

Management of Insect Sting Hypersensitivity: An Update

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Reactions to Hymenoptera insect stings are common. While most are self-limited, some induce systemic allergic reactions or anaphylaxis. Prompt recognition, diagnosis, and treatment of these reactions are important for improving quality-of-life and reducing the risk of future sting reactions. This review summarizes the current recommendations to diagnose and treat Hymenoptera sting induced allergic reactions and highlights considerations for various populations throughout the world.

Key Words: Hymenoptera allergy; venom immunotherapy; sting-induced anaphylaxis; insect sting allergy; insect sting hypersensitivity

INTRODUCTION

Allergic reactions triggered by Hymenoptera insects have been described as long ago as 2000 B.C.¹ It was not until the early part of the 20th century that the first medical reference was made for the treatment of allergic reactions to Hymenoptera.² Over the last 100 years, the knowledge base for the diagnosis and treatment of stinging insect allergy has greatly expanded.

Reactions following stings by Hymenoptera insects, primarily honeybee, wasp, yellowjacket, hornet and ant, are common. While most sting reactions are localized and self-limited, some lead to large local reactions or to systemic allergic reactions or anaphylaxis and cause death. Prompt recognition, diagnosis, and treatment of these systemic allergic reactions is important to improve the quality-of-life of such individuals and reduce the risk for future sting reactions.

This review summarizes the current recommendations to diagnose and treat Hymenoptera sting induced allergic reactions and highlights considerations for various populations throughout the world.

TAXONOMY AND IDENTIFICATION

Although Hymenoptera are commonly known to cause human stings, these insects also play an important role in crop pollination and to reduce insect pest populations. The Hymenoptera insects which cause most stings are in the family Vespidae (wasps) and include yellowjackets (*Vespula*), aerial yellowjackets (*Dolichovespula*), hornets (*Vespa*), and paper wasps

(*Polistes*); family Apidea (bees); and family Formicidae (ants) (Figure).³ Proper recognition of the insect responsible for the sting is important for appropriate management; however, most victims cannot identify the sting culprit. There are also significant regional variations in Hymenoptera populations; for example, fire ant stings are common in the southeast whereas yellowjacket stings are more common in northeast United States. Similarly, different Hymenoptera exist in various parts of the world, e.g., in Australia, the jack jumper ant (*Myrmecia pilosula*) is a major cause of Hymenoptera induced stings.

There are several defining characteristics of Hymenoptera insects and their stings that can help with correct identification. Honeybees (*Apis* sp.) and bumblebees (*Bombus* sp.) are not typically aggressive but will sting to defend their hives. Both bumble and honey bees construct their nests from beeswax in combs containing numerous hexagonal cells. Bumblebee nests are typically small, concealed, and constructed in loose, fibrous materials such as grass clippings. They are characterized by their "fuzzy" appearing hair and loud buzzing sound. Honeybees are frequently used for commercial pollination in man-made hives and their sting can often be suspected by the stinger that is left

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Received: August 17, 2012; Revised: September 18, 2012;

Accepted: September 26, 2012

• There are no financial or other issues that might lead to conflict of interest.

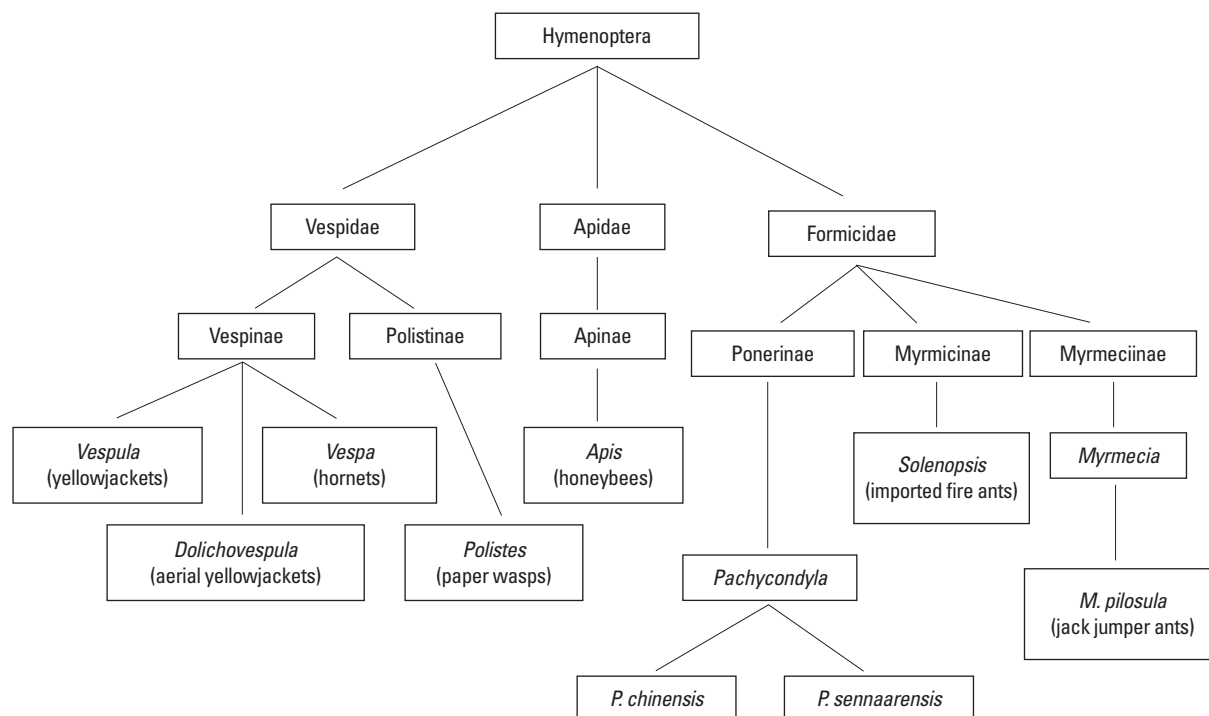


Figure. Taxonomy of Hymenoptera species.

behind in the skin. Paper wasps, yellowjackets, aerial yellowjackets, and hornets may have similar coloring and appearance, but can often be differentiated by their nests. Paper wasp nests (*Polistes* sp.) are often found under eaves or rafters of homes and other buildings and are characterized by a single paper comb with no protective envelope. Yellowjackets (*Vespula* sp.) typically make paper-like nest in concealed locations such as wall cavities, stumps, or underground locations while aerial yellowjackets (*Dolichovespula* sp.) live in large colonies and build nests near human dwellings. Imported fire ant (IFA) [*Solenopsis* (*S.* *invicta* and *S.* *richteri*)] colonies are recognizable in endemic areas by large mounds of loose soil commonly found in yards, fields, or pastures. Each colony may contain more than 200,000 ants. IFA stings are characterized by a sterile pustule which forms within 24 hours of the sting.⁴ Other ants known to induce allergic reactions in the United States include *S. xyloni*, *S. richteri*, and *S. geminata*.⁵ In addition, red harvester ants (*Pogonomyrmex*) cause allergic reactions in both the United States and Europe. Their nests are characterized by a lack of foliage surrounding the entrance to their colony. In Southeast Asia, *Pachycondyla chinensis* ants are winged and form small colonies near human dwellings, while jack jumper ants (*Myrmecia pilosula*) form colonies under rocks or small piles of gravel. They are also characterized by their ability to jump when threatened.

DEMOGRAPHICS AND SUSCEPTIBILITY

The exact incidence of human Hymenoptera stings is un-

known, but it is estimated that between 56% and 94% of adults worldwide have been stung at least once in their lifetime.⁶ In a study of subjects who moved to an endemic IFA area, 55% reported stings from such insects within one month.⁷ While most stings are self-limited, some result in large local or systemic allergic reactions. In a study of 3,236 Hymenoptera allergic subjects in North America, males accounted for over 60% of sting reactions with a median age of 30.5 years. Each subject averaged 2.7 stings during their lifetime and 89% (2,866) of the subjects reported at least one systemic allergic reaction.⁸ The prevalence of systemic allergic reactions after a sting is estimated to be between 0.15% to 0.8% in children and 0.3% to 8.9% in adults. Large local reactions, defined as pain, swelling, and erythema at the site of a sting which may involve an entire extremity, while not life-threatening, occur in 2.4% to 26.4% of the general population, but nearly 40% in those with regular exposure, such as beekeepers.⁹⁻¹³

Insect sting-related anaphylaxis accounts for over 30% of all cases of anaphylaxis seen in emergency departments.¹⁴ Mortality from insect-sting anaphylaxis in the United States ranges from 0.3 to 0.48 fatalities per 1,000,000 individuals/year or an average of 40 to 100 deaths per year and accounts for nearly 20% of all anaphylaxis related deaths.¹⁵⁻¹⁹

Evaluation for mast cell disorders, such as systemic mastocytosis, monoclonal mast cell activation syndrome, or mast cell activation syndrome, should be initiated in some Hymenoptera hypersensitive subjects. Severe, life-threatening systemic reactions following a Hymenoptera sting may be the only present-

ing clinical manifestation of these disorders.²⁰⁻²²

VENOMS

Hymenoptera venoms typically contain a mixture of 3 to 4 major proteins as well as pharmacologically active peptides and other small molecules. There are common proteins shared amongst the various Hymenoptera species, however, there are significant differences as well. Most of the protein structures for the major allergens are known and several have been produced in recombinant forms. Table 1 summarizes relevant allergens for selected Hymenoptera venoms. Phospholipases, hyaluronidases, and antigen 5 are shared amongst many species of vespids. Phospholipases found in vespid venoms differ from those found in bee venoms. IFA venoms are primarily made of alkaloids. These alkaloids do not induce allergic reactions; IFA venoms also contain 4 to 5 proteins that are responsible for such reactions. Other species of ants, such as the jack jumper ant (*Myrmecia pilosula*), contain highly allergenic proteins, but these proteins do not cross-react with other ant species.

DIAGNOSIS

Subjects with a clinical history of a systemic allergic reaction, defined as systemic signs and symptoms of anaphylaxis, following a Hymenoptera sting should undergo evaluation for Hymenoptera allergy. Following an appropriate history and physical, further evaluation, i.e., appropriate skin or *in vitro* testing, should be delayed three to six weeks because of false negative testing which can occur immediately following a sting reaction.²³ Skin prick puncture and intradermal tests are tests of choice to confirm suspected Hymenoptera allergy. Negative skin prick puncture tests should be followed by the appropriate intradermal tests, which are more sensitive in detecting IgE hypersensitivity but less specific than skin prick tests. This is especially true if a considerable amount of time has passed since the sting reaction occurred.²⁴ Such intradermal skin tests should begin with a 0.001 to 0.01 µg/mL concentration and be titrated up to 1 µg/mL, depending on clinical sensitivity. Concentrations higher than 1 µg/mL are associated with a higher incidence of false positive results.²⁵ Skin testing is safe in Hymenoptera allergic subjects, with a less than 2% risk of a systemic allergic reaction with testing.²⁶

Skin testing for suspected IFA allergy (*S. invicta* and *S. richteri*) should be considered in subjects with a history of a systemic reaction following an IFA sting. IFA are native to South America but are now endemic in the southeastern United States, Australia, Taiwan, Philippines, and China. IFA stings are common in these areas thus there is a high incidence of "false positive" skin sensitivity.^{27,28} As with other Hymenoptera species, skin prick testing is performed first followed by the appropriate intradermal testing, as necessary. The initial concentration for IFA in-

Table 1. Allergens of selected Hymenoptera venoms

Venom	Allergen	Common name	Molecular Wt. (kDa)
<i>Apis mellifera</i> (honeybee)	Api m 1	Phospholipase A2	16
	Api m 2	Hyaluronidase	39
	Api m 3	Acid phosphatase	43
	Api m 4	Melittin	3
	Api m 5	Dipeptidylpeptidase IV	100
	Api m 6	N/A	8
	Api m 7	Protease	39
	Api m 8	Carboxylesterase	70
	Api m 9	Carboxypeptidase	60
	Api m 10	Incarapin variant 2	50-55
	Api m 11	Major royal jelly protein	50
	Api m 12	Vitellogenin	200
<i>Vespula vulgaris</i> (yellowjacket)	Ves v 1	Phospholipase A1B	34
	Ves v 2	Hyaluronidase	38
	Ves v 3	Dipeptidylpeptidase IV	100
	Ves v 5	Antigen 5	23
	Ves v 6	Vitellogenin	200
<i>Dolichovespula arenaria</i> (yellow hornet)	Dol a 5	Antigen 5	23
<i>Dolichovespula maculate</i> (white face hornet)	Dol m 1	Phospholipase A1B	34
	Dol m 2	Hyaluronidase	42
	Dol m 5	Antigen 5	23
<i>Vespa crabro</i> (European hornet)	Vesp c 1	Phospholipase A1B	34
	Vesp c 5	Antigen 5	23
<i>Polistes annularis</i>	Pol a 1	Phospholipase A1B	34
	Pol a 2	Hyaluronidase	38
	Pol a 5	Antigen 5	23
<i>Solenopsis invicta</i> (imported fire ant)	Sol i 1	Phospholipase A1B	18
	Sol i 2	N/A	14
	Sol i 3	Antigen 5	26
	Sol i 4	N/A	12
<i>Myrmecia pilosula</i> (jack jumper ant)	Myr p 1	Pilosulin-1	5.5/7.5
	Myr p 2	Pilosulin-3	2-4/8.5
	Myr p 3	Pilosulin-4.1	8.1
<i>Pachycondyla chinensis</i> (Asian needle ant)	Pac c 3	Antigen 5	21

Major allergens are shown in bold.

N/A, not available.

tradermal testing is 1:1 million (1×10^6) weight/volume (w/v) of whole body extract (WBE). If these tests are negative, the concentration should be increased 10-fold until a positive response is reached or to a maximum concentration of 1:1,000 or 1:500 w/v. In Asia and Australia, several other ant species are important causes of venom-induced anaphylaxis. In Australia, stings by the jack jumper ant (*Myrmecia pilosula*) and bull ant (*Myrmecia pyriformis*) are common, while in Korea and other parts

of Southeast Asia, *Pachycondyla* species are relevant. Skin prick puncture and intradermal tests using WBE (*Pachycondyla*) or venom extracts (*Myrmecia*) are recommended to confirm suspected IgE-mediated allergy to these ant species. Intradermal concentrations of 1 µg/mL or less have been used successfully to help diagnose allergy to the jack jumper ant (*Myrmecia pilosula*), but less is known about other ant species.²⁹ Extracts for skin testing to these ant species are not commercially available.

Although skin testing is the preferred method to confirm Hymenoptera allergy, *in vitro* testing is also available and is an option for subjects that cannot undergo skin testing. *In vitro* testing should also be considered for subjects with a convincing clinical history and negative skin tests. Approximately 5%-10% of subjects with a history of systemic allergic reaction following a Hymenoptera sting will have detectable levels of venom-specific IgE but negative skin tests. Conversely, 10%-20% of subjects with positive skin tests will have no detectable *in vitro* venom-specific IgE.³⁰ There is a small subgroup of subjects with a convincing history of an IgE-mediated reaction following a Hymenoptera sting with both negative skin and *in vitro* tests. This may represent a low level of IgE production or lack of sensitivity to currently available test reagents or methods. In such subjects, skin and *in vitro* tests should be repeated within several months after the initial tests are completed.^{30,31}

Component-resolved diagnosis (CRD) involves the identification of IgE antibodies to specific components rather than the whole allergen. In food allergies, CRD may become important to identify subjects at risk for future serious allergic reactions to a food versus those that may have elevated specific IgE to a food due to cross-reactivity, e.g. peanut and birch pollen.³² CRD may also be useful in subjects with Hymenoptera allergy. Many Hymenoptera allergic subjects have cross-reactivity between bee and wasp venoms with standard skin and IgE testing, which may be due to cross-reactive carbohydrate determining reagents rather than true cross-reactivity between venom proteins. Determination of specific IgE to Api m 1 (phospholipase A2) and Ves v 5 (antigen 5), rather than to conventional venom extracts, could be useful to determine if cross-reactivity is present to both venoms, especially if the clinical history is uncertain. This could aid in the selection of venoms used for immunotherapy.^{33,34} To date, only a few venom components are fully sequenced, including Api m 1, Ves v 1, and Ves v 5.

MANAGEMENT OF STING REACTIONS

There are three kinds of reactions that occur following a Hymenoptera sting: a local reaction, a large local reaction, and a systemic reaction. Treatment indicated is predicated on the type of reaction that occurs.

A local reaction typically presents with pain, swelling, and erythema at the site of the sting. Most resolve within several hours and can be treated successfully with topical ice packs and "tinc-

ture of time". Pustules caused by IFA stings, however, are caused by the toxicity of the alkaloid component of the ant venom and do not respond to any known treatment modality.³⁵ Secondary infection is the most common complication and immediate antibiotic therapy should be initiated if it is suspected. A large local reaction presents with similar symptoms of pain, swelling, and erythema at the site of sting, but the reaction extends to a larger area of skin. Occasionally, this reaction is also associated with nausea and vomiting. The swelling associated with a large local reaction usually peaks at 48 hours after a sting and may take up to a week to resolve. Some reactions will involve an entire hand, hand and forearm, foot and leg, or one side of the face. Applications of ice packs, elevation of the affected limb, oral antihistamines and/or systemic corticosteroids may be useful to help resolve this reaction.

A systemic allergic reaction following a Hymenoptera sting can be life threatening and require prompt medical attention and long-term proper management to prevent recurrences. Systemic allergic reactions may involve more than one organ system, typically the skin, gastrointestinal, respiratory and/or cardiovascular systems. Subjects with an acute presentation should be placed in the recumbent position with the lower extremities elevated. Epinephrine is the drug of choice for any systemic allergic reaction including Hymenoptera-induced anaphylaxis. In children, 0.01 mg/kg up to 0.3 mg, intramuscularly, is recommended to be given in the anterior-lateral thigh, while 0.3-0.5 mg should be initially given in the same manner to adults. These doses of epinephrine should be repeated, as necessary, based on the clinical scenario. H1 and H2 antihistamines, glucocorticosteroids, oxygen, bronchodilators, and intravenous volume expanders as well as vasopressors are utilized to treat anaphylaxis when it does not respond to epinephrine, is protracted, or biphasic.

Once the reaction is resolved, it is imperative that individuals presenting with systemic allergic reactions be prescribed epinephrine for self-administration and given appropriate instructions for its use.³⁶ Likewise, they should be taught how to avoid being stung and given the option of having a MedicAlert bracelet (<http://www.medicalert.org/>).

Venom immunotherapy (VIT) should be prescribed for subjects with a history of a systemic allergic reaction following a Hymenoptera sting who have evidence of venom-specific IgE antibodies (Table 2). The goals of VIT are to alleviate patient anxiety about potential future stings as well as to prevent future systemic allergic reactions and even death. Once a maintenance dose is achieved, systemic allergic reactions are successfully prevented upon re-sting in 75%-95% of subjects, depending on the incriminating insect, compared to a 40% to 60% risk of a future systemic reaction in untreated subjects.^{37,38} When systemic allergic reactions do occur in a patient following VIT, with exception, they are usually mild and not life threatening.³⁹ Efficacy of such therapy is long-lasting with 80% or more of the sub-

Table 2. Patient selection for venom immunotherapy

Venom immunotherapy recommended
<ul style="list-style-type: none"> • Adults with systemic allergic reactions AND evidence of venom-specific IgE antibodies • Children with systemic allergic reactions, involving more than cutaneous manifestations, AND evidence of venom-specific IgE antibodies • Children with large local reactions to IFA who live in an endemic area of exposure and have major problems with large local reactions • Children with systemic cutaneous reaction following IFA sting • Adults with debilitating, large local reactions and a high risk of re-sting • History of systemic allergic reactions and diagnosis of a mast cell disorder such as systemic mastocytosis, mast cell activation syndrome, or monoclonal mast cell activation syndrome AND serum tryptase above 11.4 µg/L
Venom immunotherapy NOT recommended
<ul style="list-style-type: none"> • Subjects with small local reactions • Adults with large local reactions that are not at high risk of re-sting and a decrease in quality-of-life • Children with ONLY cutaneous systemic reactions to flying Hymenoptera insects • Subjects with no evidence of venom-specific IgE

IFA, imported fire ant.

jects who complete at least three years of VIT being protected for up to seven years after VIT is stopped.⁴⁰⁻⁴⁴ Because VIT is potentially life threatening, patients should receive their injections under the care of a physician trained to prescribe and administer such therapy and trained to recognize and treat systemic allergic reactions from VIT, when they occur. Such reactions are uncommon and no deaths have been reported associated with VIT.³⁹

There is less information available about IFA and other ant-induced systemic reactions. WBE rather than extracted venoms are used for IFA immunotherapy and contain venom proteins.⁴⁵ IFA WBE therapy has not been studied in a double-blind controlled fashion; however, it does appear to be effective at preventing future systemic reactions.⁴⁶ In a study of subjects who completed IFA immunotherapy, two of fifteen subjects had allergic reactions upon re-sting 18 months after cessation of VIT and these reactions were mild and cutaneous only. At 54 months post therapy, zero of nine subjects had systemic reactions following re-sting.⁴⁷ Immunotherapy for other ant species may also be available. In Australia, extracted venom rather than WBE is used to treat systemic reactions to jack jumper ants (*Myrmecia pilosula*) as demonstrated in a double-blind, placebo controlled crossover trial.²⁹ Although extracted VIT for jack jumper ant is effective, commercial extracts are not available. Extracts for VIT for ant species in other parts of the world, including Southeast Asia, remains under investigation and are also not commercially available.

CONSIDERATIONS IN SPECIFIC POPULATIONS

Children

VIT for children who have had a systemic allergic reaction following a Hymenoptera sting is safe and appears to be more effective in inducing long-term tolerance than in adults.⁴⁸ It is not indicated in children less than 16 years of age who present with a systemic allergic reaction involving only cutaneous manifestations, such as generalized urticaria, erythema or flushing, and/or pruritus.⁴⁹ In such children, 10% will have a systemic allergic reaction upon re-sting and most of these reactions will be mild and limited to the skin.^{50,51} In general, VIT is also not recommended for children with large local reactions. An exception may include children living in areas of endemic IFA exposure.

In contrast to other Hymenoptera insects, there appears to be an increased risk of systemic allergic reactions with future IFA stings in children who present with cutaneous manifestations only following their initial sting.⁵² Therefore, many experts place children with such reactions on VIT, while some do not.

Pregnancy

The decision as to whether or not VIT should be started in a pregnant subject depends on the risk/benefit of such therapy versus the likelihood that they will be stung and have a systemic allergic reaction during pregnancy. A systemic allergic reaction following a Hymenoptera sting in a pregnant subject carries significant risk to the fetus including fetal loss, possible congenital abnormalities, as well as an increased risk of maternal morbidity and even mortality. VIT is safe to continue in subjects who have already reached a maintenance dose. In a study of 43 pregnant subjects receiving VIT, only two had systemic allergic reactions, both of which were mild and did not require treatment.⁵³ There were no adverse effects on the mother or the fetus. Some experts recommend decreasing the VIT dose by 50% and reducing by half the interval between injections during pregnancy to decrease the risk of VIT-associated reactions.

Large local reactions

VIT is not routinely recommended to treat large local reactions, however, in a study of 29 subjects with a history of such reactions, VIT significantly reduced their size and duration. This benefit seemed to improve with two to four years of continued treatment.⁵⁴ VIT for large local reactions is also effective at improving the quality-of-life of subjects who are at risk of occupational or recreational exposure.⁵⁵

Mast cell disorders

Almost 8% of subjects presenting with Hymenoptera allergy have mast cell disorders.⁵⁶ These subjects appear to be at risk for severe reactions following a sting, especially if the total serum tryptase is elevated above 11.4 µg/L. Although there is con-

tinued debate about the mechanisms of these reactions in subjects with mast cell disorders, VIT is the treatment of choice to successfully prevent future reactions.⁵⁷⁻⁵⁹ These subjects are also at higher risk for adverse reactions while receiving VIT, thus premedication with antihistamines and other medications may be indicated. Although many Hymenoptera allergic subjects can be successfully treated with 3 to 5 years of VIT, subjects with mast cell disorders may require life-long therapy.⁶⁰

INITIATION OF VIT

Selection of venoms

There is no consensus about which venoms should be included when VIT is prescribed. One approach is to include venoms from the causative insect only, although correct identification of such an insect may be problematic due to similar appearances among many Hymenoptera species.^{61,62} Another approach is to include all venoms to which the patient has positive skin or specific IgE tests.^{37,63} Several venoms are cross-reactive; for example, honeybee and bumblebee mostly cross-react. Vespids are also highly cross-reactive, especially among *Vespula*, *Dolichovespula*, and *Vespa* species. *Vespula* and *Polistes* species are considered less cross-reactive and *Vespidae* and *Apidae* do not cross-react.

Treatment protocols

The maintenance dose is that which provides protection against future systemic allergic reactions and ranges from 50 to 200 µg. Most experts recommend at least 100 µg, equivalent to two bee stings and a larger number of *Vespula* stings. If a patient has a systemic allergic reaction while on a 100 µg maintenance, the dose should be increased to 150 to 200 µg.⁶⁴ These latter doses are not initially recommended due to an increased risk of VIT-associated adverse reactions; however, higher initial doses may be indicated for subjects who are at routine risk of stings, such as beekeepers.⁶⁵

Dosing for flying Hymenoptera should begin at 0.1 to 0.5 µg and be increased weekly until maintenance is reached. Once a maintenance concentration of 100 µg is achieved, dosing intervals can be gradually increased to every four weeks during the first year of therapy and subsequently to every 6 to 8 weeks and even every 12 weeks.^{66,67} For IFA, most experts agree that the maintenance dose should be 0.5 mL of a 1:100 w/v WBE, although a 1:10 w/v dose is also recommended.⁶⁸ Recommendations for dosing of immunotherapy with other ant species are currently lacking, although a maintenance dose of 100 µg has been successfully used to treat jack jumper ant (*Myrmecia pilosula*) allergy.²⁹

Although weekly dosing to reach maintenance is most common, alternatives exist. Traditional buildup requires 8 to 15 doses/weeks to reach maintenance, while rush, cluster, or ultrarush regimens allow maintenance doses more quickly.

Rush immunotherapy protocols call for three to four injections per visit, in increasing concentrations, permitting maintenance to be reached in four to seven days. This form of buildup does not seem to be associated with an increased risk of systemic reactions.⁶⁹⁻⁷¹ Ultrarush protocols are even quicker, allowing maintenance to be reached in one to two days, or even hours.^{72,73} Such protocols are also considered safe, although there may be an increased risk of adverse reactions and premedication with antihistamines and/or corticosteroids may be required. Ultrarush protocols have been studied in children and are considered safe for use in this population.⁷⁴ Cluster immunotherapy is a form of modified rush therapy in which multiple injections are given during the first visit, but subsequently, dosing more closely resembles the traditional build-up allowing maintenance to be reached in six weeks. Cluster VIT is not associated with an increased risk of systemic reactions.

For IFA allergy, experts recommend that dosing be given weekly or biweekly during the buildup phase, although Tankersley et al.⁷⁵ have shown that rush protocols are also successful.

Duration of therapy

VIT should be continued for a minimum of three to five years, although some subjects require life-long therapy.⁷⁶ Although there are no consensus recommendations for discontinuing such therapy, most experts agree that it can be stopped in subjects that meet the following criteria: decrease in venom-specific IgE to insignificant levels, conversion to negative skin testing, or completion of a finite period of treatment. Discontinuation of VIT can still be considered in subjects that continue to have positive skin tests after three to five years of treatment since 80%-90% will not have a systemic reaction upon re-sting.^{40,43} In subjects who have a history of severe, life-threatening anaphylaxis following an Hymenoptera sting and continue to have positive skin tests after five years of such therapy, caution should be exercised before discontinuing VIT since these subjects are at highest risk of future systemic reactions.^{77,78} Adult subjects, those treated for honeybee systemic reactions, subjects with systemic reactions during VIT, and those with elevated baseline serum tryptase or a diagnosis of systemic mastocytosis are at higher risk for systemic reactions following re-sting and should be considered for life-long therapy.^{79,80}

There is no consensus for the duration of therapy for IFA allergy. Most experts recommend three to five years of treatment and life-long therapy should be considered in IFA allergic subjects if they meet similar criteria as those with flying Hymenoptera allergy.⁷⁶

SUMMARY

Correctly diagnosing and instituting appropriate management of Hymenoptera allergic subjects is important to reduce morbidity and mortality associated with future stings and to im-

prove quality-of-life. A detailed medical history and correct identification of the offending insect coupled with skin and/or *in vitro* testing remains the best way to correctly identify Hymenoptera allergic subjects. Recombinant allergens, identification of venom-specific B- and T-cell epitopes, and manipulation of DNA plasmids may allow for more accurate diagnosis and treatment of Hymenoptera allergic patients in the future. Immunotherapy remains the best treatment option for subjects with a history of a systemic allergic reaction following Hymenoptera insect sting.

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