Component-Resolved Diagnostics in Insect Venom Allergy

Overview

For patients sensitized to the venom of stinging insects, a sting can be potentially life-threatening. Venoms from the Hymenoptera order of insects—commonly known as bees, wasps (vespids), and some ants—may cause allergic reactions, including anaphylaxis, which can be severe and fatal.¹ After an initial sting, the immune system of affected people may respond by producing allergen-specific IgE (sIgE) antibodies. Subsequent stings can trigger a more rapid inflammatory response. This IgE response offers a quantifiable way to understand and identify the insect venom allergen to which a patient is reacting.¹,²

Venom allergy diagnosis is supported by detection of sIgE antibodies using whole extracts or individual allergenic venom components that are found within the whole extract. Several honeybee and vespid allergens have been characterized and are available as recombinant antigens for component-resolved diagnostics (CRD). Identifying sIgE responses to specific molecular targets with CRD helps fine-tune the diagnosis by distinguishing species-specific, co-reactive, or cross-reactive sensitizations. An accurate diagnosis, in turn, facilitates treatment, including prescription of venom immunotherapy (VIT).³ For patients with a history of severe insect sting anaphylaxis and negative skin and serum test results for venom, the diagnosis can further be refined with serum tryptase testing.⁴

Reactions to stinging insect venom

Approximately 9.2% to 28.7% of adults are sensitized to Hymenoptera venom (including bees and vespids), and the prevalence of systemic sting reactions ranges between 0.3% and 7.5%.³ The frequency of honeybee venom allergy is higher in rural populations, which have a higher likelihood of exposure to stinging insects, than in urban populations. Beekeepers and their family members are especially susceptible.

Most insect stings produce a local reaction that lasts a few days and resolves without any treatment. However, some people experience large local reactions with swelling and redness surrounding the sting site that may persist for 3 to 10 days. These are usually IgE-mediated late-phase reactions, and the risk of a systemic reaction in such patients is 4% to 10%.⁴ Potentially life-threatening anaphylactic sting reactions occur in an estimated 0.4% to 0.8% of children and 3% of adults, and account for at least 40 deaths each year in the United States.⁴ Table 1 lists some of the risk factors for severe reactions.

<table>
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<tr>
<th>Clinical Markers</th>
<th>Laboratory Markers</th>
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<tr>
<td>• Very severe previous reaction</td>
<td>• Positive venom sIgE blood test or skin test</td>
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<tr>
<td>• Insect species (honeybee)</td>
<td>• High basal serum tryptase</td>
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<tr>
<td>• No urticaria or angioedema</td>
<td>• Basophil activation test (not commonly available)</td>
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<td>• &gt;45 years old, male</td>
<td>• Platelet activating factor – acetylhydrolase (not commonly available)</td>
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<td>• Frequent exposure</td>
<td>• ACE</td>
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<td>• Multiple or sequential stings</td>
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<tr>
<td>• Mastocytosis</td>
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<td>• Medications (angiotensin-converting enzyme [ACE] inhibitors)</td>
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Mastocytosis considerations

Our understanding of the role of mastocytosis (an excess of mast cells) in relation to insect venom allergy continues to evolve. The prevalence of mastocytosis is approximately 10 in 100,000 in the general population. Most cases of mastocytosis are caused by a gene mutation that results in the accumulation of mast cells in the skin or organs, such as the liver, spleen, bone marrow, and small intestines. Mast cells are widely distributed, multifunctional immune cells often found at the interface between an individual and the environment (the skin, and mucosa lining the mouth, nose, lungs, and gastrointestinal tract, for example). Mast cells play an important protective role by recognizing pathogens, by releasing biologically active granules (including histamine and heparin) into the local microenvironment through degranulation, and by signaling other immune system cells. However, mast cell activation may also initiate allergic reactions when crosslinking occurs between antigen-specific IgE and high-affinity IgE receptors on the surface of the mast cell.

Mastocytosis occurs in approximately 2% of patients with insect sting anaphylaxis, and insect sting anaphylaxis occurs in approximately 25% of patients with mastocytosis. Insect stings are the most common cause of anaphylaxis in people with mastocytosis, and their anaphylactic reactions are more likely to be severe. Yet the exact mechanisms responsible for more severe symptoms are not entirely clear. It may be that a larger mast cell population increases mediator release, that mediators are released directly into the systemic circulation, that a venom component causes direct mediator release, or that a mutation blocks timely mast cell death. Because a severe insect sting reaction may be the first symptom of mastocytosis, some experts recommend that patients with severe reactions be evaluated for mastocytosis. For people with diagnosed mastocytosis, experts recommend testing for Hymenoptera venom sensitivity, and testing basal serum tryptase for patients who have had a systemic reaction to an insect sting or during VIT.

Sensitization phenotypes

For patients who have reacted to insect sting venom, the clinical challenge is to evaluate their sensitization, assess their future risk, especially of anaphylaxis, and formulate a treatment plan. There are several phenotypes associated with honeybee and vespid allergies. A clinical phenotype describes the observable and measurable traits resulting from the interaction between a person’s genetic makeup and the environment. Approximately 20% of healthy adults will have a positive sIgE or skin test result for insect venom, especially in the months after being stung. Yet only 5% to 15% of people with asymptomatic sensitization will experience a systemic reaction to another sting, and their sensitization usually wanes. Patients who develop large local reactions have a <10% chance of a later systemic reaction. However, the chances of a systemic reaction increase to a mean 50% frequency for patients with a history of venom anaphylaxis.

Particularly when clinical history and initial assessment are inconclusive, CRD provides valuable diagnostic information. Testing with conventional venom extracts may reflect genuine sensitizations, but may also reflect cross-reactive sensitizations to homologous allergenic protein components (e.g., hyaluronidases and dipeptidyl peptidase IV homologs), or to cross-reactive carbohydrate determinants (CCDs), which are frequently found in Hymenoptera venom. Component-resolved recombinant sIgE testing can help to distinguish a primary sensitization from a cross-sensitization and identify relevant cosensitizations. Consequently, CRD may be useful in characterizing sensitization profiles and developing treatment plans.

Allergic venom components

There are multiple allergic components associated with honeybees and vespids that facilitate a more precise diagnosis (Table 2). Although whole extracts are considered first-line testing, CRD can improve clinical sensitivity and specificity. In addition, recombinant allergen components can help clarify an unclear clinical history with positive tests to both bees and wasps, a good clinical history in patients with a negative test, and plans for VIT.
Api m 3 and Api m 10 figure prominently in clinically manifested sensitization to honeybee venom. Sixty-eight percent of patients with a history of reactions to honeybee venom are sensitized to Api m 3 or Api m 10, and 4.8% are sensitized to these components exclusively. Yet these components are under-represented or absent from some of the licensed preparations used for honeybee VIT, rendering treatment less effective. Indeed, predominant sensitization to rApi m 10 (>50% of IgE to honeybee venom) is a risk factor for VIT failure.

For venom-allergic patients who test positive to honeybee and wasp venom extracts, sIgE testing with recombinant protein allergens rApi m 1, rVes v 1 and rVes v 5 can discriminate double sensitization from CCD-related cross-reactions. Similarly, the diagnostic sensitivity of the combination of recombinant allergen components rVes v 5 and rVes v 1 is reportedly as high as 92% to 98%. Thus, wasp venom CRD proves valuable in excluding nonspecific sensitization due to CCDs.

Antigen 5 is recognized as the most potent allergen in venoms of the Vespidae family (paper wasp, common wasp [yellow jacket], and European hornet), and is not found in honeybee venom. Antigen 5, present as rVes v 5 in yellow jacket venom and rPol d 5 in paper wasp venom, can identify the probable sensitizing species in 69% of allergic patients who have double sensitization. Venoms from different Polistes species are free from CCD interference; however, because of cross-reactivity between antigen 5 components in yellow jacket and paper wasp venom (Ves v 5 and Pol d 5, respectively), differentiating between vespid species stings is challenging. Incomplete cross-reactivity has been demonstrated between European and American venoms of paper wasps, necessitating the use of P. gallicus or dominulus extract for diagnostic and therapeutic purposes in Europe.

Clinical utility of component-resolved diagnostics

sIgE testing helps clarify the diagnosis of venom allergy and aids in treatment decision-making. CRD has increased the sensitivity of sIgE testing and its ability to discriminate between primary sensitization and cross-reactivity. Accurately identifying a patient’s sensitizations helps avoid unnecessary or ineffective treatment, which could, in turn, avoid new sensitizations, minimize side effects, and lower treatment costs.

Sensitization can be detected in patients with a history of a systemic sting reaction, and the results used to plan VIT of IgE-mediated bee and wasp venom allergy. This applies to patients who have had:

- a severe systemic reaction
- a moderate systemic reaction and one or more of the following: concomitant pathology such as cardiovascular disease or mastocytosis, a high risk of future stings, or anxiety about future stings
Elevated basal serum tryptase levels compared to previous baseline levels are indicative of either mast cell activation, which occurs in anaphylaxis, or of the increased total mast cell levels associated with mastocytosis. Table 3 provides recommendations and considerations for ordering serum tryptase testing. No test, other than basal serum tryptase, can predict the severity of a sting reaction.⁴

Table 3. When to Measure Basal Serum Tryptase

<table>
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<tr>
<th>Recommended</th>
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<tr>
<td>Severe reaction to a sting</td>
<td>Systemic reaction during venom immunotherapy</td>
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<tr>
<td>Hypotensive reaction</td>
<td>(VIT; to injection or sting)</td>
</tr>
<tr>
<td>Lack of urticaria in systemic reaction</td>
<td>Before discontinuing VIT</td>
</tr>
<tr>
<td>Systemic reaction with negative venom IgE results</td>
<td>Any candidate for VIT</td>
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Treatment options for venom allergies include allergen avoidance, medications, and VIT.³ Establishing primary sensitization supports the selection of the primary allergen source for VIT. The availability of CRD allows VIT, the only treatment capable of changing the natural course of this allergic disease, to be better targeted. The degree of protection provided by VIT ranges from 80% to 84% for bee venom allergy and from 90% to 95% for yellow jacket venom allergy.¹⁵

The routine availability of recombinant venom components for CRD also raises the future possibility of assessing the true prevalence of various venom allergies, and of gaining insights into the role and relevance of specific components in developing sensitization or achieving de-sensitization.₁⁶

References