CME

Reducing the sting: Diagnosis and management of Hymenoptera venom allergy

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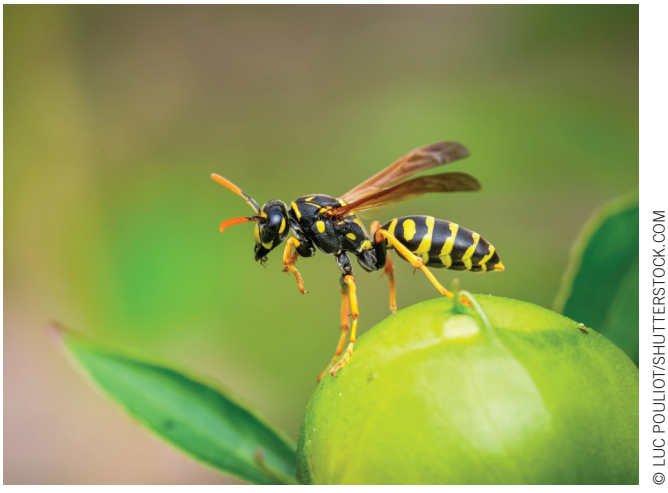
ABSTRACT

Hymenoptera species include stinging insects such as wasps, hornets, bees, and fire ants. Allergic reaction to the venom of these insects is a common presenting complaint for patients in primary care and emergency medicine during warmer months. Patients' clinical presentations may vary, and clinicians must identify the type of reaction to determine treatment and follow-up plans. Treatment of patients allergic to Hymenoptera venom should be individualized based on risk factors, reaction type, and associated comorbidities. This article reviews common features of clinical presentation, diagnosis, and the current mainstays in management of Hymenoptera venom allergy.

Keywords: Hymenoptera, venom, allergy, sting, insect, anaphylaxis

Learning objectives

- Understand the variable clinical presentations associated with Hymenoptera allergy.
- Discuss options for diagnostic testing in patients with local and systemic presentations of Hymenoptera allergy.
- Explain the appropriate management of allergic patients based on their clinical presentation.



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Hymenoptera venom allergy is a significant cause of patient morbidity and mortality in urgent, emergent, and primary care settings and is one of the most common causes of anaphylaxis in adults.[1] The species most often responsible for severe venom allergy is the Vespula, or wasp.[2] Other species whose venom commonly causes an allergic response include the honeybee, hornet, yellow jacket, and fire ant.[3] Patients who spend more time outdoors, for example those employed in the restaurant, forestry, or horticultural industries, tend to incur the highest risk because of their increased exposure. Beekeepers farm Hymenoptera species for the harvest of honey, which increases the risk of exposure as well.[1]

After being stung, most patients experience mild localized pain, swelling, and erythema at the sting site. Some develop local or systemic allergic reactions that are variable in nature. Most patients with an allergy to Hymenoptera venom will present with a large local or systemic reaction, ranging from a mildly uncomfortable skin reaction to a potentially fatal reaction. This article discusses the differences in presentation, diagnostic tools, most effective management, and follow-up plans for each type.

EPIDEMIOLOGY

Hymenoptera allergy can present a diagnostic challenge, and the patient's clinical presentation varies depending on several factors. An estimated 1% to 7% of the population develops an allergic reaction to Hymenoptera; stings in the mouth and throat typically have the worst presentation and prognosis because of the risk of airway compromise.[2] Data suggest that adults are more likely to present with severe systemic reactions than children.[1] This is likely because of the increased likelihood of being stung *again* versus developing a naïve reaction with increasing age.

The venom of many species of stinging insects can cause an allergic response, and the prevalence of stings by a given

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Key points

- The severity of allergic reaction to Hymenoptera venom varies, from a large local reaction to potentially fatal anaphylaxis.
- Patients stung by wasp species are more likely to have severe reactions.
- CRT, BAT, and serum tryptase levels are the mainstays of risk assessment and diagnosis in patients with severe Hymenoptera allergy.
- The use of CRT and BAT provide a means for targeted venom to individual venom components and is a highly effective method of desensitization.

species varies by geographic region. Some species share similar venom components, which can cause cross-reactivity and resultant "re-sting" reactions despite absence of the original offending insect.[4] For example, a patient who experiences a reaction to Vespula spp sting may also react to Vespa spp sting because of similarities in the composition of their venom.

Rates of Hymenoptera allergy are higher in beekeepers and individuals who spend more time outdoors.[1,5] Rates of allergenic stings have been steadily increasing worldwide.[6] Some researchers theorize that climate change is driving migration of native species and affecting the rate of exposure.[6]

FIGURE 1. The author's large local reaction to a Vespula sting

CLINICAL PRESENTATION

Patients presenting with Hymenoptera allergy can experience a range of symptoms, from a local reaction to systemic symptoms or anaphylaxis. The severity of the reaction depends on multiple factors, including patient genetics and other associated comorbidities.[1]

Large local reaction This type of reaction is characterized by erythema and induration greater than 10 cm in diameter (**Figure 1**). It may develop over the course of 1 to 3 days and typically takes 7 to 10 days to resolve.[7,8] Patients with large local reactions typically experience itching, pain, and sometimes blistering.

Systemic (anaphylactoid) reaction Patients who have a systemic reaction can present with a spectrum of symptoms associated with systemic allergic response: generalized urticaria, malaise, pruritus, laryngeal swelling, or angioedema. Those with a severe allergy can develop respiratory symptoms that progress to collapse, hypotension, incontinence, or syncope. Some also will experience abdominal pain, cramping, and vomiting in response to allergen inoculation.[9] Serum sickness is a rare response to Hymenoptera sting, and is characterized by fever, swelling, and joint pain.[10]

RISK FACTORS

Identifying patient risk factors associated with re-sting allergic reaction is an important piece of the puzzle, especially when determining whether a patient will benefit from venom immunotherapy. Data show that males tend to develop anaphylaxis more frequently than females.[11] Older patients develop more severe reactions overall than younger people, possibly due to the higher incidence of previous sting reactions.[11] Patients stung by wasp species also are more likely to have severe reactions.[11] A study that looked specifically at wasp and honeybee venom determined that a short sting-to-reaction time and a lack of cutaneous symptoms were directly related to increased severity of reaction.[12] IgE levels were not specifically related, but serum tryptase levels at baseline were positively correlated with severe reaction.[12] Another risk factor for severe reaction in patients with Hymenoptera allergy is the incidence of mastocytosis or other mast-cell disorders.[11,13]

DIAGNOSIS

Diagnostic testing for Hymenoptera allergy typically is multifactorial and depends on the severity of the patient's initial reaction.

Patients with a reaction to Hymenoptera venom should first be questioned about their history of sting allergy. A patient with a naïve reaction who presents with severe anaphylaxis may need more aggressive treatment, because subsequent or "re-sting" reactions may be worse or even fatal.[14]

Patients with large local reactions can potentially develop severe symptoms upon re-sting. Some may benefit from diagnostic testing and venom immunotherapy.[9,15]

Patients with anaphylactoid reactions merit diagnostic testing for both the species and the venom component that caused the reaction. Consider referral to an allergy specialist for evaluation and advanced testing, including component resolved testing (CRT), basophil activation testing (BAT), and/or serum tryptase levels (**Table 1**).

Diagnostic testing in patients with Hymenoptera allergy has improved significantly in recent years with the development of CRT, which can detect IgE sensitivities to individual antigens.[5] CRT helps to differentiate between cross-reactivity and specific species associated with allergy.[5] This allows for targeted immunotherapy based on the specific venom that caused the reaction.[5,9] CRT can now be performed on multiple agents at the same time, which allows for more rapid and accurate identification of the allergy-inducing venom.[16] CRT also provides a means to identify cross-reactivity between honeybee and wasp venom, although it cannot yet differentiate between species of wasps.[17]

BAT uses flow cytometry to identify basophils that express markers of activation after cross-linking with IgE antibodies from the allergen.[18] BAT is useful for monitoring venom immunotherapy and can determine individual tolerance to venom.[19,20] BAT should not be used as a first-line diagnostic test for Hymenoptera allergy, but can be helpful in patients who do not have positive IgE testing after a symptomatic episode.[11]

Serum tryptase elevation, regardless of cause, can serve as a predictor of a high risk of anaphylactoid reaction to future stings, especially in patients with IgE reactivity.[11,21,22] This is particularly useful when treating patients with more severe local reactions or in situations where there is increased concern for future anaphylactic reaction. Serum tryptase levels may also be elevated at baseline in patients with mast-cell disorders; patients with underlying mast-cell disorders are at an increased risk of severe reaction.[11,14] Systemic Hymenoptera reactions also can be complicated by mast-cell activation, which can increase the risk of severe systemic reaction.[13,23]

TREATMENT

Patients with uncomplicated stings (meaning that they do not experience an allergic reaction) do not need testing and only require local first aid, consisting of prompt removal of the stinger and thoroughly washing the affected area. Identification of the species involved is helpful, because some species do not deposit their stinger upon envenomation. Manage localized pain by applying ice and administering oral anti-inflammatory and/or topical corticosteroid medications as needed. Manage subsequent reactions to venom based on the type and severity of the reaction that develops.

Large local reaction Patients suffering from a large local reaction are initially managed using oral and topical corticosteroid preparations. Some clinicians recommend antihistamines for localized itching, which may occur in a patient with a large local reaction. One review argues, however, that large local reactions typically are caused by delayed mediators and do not represent a histamine response, making antihistamines useless in this scenario.[24]

Systemic (anaphylactoid) reactions Patients presenting to the ED with severe systemic reactions should be treated immediately with epinephrine and IV fluids, such as 0.9% sodium chloride solution via large-bore IV access.[10] Trendelenburg positioning helps to ensure adequate blood flow to the heart and brain if the patient is hypotensive.[10] Monitor the patient until symptoms resolve and vital signs recover. Patients with severe reactions including respiratory collapse and hypotension should be observed for a minimum of 24 hours.[10] After the reaction is controlled and the patient is stable for discharge, prescribe an epinephrine autoinjector and refer the patient to an allergist for evaluation, specific antigen testing, and possible initiation of venom immunotherapy.[3,10]

TABLE 1. Diagnostic tests used for Hymenoptera venom allergy[5,9,11,14,16-22]

Test	Method	Application	Limitations
CRT	Serum: IgE antibody detection of individual antigens	• Helps to determine species causing reaction and predict cross-reactivity • Multiple tests can be performed at the same time, leading to rapid determination of offending agent • Used to determine mode of targeted immunotherapy	Cannot differentiate between wasp species
BAT	Serum: Identification of basophils that have cross-linked with IgE antibodies reacting to the offending agent	• Can help to determine allergy in patients with negative IgE test • Used to monitor venom immunotherapy	• Not a direct measure of antibody or antigen • Less reliable for initial testing
Serum tryptase testing	Serum: Direct measurement of tryptase levels	Can predict risk of severe reaction	Can be elevated at baseline if patient has a mast-cell disorder

Venom immunotherapy is recommended in patients with anaphylactic reactions and those with large local reactions who report a negative effect on their quality of life.[25] This therapy typically is well tolerated and has a low risk of morbidity and mortality.[3,11] Therapy is 77% to 98% effective depending on the species, with honeybee venom immunotherapy being the least effective and ant venom immunotherapy being the most effective.[26]

The use of component resolved diagnosis has provided a foundation for the evolution of venom immunotherapy from a generalized, whole-venom approach to a specific venom component-based approach. Venom immunotherapy activates T regulator cells that suppress the activity of the T helper 2 cells that incite an allergic reaction.[27] By suppressing T helper 2 activity, the cascade of cytokine release, and cellular activation is inhibited.[27]

Venom immunotherapy can be given in a rush or ultra-rush protocol with multiple venom exposures within a 6- to 36-hour period, or in a cluster protocol over the course of 3 or more weeks.[28] All of these methods are proven to be safe and effective, although the slower cluster protocols typically are associated with higher rates of venom immunotherapy-induced anaphylaxis.[29] One systematic review found that 9.3% of participants experienced a systemic allergic reaction to venom immunotherapy.[30]

The American Academy of Allergy and Clinical Immunology recommends venom immunotherapy for patients who have had a systemic reaction to a Hymenoptera sting.[27] The required duration of venom immunotherapy is not documented and at present can only be determined by a sting challenge.[27] Cases of anaphylaxis have been documented in patients with Hymenoptera allergy after they discontinued venom immunotherapy, and, though rare, some patients have developed anaphylactoid responses to the therapy itself.[31] Biologics, such as omalizumab, may help to prevent adverse reactions in patients with allergy to venom immunotherapy.[31]

PREVENTION

Patients with Hymenoptera allergy should be counseled in detail on prevention strategies and management of re-sting episodes. Appropriate diagnosis and targeted venom immunotherapy in patients with a history of severe systemic reaction can significantly reduce the risk of subsequent reaction.[32]

Some patients have increased sensitivity to Hymenoptera venom after a large local reaction. The consensus is that patients with a history of a large local reaction have a 0% to 7% risk of severe systemic reaction after re-sting.[1] A recent study found that a much larger percentage experienced systemic symptoms after re-sting than originally reported in the literature, and suggested that further research is needed to validate that the percentages reported in the literature do not underrepresent the true proportion.[1] In this study, 24% of participants with a history of large local reaction went on to develop a systemic reaction after a subsequent sting.[1] The authors of this study argue that their results support the use of epinephrine autoinjectors and venom immunotherapy in patients with localized allergic reactions to venom.[1] Another subsequent study found that the 2019 Bílo study's original methods were flawed and that after closer investigation the true number of patients who were re-stung by the same species of insect was much lower than originally reported.[15] The variable data obtained by these two studies show the lack of solid data on treatment of patients with large local reactions after initial presentation. The decision of whether to initiate preventive treatment for patients with large local reactions is controversial and requires more research. At this time, the American College of Allergy, Asthma, and Immunology does not recommend diagnostic testing for patients with large local reactions and recommends conservative measures for prevention, because of the low incidence of systemic symptoms on re-sting.[33]

Patients with previous allergic reaction to Hymenoptera venom should be counseled about how to prevent subsequent stings. Patients should avoid outdoor garbage receptacles and when eating outside, cover food and drinks when not in use. The CDC also recommends that patients wear light colors, avoid perfumes, bathe daily, keep work areas clean, carry an epinephrine autoinjector, and wear a medical ID bracelet.[34]

CONCLUSION

Diagnosis and treatment of patients with an allergic reaction to Hymenoptera venom is multifactorial, depending on the type of reaction and comorbid conditions such as mastocytosis. Clinicians in primary and emergency care settings must be well equipped to manage these patients according to current guidelines, and counsel them appropriately on how to avoid future stings. **JAAPA**

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