

NEWS & VIEWS: ALGORITHMS IN ALLERGY AND CLINICAL IMMUNOLOGY

Diagnosis and treatment of Hymenoptera venom allergy

Diagnosis of Hymenoptera venom allergy (HVA) is straightforward in the majority of patients, but can be challenging in double positive and test negative patients. Test results sometimes can be confusing as patients with high skin test reactivity and high specific IgE (sIgE) levels are not at risk for severe systemic sting reactions (SSR), and conversely, patients with weakly positive or even negative tests can experience severe SSR. Venom immunotherapy (VIT) is safe, highly effective, and recommended in patients with moderate to severe SSR and in patients with SSR confined to generalized skin symptoms if quality of life is impaired.

Hymenoptera venom allergy is the most common cause of anaphylaxis in adults in Europe.¹ The rate of self-reported systemic sting reactions in European epidemiological studies ranges from 0.3% to 7.5% in adults.² The main clinical presentations are large local reactions (LLR) at the sting site and SSR. A large local reaction has been defined as a swelling exceeding a diameter of 10 cm that lasts for longer than 24 hours.³ In SSR, generalized skin symptoms including flushing, urticaria, and angioedema are defined as mild symptoms. Dizziness, dyspnea, and nausea are examples of moderate symptoms. Anaphylactic shock, loss of consciousness, and/or cardiac or respiratory arrest all define a severe SSR.

The clinical history of the reaction(s), skin testing, and detection of sIgE to venom preparations are still the mainstays of the diagnostic procedure in cases of HVA. Molecular allergy diagnosis in HVA is still evolving and currently of limited use. Some relevant cross-reactive bee and vespid allergens such as Api m 12 as well as Ves v 3 and 6

are still unavailable for routine diagnosis. Moreover, sensitivity of the available bee venom allergen panel and particularly of Api m 1 is low with 72%⁴ and 57%-62%,^{5,6} respectively. The basophil activation test (BAT) has been shown to be a useful test in double positive⁷ or negative patients,⁸ but is still not widely used. IgE inhibition assays are easier to perform and can be helpful to distinguish between cross-reactivity and true double sensitization.^{9,10} The new EAACI position paper on diagnosis of HVA is work in progress. Nevertheless, available tests and approaches to solving diagnostic problems are provided in Figure 1.

The only treatment that can potentially prevent further SSR is venom immunotherapy, which is reported to be effective in 77%-84% of patients treated with honeybee venom, and in 91%-96% of patients receiving vespid venom.¹¹ The EAACI guidelines on venom immunotherapy were published in 2018.¹¹ It aimed to provide evidence-based recommendations for the use of VIT. The guidelines have been based on a formal systematic review and meta-analysis and have been produced using the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach. In brief, VIT is indicated in children and adults with detectable sensitization and SSR that exceeds generalized skin symptoms. VIT is also recommended in adult patients with SSR confined to generalized skin symptoms if quality of life is impaired. In patients with recurrent, troublesome LLR it can be considered to reduce the duration and size of future LLR. The treatment algorithm in Figure 2 is based on the recommendations of the guidelines.

Abbreviations: LLR, large local reaction; QoL, quality of life; SSR, systemic sting reaction; VIT, venom immunotherapy.

[Correction added on 24 June 2019, after first online publication on 02 June 2019 : figure 2 has been updated in this version.]

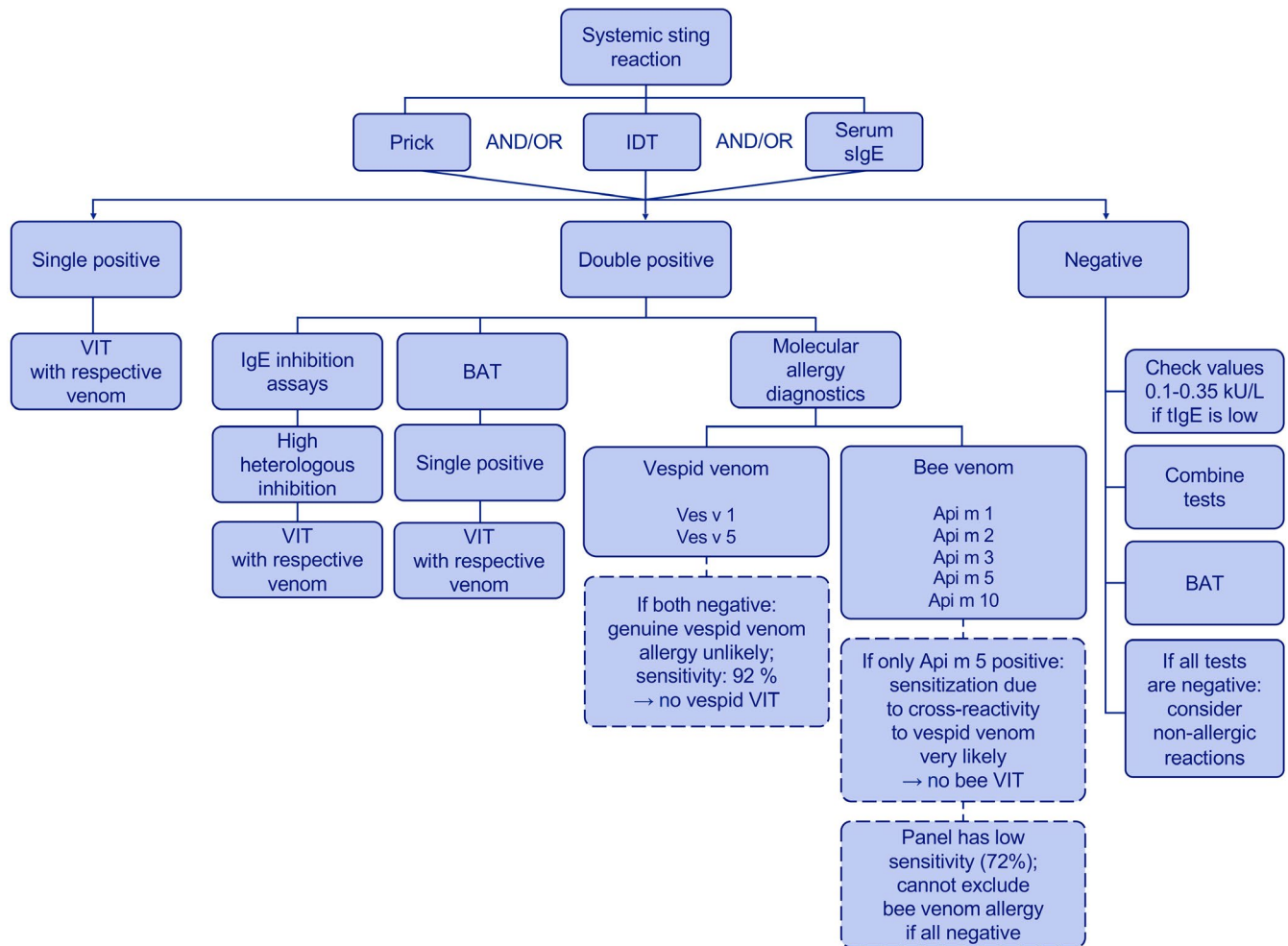





FIGURE 1 Diagnosis of Hymenoptera venom allergy. The first step in the diagnosis of Hymenoptera venom allergy is skin prick testing, intradermal testing (IDT), and/or determination of serum-specific IgE (sIgE) to venom preparations. These tests may be combined to increase sensitivity. If the test(s) are single positive, VIT with the respective venom should be initiated. In case of double positivity, reciprocal IgE inhibition assays, the basophil activation test (BAT), or molecular allergy diagnostics can be performed. Determination of IgE to CCD MUXF3 is in contrast to multiple sensitizations to pollen or food of limited use. As CCDs are different in insect venom, sensitivity of the MUXF3 assay is low with 52%. Additionally, the presence of IgE to CCDs does not exclude true double sensitization.⁷ Molecular allergy diagnostics in Hymenoptera venom allergy is currently of limited use because not all relevant allergens are available. However, if both, Ves v 1 and 5 are negative, vespid venom allergy is unlikely.¹² Sensitivity of the available panel of bee venom allergens is low. Using this panel, it is impossible to diagnose or exclude bee venom allergy, but mono-sensitization to Api m 5 may indicate cross-reactivity to vespid venom. Additionally, the BAT has been shown to have a lower risk of detecting a double sensitization. However, in case of severe systemic sting reactions and clear double positive test results VIT with both venoms should be performed. If total IgE (tIgE) is low, sIgE levels between 0.10 and 0.35 kU/L can be considered to be positive. If all tests are negative, nonallergic reactions such as panic reactions should be considered. Importantly, in patients with low tIgE, tests can be negative despite severe SSR

CONFLICT OF INTEREST

Dr. Sturm reports grants from ALK Abello, personal fees from Novartis, personal fees from Bencard, personal fees from Stallergens, personal fees from HAL, personal fees from Allergopharma, personal fees from Mylan, outside the submitted work. Dr. Arzt-Gradwohl and Dr. Varga report no conflicts of interest.

KEYWORDS

allergy diagnosis, hymenoptera venom allergy, insect venom allergy, venom immunotherapy

Gunter J. Sturm^{1,2} 
 Lisa Arzt-Gradwohl¹ 
 Eva- M. Varga³ 

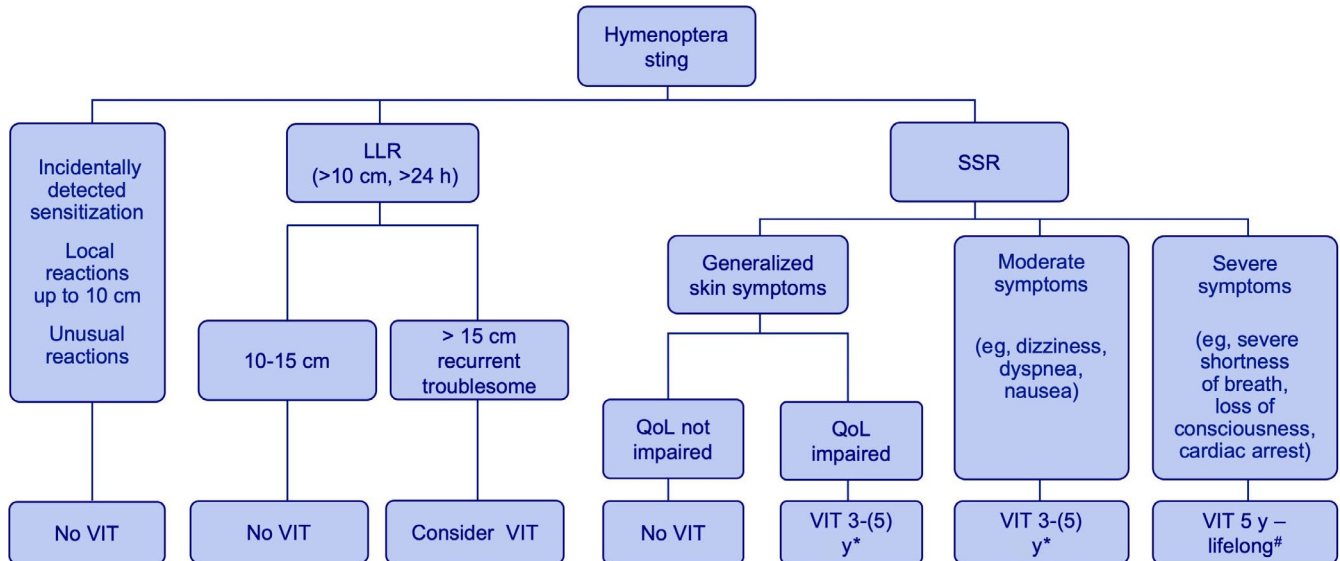


FIGURE 2 Treatment algorithm based on EAACI guidelines on venom immunotherapy.¹¹ *Consider special conditions: Cardiovascular and organ-specific autoimmune diseases must be stable; ACE inhibitor and/or beta-blocker therapy may be continued if required but patients must be informed about potential risks; VIT contraindications: malignant disease; multisystem autoimmune disease; children < 5 y; pregnancy. #VIT can also be performed in patients with remission of a malignant disease and children < 5 y, when child is likely to be cooperative. In children, treatment over 3-5 y may be sufficient.

¹Department of Dermatology and Venerology, Medical University of Graz, Graz, Austria

²Allergy Outpatient Clinic Reumannplatz, Vienna, Austria

³Mozartpraxis, Paediatric Respiratory and Allergy Outpatient Practice, Graz, Austria

Correspondence

Gunter J. Sturm, Department of Dermatology and Venerology, Medical University of Graz, Auenbruggerplatz 8, A - 8036 Graz, Austria.
Email: gunter.sturm@medunigraz.at

ORCID

Gunter J. Sturm  <https://orcid.org/0000-0002-7245-121X>

Lisa Arzt-Gradwohl  <https://orcid.org/0000-0002-5489-2070>

Eva-M. Varga  <https://orcid.org/0000-0003-3936-5608>

REFERENCES

- Worm M, Moneret-Vautrin A, Scherer K, et al. First European data from the network of severe allergic reactions (NORA). *Allergy*. 2014;69(10):1397-1404.
- Bilo BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2008;8(4):330-337.
- Bilo BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN. Diagnosis of Hymenoptera venom allergy. *Allergy*. 2005;60(11):1339-1349.
- Arzt L, Bokanovic D, Schrautner C, et al. Questionable diagnostic benefit of the commercially available panel of bee venom components. *Allergy*. 2017;72(9):1419-1422.
- Sturm GJ, Hemmer W, Hawranek T et al. Detection of IgE to recombinant Api m 1 and rVes v 5 is valuable but not sufficient to distinguish bee from wasp venom allergy. *J Allergy Clin Immunol*. 2011;128(1):247-248; author reply 248.
- Korošec P, Valenta R, Mittermann I, et al. Low sensitivity of commercially available rApi m 1 for diagnosis of honeybee venom allergy. *J Allergy Clin Immunol*. 2011;128(3):671-673.
- Sturm GJ, Jin C, Kranzelbinder B, et al. Inconsistent results of diagnostic tools hamper the differentiation between bee and vespid venom allergy. *PLoS One*. 2011;6(6):e20842.
- Korošec P, Erzen R, Silar M, Bajrovic N, Kopac P, Kosnik M. Basophil responsiveness in patients with insect sting allergies and negative venom-specific immunoglobulin E and skin prick test results. *Clin Exp Allergy*. 2009;39(11):1730-1737.
- Straumann F, Bucher C, Wuthrich B. Double sensitization to honeybee and wasp venom: immunotherapy with one or with both venoms? Value of FEIA inhibition for the identification of the cross-reacting ige antibodies in double-sensitized patients to honeybee and wasp venom. *Int Arch Allergy Immunol*. 2000;123(3):268-274.
- Caruso B, Bonadonna P, Severino MG, et al. Evaluation of the IgE cross-reactions among vespid venoms. A possible approach for the choice of immunotherapy. *Allergy* 2007;62(5):561-564.
- Sturm GJ, Varga E-M, Roberts G, et al. EAACI guidelines on allergen immunotherapy: hymenoptera venom allergy. *Allergy*. 2018;73(4):744-764.
- Korošec P, Valenta R, Mittermann I, et al. High sensitivity of CAP- FEIA rVes v 5 and rVes v 1 for diagnosis of vespula venom allergy. *J Allergy Clin Immunol*. 2012;129(5):1406-1408.