

Stinging the Conscience: A Case of Severe Hymenoptera Anaphylaxis and the Need for Provider Awareness

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ABSTRACT Hymenoptera venom allergy accounts for approximately 17% of all cases of anaphylaxis. Insect stings are a common occurrence across the world, with significant impact on active duty personnel. Venom immunotherapy (VIT) provides an effective treatment for those with systemic reactions to insect stings and other similar indications. We present a case of severe reaction to hymenoptera venom requiring an epinephrine drip and provide an overview for primary care providers on who should be referred to allergy or an allergist, carry an epinephrine auto-injector, and be a candidate for VIT. As this case demonstrates, such a framework is critical as even patients with a history of severe reactions may have a delay in referral to specialty care. The preventable morbidity and mortality associated with hymenoptera venom allergy represents a clear imperative to identify those service members at risk for future systemic symptoms and to refer them for assessment and VIT therapy. Allergy evaluation and treatment with VIT affords the opportunity for service members to be retained in the military and remain medically fit and ready for deployment around the world.

INTRODUCTION

Hymenoptera venom allergy (HVA) accounts for approximately 17% of all cases of anaphylaxis.¹ Insect stings are a common occurrence across the world, with significant impact on active duty personnel. One analysis of U.S. Department of Defense medical records in the U.S. Central Command area of operations found that approximately 1 out of every 500 clinic visits was related to insect stings.² Most insect stings result in a limited local reaction characterized by pain with minimal swelling and erythema. Of greater importance are reactions that involve systemic symptoms, as these can result in both significant morbidity and mortality. Furthermore, a history of HVA impacts both the health as well as the accession and retention of active duty military personnel.

A variety of reactions occur with insect stings, each with varying risk of systemic reaction following future stings. The more common type of these reactions is a large local reaction (LLR), which creates a large area of swelling and erythema at the site of the sting. This is an IgE-mediated late-phase reaction. There is no precise definition of a LLR, but the accepted size criteria have been described to be approximately 10 to 15 cm in diameter.³ After a LLR, systemic reactions occur 5 to 10% of the time following a subsequent sting.⁴ Particularly important for military personnel, these LLRs can cause transient disability. More severe reactions involve systemic symptoms including urticaria, angioedema, bronchospasm, tracheolaryngeal edema, and hypotension. These systemic symptoms are associated with an up to 70% risk of anaphy-

laxis with future stings.⁵ The overall risk of anaphylaxis from insect stings is estimated to be 0.4 to 0.8% in children and 3% in adults in unselected populations.⁵⁻⁷ Insect sting anaphylaxis accounts for more than 40 deaths in the United States each year.⁸ The most common symptoms leading to death is laryngeal edema and circulatory failure.

HVA can be confirmed by skin testing or by specific IgE immunoassay. Skin testing is performed using serial dilutions of five flying hymenoptera and, when indicated, fire ant venom. Specific criteria guide interpretation of this form of testing. Patients with anaphylactic reactions should also be screened for mast cell disorders, by obtaining a serum tryptase level. If it is elevated, the patient may have mastocytosis or another aberration of mast cell number or function, increasing the risk of fatal anaphylaxis.¹

Case Presentation

A 28-year-old male was found unconscious by Emergency Medical Services after being stung by an insect. The patient later reported to have been riding his motorcycle at the time, when he believed a wasp stung his right hand. The patient almost immediately began to feel weak and to experience facial flushing. He lost consciousness 1 to 2 minutes later, and was later found to be in respiratory distress with signs of peripheral cyanosis. At the scene, Emergency Medical Services delivered multiple intramuscular injections of epinephrine before the patient was taken to the hospital, where he was started on an epinephrine drip for 24 hours. He was discharged home with a 3-day course of oral steroids and multiple epinephrine auto-injectors with follow-up in an Allergy-Immunology clinic. At that follow-up clinic visit, it was also revealed that he had a prior history of allergic reactions to hymenoptera stings. When he was about 5 years old, he was stung by a honeybee and developed hives. Then, at age 22, he was stung again by an unknown flying insect, which caused him to lose consciousness upon arrival at the

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Emergency Department (ED). He was discharged with an epinephrine auto-injector by the ED but at that time it was not recommended to seek evaluation with Allergy-Immunology.

The patient's skin testing was positive at low concentrations of venom extracts to yellow jacket, yellow hornet, white-faced hornet, and wasp. He was then started on venom immunotherapy (VIT) using mixed vespid (yellow hornet, white-faced hornet, and yellow jacket) and wasp to be given indefinitely, due to the severity of his reaction. His serum tryptase level was 4 ng/mL, which is within normal limits (2–10 ng/mL).

DISCUSSION

The patient's severe reaction, particularly since it was later revealed to have been preceded by a reaction of similar severity, highlights the need for provider awareness of the availability of venom testing and effective treatment. In "Stinging insect hypersensitivity: A practice parameter update 2011" the Joint Task Force on Practice Parameters, the American Academy of Allergy, Asthma, and Immunology, and the American College of Allergy, Asthma, and Immunology, recommend referring patients with a history of hymenoptera hypersensitivity to an Allergy/Immunologist for evaluation and possible VIT.⁹ This includes any patient who has had a systemic reaction and patients older than 16 years of age with cutaneous reactions such as hives. Those with LLRs that are disfiguring or disabling or who may live or work in a remote area may also be considered as candidates for VIT. Because of this patient's severe reaction to hymenoptera venom and the significant risk of subsequent anaphylaxis (up to 70%), the patient was referred to an allergist and VIT was started. VIT reduces the risk of future life-threatening systemic symptoms to approximately that of the general population while patients remain on maintenance injection dosing (Table 1). Treatment with VIT is thus an effective treatment for patients with the above indications and evidence of venom-specific IgE on skin or blood test. Such evaluation and treatment options are particularly important considerations for military personnel, who often work and train in remote, austere, or hazardous environments in which HVA poses an increased threat.

Once a patient has a reaction to a sting, it is important to categorize which type of reaction occurred, since it will define the ultimate management of the patient. The different

type of reactions are LLR, cutaneous only reaction, and systemic reactions of different severities. LLRs usually increase in size for the first 24 to 48 and are generally greater than 10 cm in diameter. The swelling is usually accompanied by itching or pain. These reactions are mostly IgE mediated and usually are self-limited in nature. They frequently can be treated with supportive measures such as cold compress or oral antihistamines. Although this form of reaction is associated with as high as a 10% risk of systemic reaction with future stings, this rate has been consistently regarded in the literature to be below that, which should prompt consideration for VIT. This is based on the finding that the risk of systemic reactions to hymenoptera stings in an unselected skin test positive population is 17%.⁹ However, sometimes these LLRs can be disfiguring or disabling, which could significantly impact morbidity for those who live, operate, or work at home or in remote areas. This subset population should be considered as candidate for VIT, since newer evidence shows the VIT significantly reduces the size and duration of the LLR.^{9,10}

Patients should be educated on avoidance measures to decrease the likelihood of insect stings, as outlined in Table 2. However, these measures are unlikely to completely eliminate the threat of insect stings. Patients with systemic reactions should be provided with epinephrine auto-injectors and educated on their use and indications for use. For patients in the military, they should be given more than one epinephrine auto-injector, given the short duration of action of epinephrine and service members' frequent operation in more remote locations. Patients should also be educated on using medical alert devices, such as medical identification bracelets or necklaces, so that their allergy could be more readily identifiable in emergency situations.⁹ Those with lower risk of severe anaphylactic reactions should have a thorough discussion weighing the risks and benefits of carrying an epinephrine auto-injector. This includes patients with a history of LLR to stings, cutaneous only systemic reaction, and those who discontinued VIT after more than 5 years of treatment. Epinephrine is the main treatment for anaphylaxis. Although antihistamines and corticosteroids can be used in an adjunctive capacity, these medications do not replace epinephrine in the treatment of anaphylaxis. The recommended dose of epinephrine is 0.01 mg/kg, which is up to 0.3 mg

TABLE 1. Types of Reactions and Risk of Systemic Reaction With Positive Skin Test to Hymenoptera^{1,4}

Symptoms		Risk of Systemic Reaction With Next Sting Without VIT (%)	Risk of Systemic Reaction With Next Sting With VIT Maintenance (%)
Large Local Reaction	Pain, Swelling, and Erythema at the Site of A Sting	5–10	Unknown—VIT Not Indicated in Most Large Local Reactions
Cutaneous Only (Adults: >16 Years Old)	Urticaria, Angioedema	Children 5–10 Adults 10–20	2–5
Systemic Allergic Reaction	Anaphylaxis, Hypotension, Bronchospasm, and Tracheo-Laryngeal Edema	50–70	2–5

TABLE II. Preventing Insect Stings^{1,9,15}

If you have nests located around your home or work place, have the nests removed by a trained professional.
Have at least annual inspections for insect nests.
Avoid wearing brightly colored clothes or clothes that have flower patterns, instead wear light-colored, smooth-finished clothing.
Wear clothing to cover as much of the body as possible.
Avoid walking outside barefoot or with exposed feet.
Avoid scented soaps, shampoos, and deodorants as well as cologne and perfumes.
Be cautious near bushes, eaves of houses, and attics.
Always bathe daily, since sweat may anger bees.
Avoid leaving food uncovered or open trash. Wasps can be found in places where people throw away food.
If 1 stinging insect is nearby, remain calm and still, since swatting at an insect may cause it to sting.
If a stinging insect is inside your vehicle, first bring the car to a stop slowly, and then open all the car windows.
If several stinging insects attack you at once, run to get away from them. When a bee stings an individual, it can release a chemical, which may attract other bees in the vicinity. The best place to find shelter is indoors.
Do not jump in water when you are stung, since Africanized Honey Bees are known to hover above water. The bees can continue to sting you when you come up for air.

(1:1000 epinephrine) in children and 0.3 to 0.5 mg (1:1000 epinephrine) in adults.

If a patient is taking a beta-adrenergic blocker, they may not respond as well to epinephrine if they are experiencing anaphylaxis. The symptoms of anaphylaxis may be more severe, prolonged, and more difficult to treat. Providers caring for patients with a history of systemic systems with insect stings should seek alternative agents and patients should not be on a beta-blocker while receiving VIT unless absolutely necessary. If beta-blockers are continued, they should be used cautiously and shared decision making should occur with the patient.^{9,11,12} The other medications to use with caution in patient undergoing VIT are angiotensin-converting enzyme inhibitors (ACE-I). This class of medication has also been associated with more severe anaphylaxis in hymenoptera allergic patients suggested by one retrospective study; however, previous smaller studies showed no such increased risk with exposure to ACE-I.¹³ Again, the risks and benefits should be shared with the patient when prescribing an ACE-I to patient with history of insect stings or currently undergoing VIT.

All patients with severe systemic symptoms from insect stings should undergo screening for a mast cell disorder. This is done by obtaining a serum baseline tryptase level. If elevated, it should be repeated to evaluate for baseline elevation of tryptase suggestive of mastocytosis. A tryptase level is considered to be abnormal if it is greater than 11.4 ng/mL. In patients with mast cell disorders, the level is frequently greater than 20 ng/mL. If the level is elevated, the patient should undergo further testing to include a possible bone marrow biopsy to assess for other criteria of mastocytosis. It is important to recognize those patients with elevated serum baseline

tryptase levels or mastocytosis, as both are at higher risk for severe anaphylaxis if they have another insect sting.^{1,14}

If a patient is started on VIT, they are started on serial dilutions of each insect venom they are allergic to. It is not until reaching the maintenance dose that the full protective effect of VIT is in effect. In addition to the more traditional build-up schedule, using weekly injections over several months, another option is for a patient to be placed on a rush protocol. Such protocols allow patients to rapidly scale up from their initial doses of VIT to maintenance levels within days to weeks and has been shown to be as safe and effective as the weekly build-up schedules that are in more common use. This therapeutic option represents a very important tool in treating military members who may need to rapidly achieve the protection at maintenance dosing before deployment or returning to flight status. The compressed timescale may also allow a greater degree of flexibility when considering waivers and other options related to accession, commissioning, or retention. After reaching maintenance dosing, the injections are slowly spaced out over 2 to 3 years to a safe interval of 6 to 8 weeks. One investigator has shown that it was safe to go out as far as 12 weeks, but more studies must be done to replicate these findings.⁹ Usually patients can safely stop VIT after 3 to 5 years. The length of time for VIT is partly based on the severity of the reaction. In the case of our patient, since he had such a severe reaction to the hymenoptera sting, he will need lifelong VIT. Given the protective effect of VIT he will be able to remain on active duty in the military with a medical waiver and is considered world-wide deployable. Regulations regarding medical waivers for entering the military as well as retention for each service are published in each services' specific instructions: Navy Medicine (NAVMED) P-117 Article 15-2, Army Regulation 40-501 Chapter 2, and Air Force Instruction 48-123.

CONCLUSION

Systemic reactions from insect stings can be life-threatening events and must be distinguished from LLRs. It has been estimated that 50% of the deaths from insect stings occur in subsequent stings.⁹ This means that up to half of all deaths due to insect stings may be preventable if the patients were started on VIT. Primary care providers should be able to identify the common signs and categories of HVA reactions. It is imperative that primary care and ED providers refer those patients with a history consistent with systemic symptoms, cutaneous reactions (those over 16 years old), and select patients with a history of LLRs to Allergy specialists for further evaluation of insect venom allergy and potential VIT. For military personnel, stinging insects clearly pose a threat due to the prevalence of hymenoptera throughout the world and the often remote and austere environments in which military forces operate. The risk posed by insect stings to US service members has already been demonstrated in Afghanistan. The preventable morbidity and mortality associated with HVA represents a clear imperative to identify

those service members at risk for future systemic symptoms and to refer them for assessment and VIT therapy. Allergy evaluation and treatment with VIT allows those service members to be retained in the military and remain medically fit and ready for deployment around the world.

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