



MOC-CME Review

Evaluation of venom allergy

Ami Philipp, MD^{*}; Ronald M. Ferdman, MD, MEd[†]; Jonathan S. Tam, MD[†]^{*} Department of Allergy and Immunology, Greater Los Angeles Veterans Affairs Medical Center, Los Angeles, California[†] Division of Clinical Immunology and Allergy, Department of Pediatrics, Children's Hospital Los Angeles, Los Angeles, California

ARTICLE INFO

Article history:

Received for publication July 19, 2016.

Received in revised form August 8, 2016.

Accepted for publication August 9, 2016.

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- Approximately 4-6 weeks later you will receive an online outcomes assessment regarding your application of this article to your practice. Once you have completed this assessment, you will be eligible to receive MOC Part II credit from the American Board of Allergy and Immunology.

Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the algorithm for managing a patient with an insect sting reaction
- Discuss the benefits of referral of patients with venom allergic reactions to an Allergist
- List the features that identify high risk insect sting allergy patients

Release Date: October 1, 2016

Expiration Date: September 30, 2018

Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

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Ronald M. Ferdman, MD, MEd (Author)

Jonathan S. Tam, MD (Author)

Jonathan A. Bernstein, MD (Annals CME Subcommittee)

Guha Krishnaswamy, MD (Annals CME Subcommittee)

Reprints: Jonathan S. Tam, MD, Division of Clinical Immunology and Allergy, Department of Pediatrics, Children's Hospital Los Angeles, 4650 Sunset Blvd, MS 75, Los Angeles, CA 90027; E-mail: jstam@chla.usc.edu.

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2016.08.012>

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Disclosure of Relevant Financial Relationships

M.H. Grayson has received research grants from Children's Research Institute/Children's Hospital of Wisconsin, Merck, National Institutes of Health (NIH), and Polyphor. G.D. Marshall has received research grants from Amgen, AstraZeneca, Health Resources and Services Administration (HRSA) and National Institutes of Health (NIH). J.J. Oppenheimer has been a consultant/advisor for AstraZeneca, GlaxoSmithKline, Meda, Mylan, and Sunovion; has received research grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline and Novartis. G. Krishnaswamy has received research grant CSL Behring. J.A. Bernstein, A.T. Philipp, R.M. Ferdman and J.S. Tam have no relevant financial relationships to disclose. Reviewers and Education/Editorial staff have no relevant financial relationships to disclose. Any unapproved/investigative uses of therapeutic agents/devices discussed are appropriately noted.

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Clinical Vignette

An 18-year-old woman presents to clinic after a bee sting she received at a picnic caused her to break out in diffuse urticaria within 3 minutes. She denies shortness of breath or any other symptoms. Her urticaria resolved after she took 50 mg of diphenhydramine. She is wondering if there is anything that needs to be done now that her reaction is over.

Introduction

A significant number of adults (3%) and children (1%) experience systemic reactions to Hymenoptera stings, leading to approximately 40 to 100 fatalities in the United States each year.¹ However, the number of fatalities is likely an underestimate.² The Hymenoptera insects that most commonly cause allergic reactions are from the families Apidae (honeybees), Vespidae (hornets, wasps, and yellow jackets), and Formicidae (fire ants).³ Table 1 lists the characteristics of these insects. Stinging insect venom is a complex mixture of multiple components, including proteins, enzymes, vasoactive amines, and others. Several of these components contribute to the normal local reaction of pain, itching, erythema, and edema seen in all patients. In sensitized patients, proteins in venom will bind to venom specific IgE on mast cells, which causes release of classic mast cell mediators. These mediators can then cause a range of symptoms from local skin reactions to anaphylaxis and death. Systemic reactions can be divided into cutaneous only (flushing, itching, urticaria, angioedema) or reactions with extracutaneous symptoms (bronchospasm, upper airway edema, hypotension, gastrointestinal, and rarely cardiac arrhythmias and seizures). As many as 35% to 60% of patients with previous severe systemic reactions will have anaphylaxis if stung again,¹ even after 10 to 20 years. In contrast, although also IgE mediated, patients with large local reactions (defined as slow onset of swelling during 1 to 2 days of than 10 cm and contiguous with the injection site) have a less than 10% chance of a systemic reaction on subsequent stings.³

It is recommended that patients with systemic reactions to venom be prescribed an epinephrine autoinjector, taught how to use it, and referred to an allergist.¹ Allergy referral is important for preventive education, confirmation of diagnosis, and treatment.⁴ In a retrospective cohort study of 617 patients presenting to the emergency department during 1 year with a diagnosis of insect sting allergic reaction, only 3% of patients with systemic reactions received all recommended preventive treatments (discussion about avoiding the allergen, self-injectable epinephrine prescription, and referral to allergist). Only 20% of patients with systemic reactions were referred to an allergist.¹ These data are consistent with many other studies that demonstrate low allergy referrals from the emergency department in patients with systemic reactions but do not take into account patients who present to their primary care clinics instead of an emergency department. A retrospective study performed at a Veterans Affairs hospital found that of 192 patients with venom allergy during 2013 to 2014, only 23 patients (12%) were referred to an allergist from both primary care clinics and emergency departments combined (A.P., unpublished data, 2016).

Diagnostic testing for venom allergy can be performed by skin testing or IgE serum testing and is indicated for patients that are candidates for venom immunotherapy (VIT).⁵ The decision to test for Hymenoptera allergy should be based on the patient's clinical history. If a present or past systemic reaction was reported, the patient was a candidate for testing, even if he/she had a subsequent sting without reaction after the systemic reaction occurred.⁶ Skin testing should be delayed 3 to 6 weeks after the sting reaction because of false-negative test results, which can occur transiently after systemic reactions.⁹ Testing is indicated to all vespids and apids even if the patient is confident in the identification of the insect. This is because patients are able to correctly identify the culprit insect with low accuracy and because there is a possibility that there is sensitization to other venoms.⁵ If fire ants are the likely culprit, which is usually obvious by history and the characteristic

Table 1
Characteristics of Hymenoptera^{3,7}

Common name	Family	Nesting habits	Feeding habits	Aggressiveness
Honeybee	Apidae	Beeswax nests with closed hexagonal honeycombs in low structures such as tree cavities and walls, manmade hives	Nectar and pollen	Nonaggressive (when stings occur, classically leave stinger in skin)
Bumblebee	Apidae	Bunch of grapes shaped waxed nest in underground cavities, under structures or in fibrous material	Nectar and pollen	Nonaggressive (less aggressive than honeybee)
Fire ant	Formicidae	Mounds in soil (1–2 ft in diameter and elevated several inches, nondenuded of grass or weeds)	Omnivorous	Aggressive in defense of mounds (will sting in mass and multiple times in a circular pattern)
Paper wasp	Vespidae	Aerial open comb paper nests hang from pedicles in shrubs, under eaves of houses, or natural overhangs	Nectar, predacious of other insects	Aggressive in defense of nests
Yellow jacket	Vespidae	Paper nests usually underground, can be in low tree cavities or low walls	Nectar, fruit, tree sap, and predacious of other insects; scavengers	Very aggressive
Bald-faced or white-faced hornet and yellow hornet or aerial yellow jacket	Vespidae	Large aerial paper nests in tree or shrubs	Predacious of other insects, nectar, fruit; scavengers	Aggressive in defense of nests
Hornet or European hornet	Vespidae	Aerial paper nests in crevices or surrounded by a paper envelope	Predacious of other insects	Aggressive in defense of nest and around food. (fly at night and attracted to light)

sterile pustules at the sting sites, testing to only fire ant is sufficient. Diagnostic skin testing for vespids and apids typically starts with a prick test using a venom concentration of 100 $\mu\text{g/mL}$. Then, if the test result is negative, intradermal skin testing at 0.001 to 0.01 $\mu\text{g/mL}$ should be performed. If the results are negative at these concentrations, the concentration is increased by 10-fold until a positive response occurs or a maximum concentration of 1 $\mu\text{g/mL}$ is reached. A positive response is considered a 5 mm wheal or larger; however, many allergists also consider a positive result a wheal 3 to 5 mm greater than the negative control. For fire ants (tested using whole body extract), skin prick testing can start at 1:100 (wt/vol). If the results are negative, intradermal testing can be performed with initial concentrations of 1:1 million (wt/vol) and increasing if the results are negative to 1:100,000 (wt/vol), 1:10,000 (wt/vol), and then 1:1,000 (wt/vol).⁷

Although skin testing is preferred because of higher sensitivity, in vitro testing can also be performed for diagnosis. In vitro testing is also helpful if skin test results are negative in the face of a strong clinical history. If there is negative skin test result but a positive in vitro test result in patients with systemic reactions to insect sting, many clinicians will initiate VIT. There is no absolute correlation between the level of serum venom specific IgE or skin test reactivity and the severity of reaction to stings, and anaphylaxis can occur even in patients with low serum venom specific IgE levels. Rare occurrences of anaphylaxis have been reported in patients with negative skin test and in vitro test results.⁵ If skin and in vitro test results are negative but the clinical history is strongly suggestive of an anaphylactic reaction, additional testing should be performed in approximately 3 to 6 months.

Approximately 8% to 11% of patients presenting with Hymenoptera allergy have preexisting mast cell disorders.⁸ Serum tryptase should be checked in all patients with severe reactions after a sting, especially in those with hypotension and/or the absence of skin findings. Tryptase should also be checked when there is a history of a severe sting reaction but with negative skin and serum test results for venom specific IgE. If the serum tryptase level is elevated above 11.4 ng/mL, investigation into mast cell disorders should be undertaken.⁷ Baseline tryptase level should be checked after the reaction to the sting has resolved and the patient is at the baseline state of health. An elevated baseline tryptase level is associated with more severe reactions to stings in general, more

frequent treatment failure, and a greater risk of relapse after stopping VIT.⁹ If a mast cell disorder is discovered, these patients should undergo VIT indefinitely.

Administration of VIT in patients who have a systemic reaction reduces the risk of subsequent reactions to less than 5%.¹⁰ Honeybee VIT is less effective than vespid immunotherapy at preventing systemic reactions (10%–15%) and causes higher rates of systemic reactions.¹¹ Candidates for VIT include anyone with an IgE-mediated systemic reaction to venom. Children younger than 16 years do not necessarily qualify for VIT if only a cutaneous reaction occurred. Studies have found that if re-stung, the chance of anaphylaxis is less than 3%.⁵ VIT and diagnostic testing is not required in patients with large local reactions because the risk of systemic reaction is relatively low (5%–10%).¹³ In situations in which VIT is optional (systemic cutaneous reactions in older patients and large local reactions), other factors need to be considered when deciding to start VIT, such as risk of re-sting, effect on lifestyle, severity of large local reaction, underlying medical conditions, and patient or family anxiety.

For adults older than 16 years, there is some controversy about whether VIT is necessary for those with only cutaneous reactions.¹² The practice parameters are being revised currently, and guidelines may change in the future. One of the biggest draft changes is addressing the treatment of patients with purely cutaneous systemic reactions. The current draft practice parameter groups cutaneous systemic reactions with large local reactions, thus removing the recommendation for VIT. This is based on prospective studies looking at insect sting challenges that have revealed a low chance of progression and no severe reactions on re-sting in patient with cutaneous systemic reactions.⁶ One prospective study looked at live yellow jacket sting challenges in 111 patients. In only 1 of the 111 patients (0.9%) was the reaction to the challenge sting worse than the previous historical reaction.⁶

Patients taking cardiovascular medications, such as β -adrenergic blockers, are known to be less responsive to epinephrine treatment if they have anaphylaxis. Because of this, patients undergoing VIT should not be prescribed β -adrenergic blockers unless absolutely necessary. If they are unable to discontinue use of the medication before initiating VIT, cautious initiation of VIT is acceptable.⁵ Angiotensin-converting enzyme inhibitors were found in one retrospective study to increase the severity of anaphylaxis,

although other studies have found no increased risk.⁵ Many allergists will still initiate VIT in patients taking these cardiovascular medications, while also evaluating each case individually and treatment these patients more cautiously.

There is no general consensus about which venoms to include in VIT. Some authors recommend adding only the culprit venom despite positive results to other venoms during testing. This can be problematic if it is difficult to identify the culprit insect definitively. Others recommend adding all venoms to which the patient tested positive.⁵ There is also the possibility of cross-reactivity in certain insects, such as hornet and yellow jacket, because they are part of the same Hymenoptera subfamily. If a patient has positive results to more than one vespid, consider using a mixed vespid extract, which has a full dose of each venom. Venoms cannot be mixed in the same injection unless using the commercially available mixed vespid extract.¹²

Venom immunotherapy schedules typically start at doses of 0.1 to 1.0 μg and increase to maintenance dosing of 100 μg of each insect venom (300 μg of mixed venom). Young children may be effectively treated with maintenance dose of 50 μg .⁵ This is the equivalent of 2 honeybee stings and 5 to 10 yellow jacket stings. Once maintenance dosing is reached, patients come in monthly for the first year and later can be seen at 6 to 8 weeks and even 12 weeks.¹⁴ To reach maintenance dosing, patients typically step up doses weekly; however, there are accelerated dosing schedules available. Studies have found that most accelerated dosing schedules do not cause increased adverse effects, the exception being ultrarush schedules, which may have higher rates of systemic reactions.¹⁵ Some patients may need premedication with antihistamines to minimize disturbing local reactions. Conventional dosing schedules allow maintenance dosing to be achieved in 8 to 15 weeks. Modified rush or cluster protocols allow maintenance dosing to be reached in 6 to 8 weeks. Rush immunotherapy protocols allow maintenance dosing to be achieved in 3 to 6 days. Maintenance dosing can be achieved in 1 to 2 days or even hours in ultrarush protocols.^{16,17}

A minimum of 3 to 5 years is recommended for the duration of VIT. Approximately 80% to 90% of patients who complete this duration of VIT do not have a systemic reaction to a future insect sting.¹⁸ Lifelong immunotherapy is recommended in patients with honeybee systemic reactions, patients with systemic reactions during VIT, those with elevated baseline tryptase levels, or those with a diagnosis of systemic mastocytosis. These patients have a higher risk for systemic reactions after re-sting.^{9,19} Lifelong VIT can also be considered in patients with life-threatening reactions to sting before VIT. Some practitioners also prefer to see a decrease in venom serum IgE to insignificant levels or negative skin test results before discontinuing VIT, although this not universally agreed on.

Conclusion

The patient described in this clinical vignette was likely stung by one of the scavenger insects (Table 1) given her proximity to food at a picnic. She should be educated on effective ways to minimize future stings, such as caution when eating or drinking outdoors, always wearing shoes outdoors and long sleeves and pants when possible, removing debris that could attract stinging insects (eg, fallen fruit), and covering trashcans. Insect repellent products

that contain N,N-diethyl-meta-toluamide (DEET) are not effective against stinging insects. Apart from this education, however, the treatment of this patient is not as straightforward as it may seem. The current practice parameters recommend prescribing auto-injectable epinephrine, testing for venom specific IgE, and, if results are positive, starting VIT. However, the upcoming draft revised practice parameter indicates that autoinjectable epinephrine, testing, and VIT would not be routinely recommended in this scenario because of the relatively low risk of more serious systemic reactions on subsequent stings. Instead, the decision to prescribe epinephrine and VIT would be optional based on other considerations (eg, quality of life, frequency of stings) made after a thoughtful discussion with the patient regarding risks and benefits of VIT.

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