

Killer Insects: Who Is at Risk for Anaphylaxis From Insect Stings?

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Opinion statement

Patients who have had an anaphylactic reaction to stinging insect should be educated on the potential of fatality from venom allergy. These patients should be referred to an allergist/immunologist, a specialist with training in the diagnosis and management of stinging insect allergy. The three tenets of treatment for stinging insect allergy are insect avoidance measures, proper use of epinephrine, and insect immunotherapy. Avoidance is ideal but not always practical. Intramuscular epinephrine is the only effective therapy for anaphylaxis. Insect immunotherapy is proven to reduce the probability of anaphylaxis with repeat stings from approximately 60 % to less than 5 %. This reduction is not only potentially life-saving but also improves quality of life and reduces anxiety. Before starting immunotherapy, clinicians should have a discussion with patients regarding their goals of care, disease-specific anxiety level, comorbid conditions, and possible compliance issues.

Introduction

Most insect stings cause a transient, local reaction that resolves after several days. However, systemic allergic reactions to insect stings occur in up to 0.8 % of children and 3 % of the general adult population. Systemic allergic reactions are IgE-mediated and are characterized by urticaria, angioedema, nausea, diarrhea, hypotension, upper airway obstruction, or bronchial constriction. The most serious, fatal reactions are characterized by airway compromise or cardiovascular collapse [1]. The incidence of

mortality from insect stings is unknown, with a minimal estimate of at least 40 annual deaths per year in the USA according to a review of national mortality data in the USA from 1980 to 1999. This is most assuredly a gross underestimate as the incidence is likely underreported due to inability to identify the cause of sudden death and the random nature of events [2, 3]. Stinging insect allergy accounts for over 10 % of all cases of anaphylaxis presenting to emergency departments. Systemic insect reactions

are more common in young adults, but death is more common in older adults [4]. A comprehensive history of the anaphylactic episode is critically important in patient evaluation [1, 5••]. Stinging insects of the *Hymenoptera* order are responsible for the majority of patients evaluated for insect anaphylaxis. These insects include honey bees and bumblebees, vespids (hornets, yellow jackets, wasps), and imported fire ants (IFAs). Systemic reactions due to biting insects occur, particularly with reduviid bug bites, but these are not discussed in this review. Other stinging insects can cause anaphylaxis, such as jack jumper ants in Australia and Asian needle ants in Korea. This review focuses on stinging insects that most commonly cause anaphylaxis in North America.

After a flying *Hymenoptera* sting, stingers should be removed as quickly as possible because venom may be released for several seconds. An individual IFA often inflicts multiple stings, holding to the skin with mandibles while stinging repeatedly. Thus, IFAs should be removed from the skin immediately [6]. Intramuscular epinephrine is the initial drug of choice in the acute management of venom-induced anaphylaxis. Approximately 60 % of subjects with a history of anaphylaxis following an insect sting will experience similar reactions with subsequent stings. Clinicians should educate patients that venom allergy can be fatal, and they should carry epinephrine for emergency self-administration in case of a sting. These patients should be evaluated by an allergist/immunologist or other physician who is trained and experienced in the diagnosis and management of insect allergy. The diagnosis of insect allergy requires both the history of a sting event and evidence of insect-specific IgE, preferably by skin testing. Stinging insect immunotherapy is recommended for subjects with a history of systemic reactions and with specific-IgE to the

suspected insect. In children less than 16 years, immunotherapy is recommended for reactions involving more than the skin and with specific-IgE to the suspected insect [1].

Insect immunotherapy, using venoms for most insects and whole-body extracts for imported IFAs, is the only therapy that has an immunomodulatory effect on patients with stinging insect allergy [5••]. Immunotherapy reduces the risk of anaphylaxis from subsequent stings and improves health-related quality of life by reducing anxiety [7••]. For flying insect stings, patients in the USA are treated with venom immunotherapy (VIT) containing all venoms to which they have specific-IgE, as the patient's identification of the causative insect may not be accurate [1, 5••, 8]. The minimum duration of therapy is usually 3 to 5 years. Subjects with honey bee allergy, high likelihood of repeat stings, anaphylaxis during VIT, mast cell disorders, or a severe, life-threatening initial reaction should be considered for life-long therapy. Since older adults are at greater risk of death from anaphylaxis, they usually should be offered immunotherapy regardless of comorbidities. Immunotherapy should only be administered in a clinical setting equipped with resuscitative equipment, and recipients should remain under observation for at least 30 min following the immunotherapy injection. Patients with sensitivity to IFAs are treated similarly, with maintenance injections of whole-body extract (WBE) for a minimum of 3 to 5 years. The decision to stop immunotherapy is complex. Clinicians should weigh each patient's preference, lifestyle, comorbid conditions, and other risk factors when making a decision [1, 7••].

Treatment

Diet and Lifestyle

According to the Joint Task Force on Practice Parameters of Allergy and Immunology, one of the treatment tenets for patients at risk of systemic reactions from stinging insects is education regarding insect avoidance. Patients should be thoroughly educated on ways to avoid insect stings. Some of these measures include the following:

- Have trained professionals exterminate known or suspected nests in the immediate vicinity of the patient's home
- Avoid brightly colored clothing, flowery prints, or loose-fitting garments
- Avoid strongly scented perfumes, deodorants, and hairsprays

- Wear long pants, closed shoes, socks, head coverings, and work gloves when working outdoors
- Be cautious near bushes, eaves, fruit trees, and attics; avoid garbage containers and picnic areas
- Be cautious when drinking from previously opened soda cans and keep food covered when eating outdoors; use drinks with lids and beware of insects inside straws or canned drinks
- Consider having available approved insecticides effective from a distance
- Do not crush or swat insects; when some insects are injured, they send chemical signals that incite other insects to attack [1].

Pharmacologic Treatment

The second tenet of treatment identified by the Joint Task Force on Practice Parameters of Allergy and Immunology is the availability of emergency medication.

- Epinephrine is the drug of choice for the treatment of anaphylaxis. It is the only medication that reduces hospitalization and death. Stimulation of the alpha-1 receptors prevent and relieve airway edema, hypotension, and shock. Its beta-1 agonist effects lead to increased force and rate of cardiac contractions, and its beta-2 agonist effects lead to bronchodilation and decreased mast cell and basophil mediator release. Patients with a history of stinging insect allergy are advised to carry self-injectable epinephrine. These patients should be educated on how to self-administer epinephrine and under what circumstances to do so. There are no contraindications to the use of epinephrine in the setting of anaphylaxis [1].
- Education provided by health professionals is helpful for patients and their caregivers to improve administration of epinephrine and management of anaphylaxis. Specific education programs reduce the anxiety of affected subjects [9•].

Epinephrine

Standard dosage: 0.3 mg (adults), 0.15 mg (children) [ideal dose is 0.01 mg/kg but auto-injectors only available at two doses]; injected intramuscularly into the anterolateral aspect of the thigh

Contraindications: No contraindications in the setting of anaphylaxis.

Main drug interactions: Epinephrine's effects may be diminished in subjects chronically receiving alpha-1 antagonists or beta-blockers.

Main side effects: Cardiac arrhythmia, chest pain, hypertension, ischemic vascular disease, tachycardia, anxiety, diaphoresis, pallor, nausea/vomiting, and tremor

Special points: Epinephrine is the only medication that reduces hospitalizations and death from anaphylaxis [1]; consider dose reduction of epinephrine in patients with known uncontrolled hypertension or cardiac arrhythmia

Cost/cost-effectiveness: Epinephrine is inexpensive but auto-injectors are expensive; however, life-saving potential makes the therapy cost effective (US \$190.00 to 247.00 for one auto-injector).

Flying Hymenoptera Venom and Imported Fire Ant Whole-Body Immunotherapy

Insect immunotherapy is the third tenet of treatment. It is the only treatment that is immunomodulatory and reduces risk of systemic reactions with subsequent stings by 50 % or more [1, 5••].

- Patients with flying *Hymenoptera* sting allergy are generally treated with all venoms (honeybee, wasp, yellow jacket, and/or mixed vespids) to which they have a positive skin test or serologic result, as the patient's identification of the responsible insect may not be accurate. This approach also provides maximal protection for future sting events [1, 8, 10]. Some clinicians use single venoms for venom immunotherapy (VIT) when circumstances strongly support a specific causal insect [10, 11]. Measurement of baseline tryptase levels prior to initiation of insect immunotherapy is an important predictor of the severity of sting reactions, the risk of systemic reactions during immunotherapy, the probability of immunotherapy failure, and the risk of relapse after immunotherapy cessation. A baseline tryptase level is a consideration to rule out mast cell disorders, with concentrations >11.5 ng/mL supporting further investigation [1]. A variety of schedules are used for VIT, including conventional, rush, or modified rush with a starting venom dose of 0.05–0.1 mL of 0.01–1 mcg/mL. The schedules vary as to how quickly maintenance dose is achieved. A VIT maintenance dose of 100 mcg (300 mcg for mixed vespids) is usually given every 4 weeks [5••]. Many physicians favor a 4-week schedule for 12 to 18 months, followed by 6- to 8- or even 12-week intervals [1]. For patients who experience a subsequent systemic sting reaction from the same insect used in VIT, an increase in the maintenance dose to 200 mcg may provide additional protection. A subject with a severe systemic reaction while receiving maintenance VIT may benefit from repeat testing to determine if an additional insect sting allergy has developed [1]. VIT is well-tolerated by most patients. The most common adverse effects are local reactions at the site of injection. Approximately 3 to 12 % of patients have VIT-induced systemic reactions [12, 13]. The National Institute for Health and Care Excellence (NICE) estimated that VIT-related adverse reaction rate is 2 % per injection in the initial phase and 0.26 % per injection in the maintenance phase [7••, 14]. Patients receiving honey bee VIT and those with elevated baseline tryptase measurements are at an increased risk for systemic reactions to VIT. Patients receiving concomitant beta-blocker and/or angiotensin-converting enzyme medications may also be at an increased risk. Ideally, patients should not be on these medications unless absolutely necessary. After a systemic reaction from VIT, clinicians should modify the dose, usually to the last tolerated dose or one tenth of the dose causing the reaction, with careful dose escalation to maintenance [1]. Pre-treatment with omalizumab (monoclonal humanized anti-IgE) in patients with recurrent systemic reactions from VIT is

efficacious for improving tolerance of therapy; however, omalizumab is not approved for use in subjects having reactions to VIT [15]. VIT usually should be continued for a minimum of 3 to 5 years, although the decision to discontinue treatment requires clinical judgment and patient input. Honey bee allergy, high likelihood of repeat stings, anaphylaxis during VIT, mast cell disorders, or severe, life-threatening initial reaction may require life-time therapy. Some clinicians discontinue VIT when there is evidence of a decrease in specific-IgE or increase in specific-IgG. However, there are insufficient data to support a clinical decision to discontinue therapy based solely on immunologic changes. Clinicians should weigh the patient's preference, anxiety level, quality of life, risk of exposure, comorbid conditions, and other factors when making a decision [1, 5••, 7••].

- Patients with imported fire ant (IFA) allergy are treated in a similar fashion as those receiving VIT except WBE therapy (WBE-IFA) is used instead of purified venom. There are less data proving efficacy of WBE-IFA therapy compared to VIT, but available studies do show benefit and venom antigens are present in the WBE [1, 16, 17]. Purified IFA venom is not commercially available. Conventional and rush schedules have been used with a starting dose of 0.05 mL of a 1:100,000 weight/volume (*w/v*) WBE solution. The optimal monthly maintenance dose has not been established, but 0.5 mL of 1:100 or 1:10 *w/v* WBE is generally used [7••]. This dose contains roughly the same amount of venom as 19 fire ant stings [18]. A disadvantage of WBE for IFA immunotherapy is that it contains significant amounts of nonallergenic proteins [19]. IFA-WBE is not standardized and therefore there is more potential for variability in efficacy [20]. The adverse effects of WBE-IFA immunotherapy are similar to VIT. Patients with recurrent systemic reactions on WBE-IFA immunotherapy have also successfully used omalizumab as pre-treatment [21, 22]. The optimal duration of treatment is not known, but most physicians suggest WBE-IFA immunotherapy for 3–5 years unless the same life-time therapy factors mentioned for VIT are present. The value of repeat testing with IFA-WBE is unproven as a means to influence the decision to discontinue [1].

Hymenoptera Venom Immunotherapy

Standard procedure: Build up to maintenance dose of 100 mcg per insect (300 mcg for mixed vespids) monthly for 3–5 years; life-time therapy in specific situations

Contraindications: No absolute contraindications in patients with history of anaphylaxis

Complications: Local reactions; risk of anaphylaxis due to immunotherapy

Special points: It is the most effective form of immunotherapy available

Cost/cost-effectiveness: Average cost of full treatment approximately US \$3300 [7••].

Imported Fire Ant Whole Body Extract Immunotherapy

Standard procedure: Build up to a maintenance dose of 0.5 mL of 1/100 w/v (some use 1/10 w/v) extract; life-time therapy in specific situations

Contraindications: No absolute contraindications in highly exposed patients with history of anaphylaxis

Complications: Local reactions; risk of anaphylaxis

Special points: Non-standardized WBE

Cost/cost-effectiveness: “Paucity of pharmacoeconomic data” [1].

Emerging Therapies

- Due to the treatment burden with traditional immunotherapy requiring build-up to monthly injections in a supervised clinical setting, sublingual immunotherapy (SLIT) has been investigated. A randomized control trial showed no evidence that SLIT is less effective than VIT, but the study was based on a small number of participants [23–25]. Randomized control trials with large sample sizes are needed for further investigation of SLIT as a treatment option.
- Omalizumab has been effective as pre-treatment for patients that have had recurrent systemic reactions to VIT. At this time, this is an off-label indication for use [15, 21, 22].
- Component-resolved testing using recombinant allergens and basophil activation tests may enhance the specificity of diagnostic accuracy. These tests may have a utility when the diagnosis is unclear or to identify culprit insect for therapy [26].

Pediatric Considerations

- Since education is a mainstay on the treatment of venom anaphylaxis, caregivers for children should be educated on avoidance measures and epinephrine administration.
- The recommended epinephrine dose for pediatric population is 0.01 mg/kg [1]. Since commercial auto-injectors only available in 0.15 and 0.30 mg, dosing flexibility is limited. When the recommended epinephrine dose is between 0.15 and 0.30 mg or less than 0.15 mg, clinicians should consider prescribing higher than recommended dose since the risk of epinephrine in children is negligible
- A lower maintenance dose of 50 mcg for VIT may provide effective protection with improved safety profile in the pediatric population [7••, 27]. The efficacy of the lower dose is debated.

Compliance with Ethical Standards

Conflict of Interest

Dr. Patel declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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