



An update on venom allergy

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Purpose of review

Allergic reactions to stinging insects may be unexpected, frightening, and severe. A clear understanding of recent advances in the field facilitates appropriate care of children who experience severe reactions to hymenoptera stings.

Recent findings

Recent investigations have underscored the importance of appropriate patient selection for potentially life-saving venom immunotherapy. Venom immunotherapy is effective in preventing future anaphylaxis from hymenoptera stings. Immunotherapy is indicated for patients with a history of anaphylaxis. Children who develop large local swelling or strictly cutaneous systemic reactions generally do not require immunotherapy. Component resolved diagnostic testing has been investigated to clarify the possibility of multiple venom allergies in patients with sensitization to multiple venoms.

Summary

Rapid recognition and treatment of anaphylaxis are critical. Subsequent education about avoiding future stings and attention to emergency preparedness with appropriate prescription of self-injectable epinephrine is important. Referral of patients who have experienced venom-associated anaphylaxis for possible venom immunotherapy can prevent future severe episodes of anaphylaxis resulting from stings.

Keywords

component resolved diagnostic testing, hymenoptera allergy, venom immunotherapy

INTRODUCTION

Allergic reactions to hymenoptera stings may be severe and potentially life-threatening. Confirmation of hypersensitivity requires skin testing and measurement of specific IgE against individual types of hymenoptera. Recent investigations have focused on epidemiology and risk factors for venom-associated anaphylaxis, attempts to improve diagnostics, and further demonstration of the effectiveness of venom immunotherapy for appropriately selected patients. An updated practice parameter from the Joint Taskforce on Practice Parameters is an excellent resource for the diagnosis and management of hymenoptera allergy in the USA [1]. Krishna *et al.* [2] also recently published guidelines for the diagnosis and management of hymenoptera allergy in the United Kingdom on behalf of the British Society for Allergy and Clinical Immunology.

EPIDEMIOLOGY

Stinging insect hypersensitivity occurs in 0.4–0.8% of children and 3% of adults [1]. In the United States, responsible hymenoptera include wasp, yellow jacket, white-faced hornet, yellow-faced

hornet, honeybee and fire ant. Although honeybees tend to be less aggressive, they may be a significant cause of venom hypersensitivity [3]. Bumblebees also tend to be less aggressive; although earlier studies showed a high degree of cross-reactivity with honeybee venom, a recent report by Cruz *et al.* [4[■]] suggested that cross-reactivity may be lower than previously assumed.

Harduar-Morano *et al.* [5] recently published a population-based epidemiologic study of emergency department visits for anaphylaxis in Florida. Two thousand, seven hundred and fifty-one patients with anaphylaxis were identified in the

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KEY POINTS

- Patients who have experienced venom-associated anaphylaxis should be educated regarding avoidance of future stings, prescribed self-injectable epinephrine, and referred to an allergist for testing and desensitization.
- Component resolved diagnostic testing may be incorporated into venom hypersensitivity diagnostic testing in the future, but the standard of care currently involves titrated venom intradermal skin testing in an allergist's office, measurement of venom-specific IgE, and in severe cases consideration of baseline serum tryptase measurement.
- Referral of patients who have experienced venom-associated anaphylaxis for possible venom immunotherapy can prevent potentially life-threatening episodes of anaphylaxis resulting from future stings.

study period of 2005–2006. Venom anaphylaxis was most likely to occur from August through October. As highlighted in this study, stings are more likely to occur during warmer months and during outdoor activities. In particular, both eating and drinking outdoors may increase the risk of stings, as stinging insects may be attracted to foods and beverages. This risk was illustrated in a case report by Stoevesandt *et al.* [6[■]] in which a 27-year-old woman unexpectedly developed generalized hives and facial angioedema 20 min after drinking orange juice from an opaque bottle that had been left open and unattended during the summertime. She subsequently experienced difficulty swallowing, hypotension, and vomiting. When she examined her vomit, she found a dead yellow jacket, which she did not recall swallowing or stinging her. Risk factors for re-sting include outdoor occupation, beekeeping, or living near areas where bees are kept [7[■]].

Yavuz *et al.* [8[■]] recently evaluated severe systemic reactions to insect venom during childhood. In this cohort of 76 children, the mean age of children at the time of reaction was 8.3 ± 3.4 years. In this group, only 66% of children had reported previous stings. This may be important, as often patients do not recall prior hymenoptera stings before the episode of venom-associated anaphylaxis. Ninety-nine percent of children experienced involvement of the cutaneous system. A history of comorbid atopic disease and eosinophilia were risk factors for more severe reactions.

Typical insect sting reactions are characterized by temporary local swelling that resolves within several days without treatment. Atypical reactions may include large local reactions and systemic reactions. Large local reactions are characterized by an

increase in size over 24–48 h, swelling to more than 10 cm in diameter contiguous to site of the sting, and resolution in 5–10 days [1]. Mild systemic reactions are characterized by hives and/or angioedema distant to the sting site without any oropharyngeal or other organ system involvement. Moderate systemic reactions involve additional organ systems with symptoms that may include wheezing, coughing, and abdominal cramping. Severe systemic reactions may involve marked respiratory distress, marked hypotension, syncope and cardiovascular collapse [9]. Future episodes of anaphylaxis following a sting may be similar to previous stings, but progressive reactions may occur. Valentine *et al.* [10] demonstrated over two decades ago that mild systemic reactions in children are unlikely to progress to more severe reactions on subsequent stings. In children aged 16 years and under whose reaction was limited to cutaneous manifestations without oropharyngeal involvement, 9.2% experienced a similar reaction with a future sting and no patients experienced a reaction more severe than the index mild systemic reaction.

Systemic reactions may occur from massive envenomation from multiple stings. Such patients who experience anaphylaxis may benefit from venom immunotherapy if venom sensitization is identified on subsequent testing. Serum sickness may be mediated by venom-specific IgE and may present in a more delayed fashion with pronounced arthralgias. Patients with demonstrable venom-specific IgE and a history of serum sickness may also benefit from venom immunotherapy. In a recent case report Wong *et al.* [11[■]] described a case of delayed-onset cold anaphylaxis following a hymenoptera sting. Although cold contact urticaria classically presents with urticarial wheals and/or angioedema within minutes of cold exposure, serious anaphylaxis may occur. Although most cases of cold contact urticaria are primary, the authors reported a secondary case presenting 12 days after a wasp sting. The patient had no previous cold urticarial symptoms, but following a wasp sting developed cold-associated symptoms that progressed to include lightheadedness, palpitations, vomiting, diarrhea, and generalized urticaria. The patient did have a history of large local reactions to stings and a positive 5-min cold stimulation test during subsequent evaluation. Positive hymenoptera intradermal skin testing was demonstrated. Over the ensuing year, cold-associated symptoms gradually improved but then recurred two weeks following a subsequent sting.

DIAGNOSTICS

During acute anaphylaxis, histamine and tryptase are released from degranulating mast cells. As

tryptase has a longer serum half-life, it is usually the preferred mediator assessed during acute allergic reactions to evaluate for mast cell degranulation. Borer-Reinhold *et al.* [12] recently emphasized the importance of comparing acute serum tryptase levels with baseline measurements. In their report, 40% of patients with systemic venom reactions experienced a rise in serum tryptase above 11.4 ng/ml (the upper limit of normal by many laboratory assays); however, an additional 45% of patients with systemic reactions had serum tryptase levels increase above 135% of baseline (but within the normal range for the assay). The authors concluded that a relative tryptase increase to above 135% of baseline during a suspected hypersensitivity reaction indicates mast cell activation, even below a level of 11.4 ng/ml.

Patients who have experienced anaphylaxis following a sting are highly likely to benefit from venom immunotherapy to decrease the risk of subsequent venom-associated anaphylaxis. Appropriate patient selection involves demonstration of specific venom hypersensitivity, which involves titrated intradermal skin testing. Although skin testing is the most sensitive method for demonstration of venom hypersensitivity, evaluation may also require specific IgE measurements to individual venoms. Patients may be anergic to testing for up to 6 weeks following a venom-associated anaphylactic reaction; therefore, testing is usually deferred for this period after a recent reaction [1]. However, even in patients who are tested after this period, those with negative tests but a strong clinical history may need to have testing repeated after 6 months.

Severe venom-associated anaphylaxis may indicate the possibility of undiagnosed mastocytosis. An elevated baseline serum tryptase indicates a risk for systemic mastocytosis. Wimazal *et al.* [13[■]] recently examined a series of 137 consecutive patients with mastocytosis receiving prophylactic antihistamines. Forty-two patients (31%) suffered one or more mediator-related symptoms (hypotension, headache, flushing, abdominal cramping, diarrhea) following a sting. Twelve percent of patients developed severe life-threatening events. One fatal event, one life-long disability from cerebral hypoxia, and two severe recurrent cases of venom-associated anaphylaxis were recorded.

Diagnostic dilemmas may result when patients with mastocytosis experience severe anaphylaxis following hymenoptera stings but present with negative testing to hymenoptera (by titrated intradermal testing and serum specific IgE testing) on evaluation. Bonadonna *et al.* [14[■]] evaluated the potential role of the basophil activation test in this population of patients. Unfortunately, neither the

basophil activation test nor increasing the maximum intradermal testing concentration to 10 µg/ml demonstrated incremental predictive value. In contrast to these data, evidence suggests that there may be some ability of the basophil response test to predict tolerance following a course of immunotherapy [15[■],16[■]].

Because positive testing to multiple venoms may result from cross-reactive carbohydrate determinants or specific IgE antibodies to several venoms, recent interest in venom allergy diagnostics has involved the use of component resolved diagnostics. These tests determine specific IgE antibodies to recombinant species-specific major allergens devoid of cross-reactive carbohydrate determinants. In a study of 56 venom-allergic patients receiving immunotherapy, Shin *et al.* [17[■]] demonstrated comparable positive and negative predictive values of rVes v 5-specific and rPol d 5-specific IgE detection with conventional venom-specific IgE ($r=0.762$ and $r=0.757$). Eberlein *et al.* [18[■]] found that 56% of patients with double positivity with standard IgE measurements had double positivity by component resolved diagnostic testing. A recent study by Muller *et al.* [19[■]] demonstrates that only 47% of such dual sensitized patients reacted to both species on component diagnostic testing. Relevance of these findings is limited by the lack of controlled sting challenges to the culprit insect (due to ethical limitations on sting challenges) [18[■]]. As pointed out by Sturm *et al.* [20], even these new novel tests may lead to false-positive and false-negative results. Consequently, none of these tests can be regarded as the gold standard to find clinically relevant sensitization, and whole venom testing remains the first approach to diagnosis [21[■]].

Historically, the ImmunoCAP (Phadia, Uppsala, Sweden) specific IgE system has been considered to have the greatest predictive index. However, Watanabe recently published data indicating that the IMMULITE 3gAllergy system demonstrated improved sensitivity and specificity; results were also more likely to agree with the systemic reaction history [22[■]].

MANAGEMENT

Severe anaphylaxis to venom in untreated patients may be life-threatening, as illustrated by a case report in which a 53-year-old previously healthy man developed an erythematous rash, chest discomfort, loss of consciousness, hypotension, and ECG changes with ST-segment elevations in II, III, and avF leads compatible with myocardial ischemia following a sting [23[■]]. Risk factors for severe venom-associated anaphylaxis include elevation of baseline

serum tryptase, older age, concomitant disease, and concurrent medication. Stoevesandt *et al.* [24[■]] recently reported a single-center observational cohort including 657 patients fulfilling criteria for venom immunotherapy. Risk factors from this study again included baseline serum tryptase elevation and older age. Additional risks included rapid development of symptoms following the sting (less than 5 min) and the absence of urticaria or angioedema during anaphylaxis.

Patients who have experienced venom-associated anaphylaxis should be taught to avoid stinging insects. Self-injectable epinephrine is recommended for all patients who have experienced anaphylaxis. The cost-effectiveness of a lifetime supply of self-injectable epinephrine for children who have experienced a mild systemic reaction involving only the cutaneous system with low risk for progression has been questioned [25]. Although some have recommended this as a standard of practice [26], a current practice parameter recommends this as a preference-sensitive intervention [1]. A new pocket-sized epinephrine autoinjector that provides audiovisual cues has been approved in the United States and may be an attractive option for some patients [27].

Venom immunotherapy (VIT) involves the gradual induction of tolerance by the administration of increasing amounts of relevant extracted venom to allergic individuals. Three decades ago, this therapy was shown to be effective compared with whole body hymenoptera extracts [28]. Today, whole body extract is only recommended for fire ant immunotherapy, as fire ant venom extract is not commercially available and fire ant whole body extract has been shown to contain relevant venom allergens [1]. Boyle *et al.* recently published a systematic review of the efficacy and safety of VIT, in which 392 participants from six randomized and one quasi-randomized control trial were identified. Participants included both children and adults with previous systemic or large local reactions receiving either sublingual (one trial) or subcutaneous venom immunotherapy. The finding that VIT was effective even in such a heterogeneous population was impressive. In fact, when assessed by either field sting or controlled intentional challenge sting procedures, only 2.7% of treated patients experienced a subsequent systemic allergic reaction, compared with 39.8% of untreated subjects [risk ratio (RR) 0.1, 95% confidence interval (CI) 0.03–0.28]. In addition to preventing severe allergic reactions, venom immunotherapy was also effective in preventing large local reactions to stings (RR 0.41, 95% CI 0.24–0.69) and for improving quality of life. While the therapy is generally considered safe, there

is a risk of systemic adverse reaction to VIT during treatment: 9.3% of subjects experienced such a reaction compared with 0.7% of subjects who did not receive VIT (RR 8.16, 95% CI 1.53–43.46) [29[■]]. Incorvaia *et al.* [30] highlighted a higher rate of systemic reactions to VIT for honeybee-sensitive patients versus vespid-sensitive patients. Bilo [31] recently reviewed strategies for reducing adverse reaction to immunotherapy, including pretreatment with anti-IgE in some cases.

The mechanism of VIT involves alterations in numerous biomarkers, including interleukin-10 (IL-10), which is important in tolerance. Riccio *et al.* [32[■]] have also demonstrated significant decreases in a protein involved in activation of T lymphocytes called cytotoxic T lymphocyte associated antigen-4 (CTLA-4) during immunotherapy, which plays a role in inhibition of antibody formation. These decreases were apparent as early as 24 h into therapy, and parallel increases in IL-10 were observed during the study.

Rapid approaches to VIT allow patients to reach protective doses sooner. The time necessary to reach maintenance doses may take months, days, or even hours depending on the protocol used. Traditionally, rush and ultra-rush protocols have been associated with a greater rate of adverse reactions: Brown *et al.* [33[■]] found higher rates of symptoms associated with ultra-rush buildup (65% of patients versus 29%, $P < 0.001$) and severe reactions (12 versus 0%, $P = 0.029$) in a study of 213 patients. However, Patella *et al.* [34[■]] recently demonstrated similar rates of adverse reactions for patients receiving ultra-rush, rush, and slow protocols (1.99, 3.7, and 3.9% during build-up).

Duch *et al.* [35[■]] recently suggested the use of sting challenge to assess VIT effectiveness in allergic patients, particularly those in whom unusual species of hymenoptera may be responsible for anaphylaxis. However, Golden *et al.* [1] and Freeman [36] highlight that sting challenges are not consistently reproducible, are associated with considerable risk, and are not included in the standard management of insect hypersensitivity in the United States.

CONCLUSION

Careful selection of children with venom allergy may allow administration of life-saving venom immunotherapy. Families of children who have experienced allergic reactions to hymenoptera should be educated on appropriate avoidance of stings and treatment of future reactions. Emergency preparedness involves making sure self-injectable epinephrine is available for patients who have experienced anaphylaxis. Venom immunotherapy

may be indicated to improve quality of life for patients and families as well as to decrease future risks of severe allergic reactions.

Although children with large local or strictly cutaneous systemic reactions are generally not at increased risk of anaphylaxis, those with a history of anaphylaxis appear to be at significantly increased risk for recurrence of symptoms if re-stung. Patients with venom allergy should be educated regarding avoidance of stings and self-injectable epinephrine should be prescribed for patients with anaphylaxis. We recommend that adults with any systemic reaction and all patients who experience moderate-to-severe systemic reactions be referred to an allergist for testing and consideration of desensitization to prevent future reactions.

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Conflicts of interest

There are no conflicts of interest.

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