

Hymenoptera (Apid and Vespid) Allergy: Update in Diagnosis and Management

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Allergic reactions to Hymenoptera stings range from large local reactions to life-threatening anaphylaxis. Over the last 20 years, significant progress has been made using venom extracts in the diagnosis and treatment of Hymenoptera allergy. Despite these advances, there is still room for improvement in increasing the sensitivity of venom allergen skin testing. The venom allergic patient with negative skin tests poses special problems in management. It is important to note their increased risk with a subsequent sting. Guidelines to be used in determining the duration of venom immunotherapy are still evolving. Knowledge of the risks of discontinuing venom immunotherapy and risk factors associated with anaphylaxis with subsequent stings are required to form an individualized approach to treatment.

Introduction

Allergic reactions to insect stings range from local swelling and pruritus to anaphylaxis to death. Prevalence of severe allergic reactions to stinging insects ranges from 0.4% to 0.8% in children to 3% in adults [1,2]. Stinging insect anaphylaxis accounts for at least 40 deaths per year in the United States [3]. It is quite likely that this number is higher because of cases where the stinging insect anaphylaxis is not detected or reported. More commonly, reactions consist of widespread local reactions in approximately 15% of adults. [2] Fully characterizing the extent of the allergic reaction to the stinging insect and proper identification of the insect by visualization and skin testing are imperative in outlining a complete management plan to decrease risk of severe anaphylaxis with a subsequent sting. Once the stinging insect is identified by skin testing, immunotherapy may be instituted to significantly decrease the risk of anaphylaxis with a subsequent sting. Difficulties arise in dealing with the negative skin test reactor with a strong clinical history of stinging insect reaction. The length of time immunotherapy is required has recently been called into question and needs to be addressed on an individual basis based on risk factors.

Identification of Stinging Insects

The stinging insects belong to the order Hymenoptera of the class Insecta. The Hymenoptera are further divided into the apid and vespid families. The apid family includes honeybees and bumblebees, and the vespid family includes yellow jackets, wasps, and hornets. Though members of the same family and despite the presence of some cross-reactivity between the venoms, the vespids differ in venom antigenicity, appearance, habitat, and aggressiveness. Thus, yellow jackets, wasps, and hornets are not interchangeable, and separate venoms are used in immunotherapy.

The major allergenic components of honeybee venom are phospholipase A₂, hyaluronidase, acid phosphatase, allergen C, and melittin. Recently, a new bee venom allergen has been identified, Api m 6 [4•]. This 8-kD protein was recognized by IgE antibodies in greater than 40% of bee-sensitive patients. Studies of this kind are important in an attempt to identify all the allergens from the venom. It appears this would be necessary to achieve protection with recombinant peptide immunotherapy. A pilot study with T cell epitope immunotherapy for phospholipase A₂, the major bee allergen, resulted in protection in three of five patients with live bee stings [5]. In the two with a reaction, it appeared the patients were sensitized to other bee venom allergens besides the phospholipase A₂. The major allergenic components of the vespid venoms are phospholipase, hyaluronidase, and antigen 5. Though similar, the cross-reaction between the apids and vespids is limited.

There are characteristics of the apids and vespids that may be helpful in implicating which stinging insect has caused a reaction. Though these characteristics are helpful, they are not definitive, and positive skin testing is required to commence immunotherapy. Honeybees are generally docile and do not sting without provocation. Honeybee nests may be found in tree hollows or buildings. Honeybees always leave a barbed stinger and attached venom sac. Therefore, the presence of a stinger implies a honeybee sting, though vespids may leave a stinger in 4% to 8% of cases [6]. Yellow jackets are ground-dwelling insects and may be encountered during yard work. They tend to sting with minimal provocation and are attracted to human food. Hornets build large paper-like hives that are found in trees. Wasp nests have a honeycomb appearance and typically are found under house eaves,

outdoor furniture, or shrubbery. Characteristics of the Hymenoptera are outlined in Table 1.

Reactions to Stinging Insects

Typically, a sting reaction results in pain, erythema, and swelling at the site of the sting. The presence of the pain helps separate it from an insect bite. The symptoms usually resolve in a few hours. Application of a cold compress or use of analgesics may be used to help relieve symptoms.

Large local reaction

A large local reaction is similar but involves more extensive erythema and edema. A usual scenario is a sting on the hand resulting in erythema and edema involving the entire forearm without any skin manifestations elsewhere. This reaction typically peaks at 48 hours and lasts a few days. Though the mechanism is unclear, it appears that it is IgE-mediated as a large number of patients will have positive skin tests to the stinging insect. If stung again by the same insect, the same reaction usually occurs. The risk for anaphylaxis with a subsequent sting is less than 5% [7]. Venom immunotherapy does not help reduce the risk of subsequent large local reactions with future stings. Venom immunotherapy is not recommended in patients with large local reactions only.

Anaphylaxis

Systemic reactions to insect stings may range from mild (dermal only) to life threatening. Dermal reactions include urticaria and angioedema. Symptoms of anaphylaxis from stinging insects are similar to anaphylaxis of any cause and include urticaria, angioedema, bronchospasm, tachycardia, hypotension, vomiting, and diarrhea. Symptoms of anaphylaxis usually begin within 10 minutes of the sting, though delayed anaphylaxis has been reported [8]. Interestingly, repeat sting by the identical species of stinging insect will result in repeat anaphylaxis in only 30% to 60% of patients with the higher percentage in those with a more severe initial reaction [9–11]. There does not seem to be good correlation between the severity of the reaction and the size of the reaction to the skin test or titer of venom-specific IgE. Some anaphylactic reactions may be followed by a late-phase reaction occurring 4 to 12 hours after the initial reaction [12]. The mechanism of the late reaction is poorly understood, and the patient should be observed for 8 to 12 hours after the sting.

Toxic reaction

Toxic reactions to stinging insects may occur in a person after multiple (50 to 100) simultaneous stings. Clinically, the reaction resembles anaphylaxis. These reactions are likely due to the vasoactive amines, peptides, and enzymes found in the venom and are not allergic in mechanism. This type of reaction may cause IgE sensitization, putting these patients at a higher risk of an allergic reaction with a subsequent sting.

Diagnostic Testing

Because the stinging insect is often not easily identified by the patient, skin testing is performed to both the apids and vespids. Though these families have similar enzymes, there is little cross-reactivity. Honeybees are not native to North America and were not present until imported by the colonists. Immunochemical distinction is shown by lack of cross-reactivity between hyaluronidase enzyme in the honeybee and the vespids. However, the enzyme may be positive across the vespid family—yellow jacket, yellow hornet, and white-faced hornet. It is difficult to know if this represents antibody to one venom with cross-reactivity to several venoms or increased susceptibility to an allergic reaction from a number of venoms. Radioallergosorbent (RAST) inhibition studies may help determine this. Timing is critical in the skin testing. Skin tests performed within 4 weeks of the reaction may be falsely negative [13]. The mechanism for this is unknown. Therefore, if the skin tests are negative when performed within this time frame, they should be repeated at least 4 weeks after the time of the reaction.

Skin tests are performed initially by prick and, if negative, then intradermally. Initial intradermal tests use concentrations of 0.001 to 0.01 $\mu\text{g/mL}$. If testing at these concentrations is negative, the dose is increased in tenfold increments to a maximal test dose of 1 $\mu\text{g/mL}$. Positive responses at these concentrations are considered indicative of IgE venom-specific sensitivity, though there is concern about possible irritant reaction at 1 $\mu\text{g/mL}$ concentration [14]. Skin tests to Hymenoptera are safe, with a severe reaction to the test occurring in only 0.25% of patients [15]. There have been occasional reports of patients with a strong history of allergic reaction to stinging insects in whom the skin tests were negative and who subsequently reacted to later stings, but there has been little guidance available for managing these patients. Recently, Golden *et al.* [16••] published the first report to specifically look at the response to sting challenges in a large number of patients with negative skin testing. In the 51 patients sting challenged, 11 (22%) reacted. Of the responders, nine (of 37 with positive RAST) had positive RAST testing with venom-specific IgE levels of 1 ng/mL and two (of 11 with negative RAST) had negative RAST testing. The vast majority of those challenged were sensitive to yellow jacket, with only two patients sensitive to wasp. There were no honeybee-sensitive patients challenged. The reaction rate was higher in patients with negative skin tests and positive RAST (24%) than negative skin tests and negative RAST (14%), though this was not statistically significant because of the small number of patients in the latter group. They recommend RAST evaluation in patients with negative skin testing and repeat skin testing at 3 to 6 months. In general, though, RAST testing is not considered a substitute for skin testing because of an approximately 20% lower sensitivity [14,16••]. Improved diagnostic tests are still needed in venom allergy.

Table 1. Characteristics of Hymenoptera (apids and vespids)

Family	Common names	Allergens	Distinguishing traits
Apidae	Honeybee	Phospholipase A2	Leave stinger and sac
	Bumblebee	Hyaluronidase	Nonaggressive
	Sweatbee	Melittin	Live in hives, tree hollows
		Acid phosphatase	
		Api m 6	
Vespidae	Yellow jacket	Phospholipase A1	Aggressive, live in ground
	Yellow hornet	Hyaluronidase	Feed on human food
	White-faced hornet	Acid phosphatase	Make paper-like nests
	Paper wasp	Antigen 5	Make honeycomb nests

Table 2. Candidates for venom immunotherapy

Reaction to insect sting	Patient population
Severe anaphylaxis	Children, adults
Moderate anaphylaxis	Children, adults
Urticaria only	Adults
Large local reaction	None

One of the major reasons for performing skin testing is to determine suitability for immunotherapy. Patients with positive skin testing who have experienced a systemic reaction to Hymenoptera are considered suitable candidates for immunotherapy. There is a distinction, though, between children and adults who have urticarial reactions only. Children with urticarial reactions only have not been shown to be at significantly higher risk if stung again; therefore, immunotherapy is not indicated for this group [17••]. In adults, however, a generalized urticarial reaction is considered an indication for immunotherapy. Large local reactions only are not an indication for immunotherapy; therefore, testing should be pursued only for other reasons. Table 2 summarizes indications for venom immunotherapy.

For people who have never had a reaction to insect stings, testing is not indicated. Approximately 15% of people who have never had a sting reaction will have a positive skin test to venom. [18]

Acute Management

The initial steps in the treatment of anaphylaxis due to insect sting is the same for any cause of anaphylaxis. This includes control of the airway, breathing, and circulation. Epinephrine is the main medication used to counteract anaphylaxis and should be given as soon as possible. This can be given intramuscularly or subcutaneously. The usual dosage is 0.3 to 0.5 mL of 1:1000 epinephrine, which is equivalent to 0.3 to 0.5 mg. The dosage for children is 0.01 mg/kg. In patients with severe or protracted reactions, multiple doses of epinephrine may be necessary in addition to other supportive measures, such as intravenous fluids, vasopressors, and oxygen. If symptoms persist, systemic steroids also should be administered. If the

stinging apparatus is identified, it should be gently removed with care taken not to squeeze the venom sac, which could result in the deposition of more venom. All patients with a history of anaphylaxis to Hymenoptera should carry self-injectable epinephrine.

Venom Immunotherapy for Bees and Vespids

Venom immunotherapy has been shown to be highly effective in reducing the risk of a subsequent sting reaction in patients with sensitivity. A number of studies indicated that venom immunotherapy prevents systemic symptoms in 97% of patients [17••,19,20]. Some studies, though, showed a comparatively decreased efficacy for honeybee immunotherapy, reporting an 80% to 90% prevention rate [21]. The reason for this is not clear, though the amount of venom injected by yellow jackets is 2 to 3 µg, compared with 50 µg for honeybees.

There are varying schedules for venom immunotherapy. Most schedules initiate immunotherapy with 0.1 µg and reach a maintenance dose of 100 µg. Some allergists have advocated using 50 µg as the maintenance dosage, though there is some concern about decreased protection [22]. The amount of time to reach maintenance may vary from hours to a few days with aggressive dosing. These regimens, though, may be associated with a high number of systemic side effects. The "rush" and "rapid" schedules can attain maintenance dosage in approximately 2 to 3 weeks. Typical dosage schedules result in maintenance dosage in 11 weeks.

Once maintenance dosage is reached, immunotherapy injections are typically given every 4 to 6 weeks. A recent study by Goldberg and Confino-Cohen [23••] supports a maintenance dosage schedule extension to an injection every 3 months. They studied 154 patients, 36 of whom received a field sting and 44 who were given deliberate stings while on the 3-month interval regimen. The rate of systemic reactions to the immunotherapy was 2.6%. One of the 36 patients (3.8%) and two of the 44 patients (4.5%) had mild systemic reactions to their stings. The 3-month interval maintenance dosage was discontinued after a total of 5 years of immunotherapy. Two of 24 patients (8.3%) stung after discontinuation of immunotherapy had mild systemic reactions, both were to yellow jacket. These

occurred 53 and 59 months after immunotherapy discontinuation. Deliberate stings were performed to honeybee-sensitive patients during a mean time period of 43.1 months after discontinuation of immunotherapy. Only one of 22 patients (4.5%) had a mild reaction to the sting. Overall, these data support the safety and efficacy of a 3-month maintenance interval during the administration of immunotherapy and its continued effectiveness after discontinuation of immunotherapy.

The Hymenoptera venom study reviewed 1410 patients undergoing venom immunotherapy and found systemic reactions in 12% of the patients. Of all the reactions, there was often more than one reaction per patient; 9% were severe [24]. These rates are similar to those seen with aeroallergen immunotherapy. This underscores the importance of observation for 30 minutes after an immunotherapy injection. In an effort to decrease allergic side effects from the immunotherapy, pretreatment with antihistamines has been shown to decrease both local and systemic side effects when given on days of immunotherapy [25]. Concern has been raised over whether this could alter the effectiveness of the immunotherapy. In a retrospective study, 41 patients were rechallenged either by a field sting or sting provocation after 3 years of venom immunotherapy [26]. Twenty patients were pretreated with terfenadine during the first 3 weeks of rush immunotherapy and 21 were given placebo. Six patients had a reaction to the sting challenge and, interestingly, all were in the placebo group. This suggests that the pretreatment with terfenadine may have increased the efficacy of the immunotherapy. Further prospective studies are needed to confirm these findings.

The length of immunotherapy required for prolonged protection from a stinging insect reaction is still evolving. Earlier studies, which observed patients for 1 to 3 years after discontinuation of 3 to 5 years of venom immunotherapy, showed a protection rate of 83% to 100% [17••]. One of the criterion for discontinuing immunotherapy has been the conversion from a previously positive skin test to a negative skin test. This occurs, though, in only approximately 20% of patients undergoing 3 to 5 years of immunotherapy [27]. Even despite a conversion to a negative skin test, some patients will experience a systemic reaction [28]. The severity of anaphylaxis prior to treatment plays a role in determining future risk. Subsequent anaphylactic reactions to sting after discontinuation of immunotherapy were seen in 4% of patients with initial mild anaphylaxis, 5% of those with initial moderate anaphylaxis, and 15% of those with initial severe anaphylaxis [27]. Further studies have looked at the risk of a systemic response to a sting up to 7 years after the discontinuation of immunotherapy. Golden *et al.* [28] reported on 26 patients who had field re-stings with five (19%) developing systemic reactions again. Another study reported on 200 patients re-exposed by mainly field stings, with 12.5% developing a systemic reaction [29]. The majority of the reactions were to bee venom.

Table 3. Risk factors for developing allergic reaction to insect sting after discontinuation of venom immunotherapy

Severe initial anaphylactic reaction
Bee venom sensitivity
Older age
Allergic reactions to immunotherapy injections
Allergic reactions to stings during immunotherapy
Short (<3 years) duration of immunotherapy

It is clear that the risk for a systemic reaction to a sting is higher after the discontinuation of immunotherapy than it is while on the maintenance injections. Though the earlier studies suggested that venom immunotherapy could be stopped after 3 to 5 years, the optimum length of therapy should be individualized. Risk factors for a systemic reaction after the discontinuation of immunotherapy include honeybee (as opposed to vespid) allergy, severity of anaphylaxis prior to onset of immunotherapy, older age, and reaction during therapy to either a field sting or the immunotherapy itself (Table 3). One approach to counseling patients on whether to continue or discontinue the immunotherapy is to outline their risks as follows: 1) the chance of a systemic reaction with a subsequent sting approaches 10%, even if the sting occurs 10 years later; 2) although most reactions are mild, there is a small chance of a life-threatening reaction; and 3) the only way to maintain the lowest risk, approximately 2%, is to continue the venom immunotherapy [30].

Conclusions

Stinging insect allergy is a potentially life-threatening situation. Though the diagnosis and treatment for Hymenoptera allergy has improved considerably over the last 20 years, it is not currently perfect. Difficulties arise in the management of the negative skin test reactor and in determining the optimum duration of immunotherapy. Continued improvement in the *in vivo* and *in vitro* sensitivity of diagnostic testing and optimizing available treatments and consideration of other treatments, such as T cell epitope peptides, remain challenges for the future.

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