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. The rate of self-reported systemic sting reactions in European epidemiological studies ranges from 0.3% to 7.5% in adults. 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. 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% and 57%-62%, respectively. The basophil activation test (BAT) has been shown to be a useful test in double positive or negative patients, 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. 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. The EAACI guidelines on venom immunotherapy were published in 2018. 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.]
**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

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**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.

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