as a large local reaction. Individuals who develop large local reactions typically have a similar reaction on a subsequent sting. Patients with large local reactions have an approximate 7% (range, 4–15%) chance of a systemic (generalized urticaria) reaction to a future sting.¹ The risk of anaphylaxis in these individuals is <5%, and, therefore, patients do not require IT.^{1,2} Rare reactions include serum sickness for which IT may be indicated. In serum sickness, there is urticaria, painful arthralgias, malaise, and fever approximately 7 days after an insect sting.⁴ There is a risk of anaphylaxis with a repeated sting in these individuals, so IT should be considered when the skin test result is positive. Neurologic-, nephritic-, vasculitic-, and encephalitic-like reactions are other rare reactions that have been reported to occur up to 2 weeks after the implicated sting. Toxic reactions occur after multiple simultaneous stings, which results in hypotension, cardiovascular collapse, and, possibly, death. IT is indicated for toxic reactions when patients have positive skin test results. Because it is an allergic emergency, with sudden onset and rapid progression, anaphylactic reactions to stinging insects imply a risk of death.

TESTING

The immediate-onset (anaphylactic) reactions are mediated by immunoglobulin E (IgE) antibodies to particular or cross-reacting venoms.^{1,2,5} This results in mast cell activation, which leads to mediator release with cutaneous and systemic signs and/or symptoms of anaphylaxis. Fifty percent of adult subjects (range, 25–75%) and as high as 20–32% of children with a history of anaphylaxis from a previous sting will have anaphylaxis with a repeated sting.^{1,2} Moreover, IT for these individuals provides protection from anaphylaxis in 97% of re-stings.^{1,2} Thus IT is indicated for patients with a history of anaphylaxis and positive skin test results (that demonstrate venom-specific IgE antibody).

Testing should be done at least 3 weeks after the suspected anaphylactic event because it may take 2–3 weeks for venom-specific IgE to become detectable. Some patients have a convincing history of anaphy-

Table 1 Indications for VIT in patients with positive skin test results

Reaction	VIT
"Normal" transient pain, swelling	No
Extensive local swelling (large local)	No
"Mild anaphylaxis" (also known as systemic reaction): generalized urticaria	No*
Moderate or severe anaphylaxis	Yes
Serum sickness	Yes
Toxic reaction	Yes
Indolent systemic mastocytosis	Yes#
Mast cell activation syndrome	Yes#

VIT = Venom immunotherapy.

* Controversial in children, adolescents, and adults; VIT may be indicated in patients with "frequent exposure, impaired quality of life, or underlying medical conditions" (from Ref. 1).

In some patients, an argument can be made to even treat with immunotherapy those patients with negative skin test results to venom.

laxis but negative skin testing results. This may represent a nonimmunologic reaction or perhaps a loss of reactivity when there is a remote history of a sting reaction.^{1,2} If the initial skin test is negative then repeated skin testing is advisable after 3–6 months.^{1,2} Some experts have argued that *in vitro* testing⁶ is advised in this setting, but the administration of IT should be with an extract that causes a positive skin test result. Children < 16 years of age and with a history of a cutaneous systemic reaction (hives and/or angioedema¹) do not necessarily require venom IT (VIT) because it is less likely that they will experience severe anaphylactic shock with future stings.¹

In particular cases, it may be appropriate to administer VIT to a child or adolescent who has experienced acute urticaria and angioedema and who has positive skin test results. In accordance with the 2016 practice parameters, VIT generally is not required for patients ages > 16 years who have "only" experienced cutaneous systemic reactions.¹ (Table 1). Baseline tryptase concentrations are elevated (>11.4 ng/mL) in a subset of patients with known venom hypersensitivity. Some of these patients were found to have occult indolent systemic mastocytosis or monoclonal mast cell activation syndrome.⁷ Venom-associated anaphylaxis may be the presenting finding of indolent systemic mastocytosis or the monoclonal mast cell activation syndrome. The estimated frequency of indolent systemic mastocytosis in adult patients with an insect allergy is 2%, whereas insect allergy in patients with indolent systemic mastocy-

tosis is estimated at a 25% frequency.¹ Basophil activation testing may add sensitivity to a diagnosis and might, someday, help predict which patients are at risk of severe anaphylaxis¹

VIT DOSING AND SCHEDULES

Refer to Table 1 for VIT indications. Skin testing is administered by using five Hymenoptera venom protein extracts: honeybee, yellow jacket, yellow hornet, white-faced hornet, and wasp. Typically, testing starts with a prick test at 0.01 $\mu\text{g}/\text{mL}$ if the reaction was very severe, with subsequent intradermal testing at 0.0001, 0.001, 0.1, and 1.0 $\mu\text{g}/\text{mL}$. For fire ants, whole-body extracts are used for skin testing. In most cases, IT is administered with all the venoms that tested positive. Therapy for VIT begins at 0.05 μg , with incremental doses every week until maintenance dosage of 100 μg (300 μg if mixed vespids) is achieved. Once the patient has reached maintenance, he or she can gradually convert to monthly injections the first year and then perhaps every 6 to ≥ 8 weeks during the subsequent 3 years or until the skin test result becomes negative. VIT decreases the risk of re-sting reaction in adults from 60% to 3%.² A patient having undergone or still undergoing VIT is still at risk of developing an anaphylactic (systemic) reaction if stung, so he or she should always carry an epinephrine autoinjector. The rate of systemic reactions to VIT is 3–12% per course of IT, which is similar to aeroallergen IT.^{3,8}

TREATMENT

Avoidance is a major therapeutic intervention in preventing death from these insects. Measures include wearing long-sleeved, light-colored clothing, shoes, and hats; and being cautious in picnic areas, by covering food, avoiding drinking from open beverage cans, and not wearing perfume or cologne. Fire ant mounds are orange in color and can be found present underground for up to 20 feet. Thus, there is a case for wearing shoes or hard sandals and for avoiding areas where there are fire ant mounds.

Along with teaching self-administration of the epinephrine autoinjector, it is important to emphasize the need to carry an epinephrine autoinjector at all times, regardless of whether the patient has received VIT.^{1,2} Teach the patient to know that anytime he or she uses an epinephrine autoinjector, he or she needs to go to the hospital for further evaluation. Acute medical therapy for systemic reactions includes the usual treatment for anaphylaxis: intramuscular epinephrine (or intravenous if the patient is hypotensive), H_1 antihistamines, corticosteroids, intravenous hydration, and other supportive therapy for distributive shock. Discontinuation of VIT usually occurs

after 4 to 5 years, despite a persistently positive skin test result or when skin test results become negative after 4 years of injections.² This recommendation is based on evidence 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; however, one might consider almost indefinite IT in patients with severe anaphylaxis complicated by shock or loss of consciousness or the patient's occupation or level of exposure (e.g., a fireman).

IMMUNOLOGY

- IgG antibodies are capable of blocking *in vitro* venom-induced histamine release from basophils of patients who are allergic.
- Passively administered immunoglobulin from beekeepers provides temporary immunity from venom anaphylaxis in patients who are sensitive.
- The concentration of IgG produced is proportional to the amount of exposure to venom.

CLINICAL PEARLS

- Appropriate, prompt treatment of anaphylactic reactions to venom stings is indicated, with intramuscular epinephrine first (before H_1 antihistamines or corticosteroids).
- Teach patients avoidance measures, such as wearing light-colored clothing, avoiding perfumes, and not walking barefoot on the grass or sand.
- Classification of an allergic reaction and demonstration of antivenom or anti-fire ant extract IgE antibodies helps to determine when IT is necessary.
- Risk factors for severe anaphylaxis to insect stings or VIT include a basal tryptase concentration of >5 ng/mL, possibly the use of angiotensin-converting enzyme inhibitors, vespid allergy, older age, and male sex.⁹
- The number "needed to treat"¹⁰ for an adult patient receiving VIT for a history of anaphylaxis to stinging insect and positive skin test results is 2 ($1/[0.60 - 0.03]$) or $1/0.57$ derived from $1/(\text{the risk of anaphylaxis in the untreated group} - \text{the risk of anaphylaxis in the treated group})$. This is a remarkably low number. For children in whom the risk of a repeated anaphylactic reaction after IT is approximately 20%, the number needed to treat is $1/(0.20 - 0.03)$ or 6, also a very low number. (Few treatments of any kind for any condition are as effective as VIT).

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