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Venom Immunotherapy in 2025: Practical Insights for Community Allergists

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Introduction

Hymenoptera venom allergy (HVA), caused by stings from bees, wasps, hornets, and yellow jackets, is one of the most common identifiable causes of anaphylaxis in adults.[1] While local reactions are common, systemic responses can be fatal. Venom immunotherapy (VIT) offers long-term protection and is often curative.[2-4] Introduced in the 1920s, VIT remains the only disease-modifying treatment for HVA.[5]

Hymenoptera Venom Allergy Background

HVA affects up to 3% of adults and 0.8% of children.[5] Hymenoptera stings can trigger a range of reactions. Large local reactions, while uncomfortable, are not predictive of future systemic reactions and generally do not warrant VIT. Systemic reactions extend beyond the sting site, and may include urticaria, angioedema, respiratory distress, gastrointestinal symptoms, or hypotension, and require a thorough evaluation.[2-4] The Ring and Messmer classification (**Table 1**), widely used in both research and clinical guidelines, categorizes systemic reactions from Grade I (cutaneous only) to Grade IV (life-threatening).[2,3] Even generalized urticaria following a sting may justify assessment for VIT, especially in high-risk individuals, as will be discussed.

Diagnosis of Hymenoptera Venom Allergy

Accurate diagnosis of HVA requires integrating a comprehensive clinical history with venom allergy testing.

Clinical history: A detailed history is essential. Clinicians should document the suspected insect, nature and severity of the sting reaction, timing of symptom onset and resolution, and any treatment administered. Contextual factors, such as the setting (e.g., outdoors, near flowers or food)

Grade	Skin[1]	Abdomen	Respiratory tract	Cardiovascular system
I	Pruritus, Flush, Urticaria, Angioedema	–	–	–
II	Pruritus, Flush, Urticaria, Angioedema	Nausea, Cramps	Rhinorrhea, Hoarseness, Dyspnea	Tachycardia (↑ ≥20 bpm), Hypotension (↓ ≥20 mmHg), Arrhythmia
III	Pruritus, Flush, Urticaria, Angioedema	Vomiting, Defecation	Laryngeal edema, Bronchospasm, Cyanosis	Shock, Loss of consciousness
IV	Pruritus, Flush, Urticaria, Angioedema	Vomiting, Defecation	Respiratory arrest	Cardiac arrest

Table 1. Severity scale for the classification of anaphylactic reactions (according to Ring and Messmer); *adapted from Ruëff et al.*[2]

[1]Generalized skin symptoms apart from the sting area

Classification is based on the most severe symptom encountered (none of the symptoms are obligatory).

and distinguishing features (e.g., presence of a retained stinger) should be noted. Additionally, relevant co-factors, such as exercise, alcohol consumption, or medication use, should be recorded. While history alone rarely identifies the culprit insect, it remains valuable in guiding diagnostic testing and management.

Skin prick tests (SPT) and intradermal tests (IDT): These tests should be reserved for individuals with a history suggestive of systemic reactions, as asymptomatic sensitization is common. Traditionally, testing begins with a 100 µg/mL SPT, followed by incremental IDT up to 1.0 µg/mL. However, several studies support a safe and efficient single-step IDT using the 1.0 µg/mL concentration.[2-4,6] A graded approach may still be warranted for patients with severe sting reactions. Testing performed too soon after a sting can fall within a refractory period, and may yield false negatives in up to 50% of patients; therefore, retesting after 4 to 6 weeks is recommended.[2-4]

In-vitro testing: Guidelines permit either skin testing or in vitro testing as a first step, depending on practicality. Specific IgE (sIgE) to whole venom extracts is commonly used, though component-resolved diagnostics (CRD) are increasingly accessible in community settings. CRD helps distinguish true double-venom allergy from cross-reactivity, especially when the culprit insect is uncertain or test results are ambiguous. For example, a relatively common situation is a patient who appears to be sensitized to both honeybee and yellow jacket venoms on standard sIgE tests. CRD assesses sensitization to specific venom components, improving diagnostic precision and guiding appropriate venom selection (**Figure 1**). sIgE to rApi m 1 is highly specific for honeybee allergy and helps exclude false positives related to cross-reactive carbohydrate determinants. Among vespids, major species-specific allergens include Ves v 1 and Ves v 5; for Polistes species, Pol d 1 and Pol d 5 are commonly used. Identifying the exact venoms to which a patient is truly sensitized informs immunotherapy selection and may influence cost, as VIT is not universally publicly funded. When clinical history and CRD do not clarify sensitization, immunotherapy with both venoms may be warranted, particularly in high-risk patients.[1,4] CRD may also help predict VIT outcomes and guide dosing; for instance, predominant Api m 10 sensitization has been identified as a risk factor for honeybee VIT failure, and higher maintenance doses may be considered in these cases.[7]

Basal serum tryptase: Measuring baseline serum tryptase is particularly important in patients with severe reactions (Grade III or IV), hypotension without urticaria, or systemic reactions despite negative venom-specific IgE.[4] Elevated levels may indicate an underlying mast cell disorder, such as mastocytosis or hereditary alpha-tryptasemia (HαT), both associated with increased reaction severity and implications for VIT management.[1-3] HαT is a relatively common genetic trait caused by increased TPSAB1 copy numbers and is linked

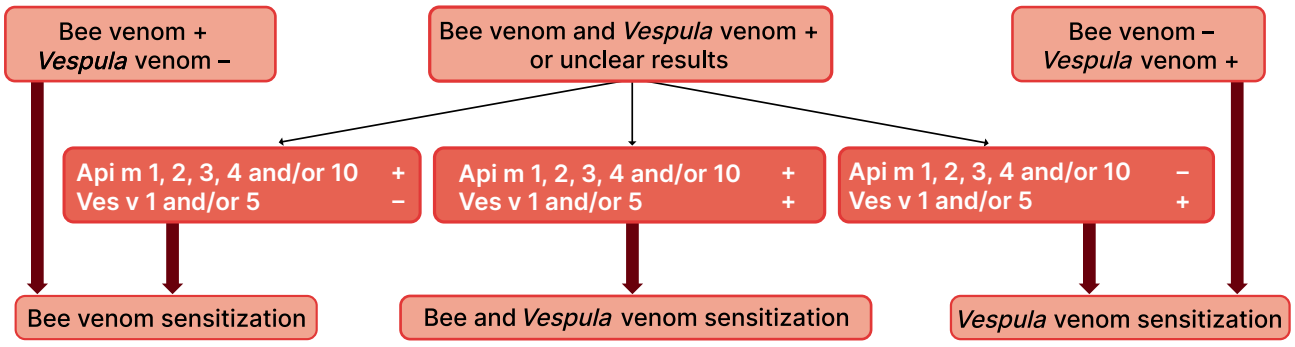

Figure 1. Stepwise diagnosis using whole venoms (bee venom and Vespula venom) along with allergen components from bee venom (Api m) and Vespula venom (Ves v); *adapted from Ruëff et al.*[2]

to more severe venom-induced anaphylaxis. Evaluation for HαT and clonal mast cell disease should be considered when baseline serum tryptase exceeds 8 ng/mL.[1] These patients may require extended treatment duration or higher maintenance doses.

Basophil activation test (BAT): A specialized assay that measures basophil activation after venom stimulation. Currently, its use is largely limited to research rather than routine clinical practice.

Indications for Venom Immunotherapy

The decision to start VIT requires a documented systemic sting reaction and confirmed venom sensitization. Patients with only local reactions generally do not require testing or VIT.[2-4]

- **Severe systemic reactions (Grades II–IV):** VIT is strongly recommended for moderate-to-severe reactions with confirmed venom sensitization.[2-4]
- **Isolated cutaneous reactions (Grade I):** VIT may be offered when additional risk factors are present, such as a high likelihood of future stings, significant quality-of-life impact, presence of a mast-cell disorder or elevated tryptase, or relevant cardiovascular disease or treatment with beta-blockers or ACE inhibitors.[2-4]
- **Children:** VIT is safe and effective; even mild systemic reactions may warrant treatment to prevent escalation and reduce anxiety.[3,8]
- **Large local reactions:** VIT is usually unnecessary but can be considered for very frequent, disabling reactions, such as in beekeepers.[2-4]

Contraindications and Precautions

Below are the main contraindications and precautions for initiating or continuing VIT, drawn from current guidelines:

- **Absolute contraindications:** Severe, uncontrolled asthma; unstable cardiovascular disease; immune-complex or severe autoimmune disease; and active malignancy undergoing cytotoxic chemotherapy.[2-4]
- **Pregnancy:** Initiating VIT during pregnancy is generally not recommended. However, a well-tolerated maintenance regimen started prior to conception may be continued after an individualized risk-benefit discussion.[2,4]

- **β-blockers and ACE inhibitors:** These medications may exacerbate anaphylaxis and reduce epinephrine effectiveness, but they are not absolute contraindications to VIT.[1-4] Patients should be informed of these potential interactions, and coordination with their cardiovascular specialist is advised to consider alternative agents when feasible.[2] In patients with heart failure, however, ACE inhibitors are generally continued given their proven survival benefit.[2] Optimizing underlying cardiac disease typically outweighs theoretical VIT risks, since cardiovascular comorbidities significantly increase HVA mortality.[1,2] When discontinuation of β-blockers or ACE inhibitors is not possible, VIT should be administered with extended post-injection observation and readiness for anaphylaxis management.[4]

Venom Immunotherapy Protocols and Administration

VIT is administered with gradually increasing doses to induce desensitization and long-term protection.

Venom selection: Choose venoms matching confirmed allergic sensitization. As mentioned, CRD are especially useful when dual sensitization or an uncertain culprit insect is suspected. For vespid allergy, a single *Vespula* extract usually suffices because of strong cross-reactivity, whereas *Polistes* allergy requires a specific *Polistes* extract.[2,3]

Dosing: The standard maintenance dose is 100 µg for both bee and wasp venoms. High-risk bee-allergic patients (e.g., those with mastocytosis, severe previous reactions, or elevated tryptase) may benefit from 200–400 µg. Mixed-vespid products use 300 µg.[2-4] In children, 50 µg can be adequate, though 100 µg is often preferred.[4]

Updosing Protocols

Different protocols aim to balance speed and safety:

Conventional protocol: Involves weekly or bi-weekly injections over 4 to 6 months.[3,4] This is generally considered the safest approach

Rush protocols: Achieve the maintenance dose rapidly, typically within days to weeks, through multiple daily injections. These protocols offer quicker protection but carry a higher risk of systemic reactions during updosing. They can significantly enhance patient convenience and provide faster protection, a critical advantage for highly anxious patients or those with high occupational exposure risk.[3-5] A novel 3-session outpatient rush venom immunotherapy protocol described by McCarthy et al. has demonstrated promising results for safety and efficacy.[9]

Ultra-rush protocols: The most rapid protocols, reaching maintenance within hours or a single day, typically in a hospital setting due to the highest risk of systemic reactions. Such protocols should be considered for high-risk patients needing exceptionally rapid protection (e.g., beekeepers).[3,4]

Maintenance dosing: Once the target dose is achieved, injections are usually administered every 4 weeks; many guidelines allow extension to 6 weeks from year 2 or 3.[2-4]

Premedication: A non-sedating H1 antihistamine before each injection can reduce local and mild systemic reactions but does not reliably prevent severe events.[2,4]

Duration of Venom Immunotherapy

VIT is generally continued for 3 to 5 years, but discontinuation must be individualized according to each patient's risk factors and preferences.

- **Severity of initial reaction:** Patients who experienced severe systemic reactions involving cardiovascular compromise (Grade IV anaphylaxis) face a higher risk of relapse and often benefit from extended or lifelong therapy.[2-4]
- **Mastocytosis or elevated baseline serum tryptase:** Those with mast cell disorders or persistently elevated baseline tryptase have increased risks of systemic reactions, treatment failure, and recurrence. All major guidelines recommend lifelong VIT for this population regardless of sting severity.[2-4]
- **Systemic reactions during VIT:** A systemic reaction to a field sting while on maintenance indicates insufficient protection. In such cases, clinicians may increase the maintenance dose, shorten injection intervals, or prolong the overall duration of therapy.[2-4]
- **Pediatric patients:** Children typically achieve excellent long-term outcomes. Multiple studies support discontinuing VIT after 3 years in most pediatric cases.[2-4]

- **Patient-specific factors:** Individuals with high occupational or environmental exposure, significant anxiety about future stings, or uncertain sting history may reasonably continue VIT beyond 5 years. These contextual factors should guide shared decision-making.[2-4]

Currently, no validated biomarker reliably predicts long-term protection; thus, repeat skin tests or specific IgE measurements before discontinuing therapy are not recommended.[3,4,10]

Safety and Management of Adverse Reactions

Venom immunotherapy (VIT) is generally well tolerated, with most adverse reactions being mild and localized.

Local reactions: Swelling, erythema, and pruritus at the injection site are common and typically self-limiting. Non-sedating H1-antihistamines are frequently used for symptom relief and may be taken prophylactically to improve tolerability, as mentioned. Leukotriene receptor antagonists such as montelukast have also been used as adjuncts, although supporting evidence is limited. Topical corticosteroids may also be used.[2]

Systemic reactions: These can occur during both the build-up and maintenance phases. Risk factors include rapid updosing protocols, higher venom doses, concurrent infections, physical exertion, and underlying mast cell disorders. Such reactions should be managed according to standard anaphylaxis protocols. After a systemic reaction to VIT, therapy can be continued with consideration for premedication with an H1-antihistamine and modification of the updosing schedule.[2-4]

Omalizumab: For patients with recurrent systemic reactions despite dose modifications, or those with severe mastocytosis, off-label use of omalizumab has shown benefit.[2,3,5] However, no standardized protocol currently exists regarding its timing or dosing.

Efficacy of VIT and Its Assessment

VIT is highly effective in preventing systemic allergic reactions to future stings. A systematic review and meta-analysis reported systemic reactions on re-sting in only 2.7% of VIT-treated compared with 39.8% of untreated controls.[8] In addition to reducing clinical reactivity, VIT significantly improves quality of life by decreasing anxiety and fear of future stings.[4] Protection typically begins within the first few months of therapy and is sustained throughout the maintenance interval.[2-4] Although laboratory markers such as specific IgE levels or basophil activation tests may change during treatment, they are not routinely used for clinical decision-making. The absence of systemic reactions to field stings remains the most reliable indicator of successful VIT.

Conclusions

Recent advances have made VIT more precise and adaptable. Component-resolved diagnostics guide precise venom selection, and accelerated updosing protocols safely shorten the induction phase. Individualized risk stratification with baseline tryptase and hereditary alpha-tryptasemia screening enables tailored management. Adjunctive omalizumab and flexible maintenance schedules further reduce barriers and sustain protection. Together, these innovations empower allergists to deliver a truly patient-centred, individualized approach to VIT.

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