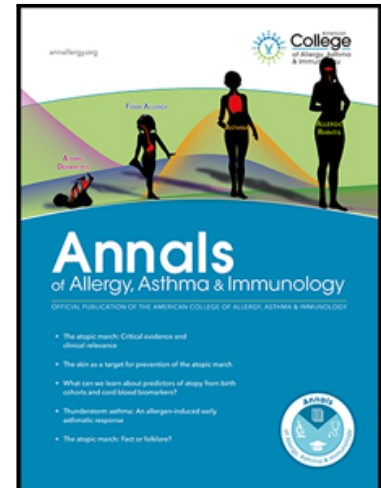


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Immunotherapy with insect venoms: Entomologist's expertise secures choice of treatment

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Simon Schneider: Clinically supervised the 1st case and wrote the manuscript together with L.Li

Volker Maus: Identified the insects from photographs and revised the manuscript

Tilo Biedermann: Revised and edited the manuscript

Knut Brockow: Had the idea of the publication, revised and edited the manuscript

Hymenoptera venom allergy may lead to severe allergic reactions to the point of life-threatening anaphylaxis. Between 0.3%-7.5% of adults [1] and 0.15-3.4% of children [2] develop systemic anaphylactic reactions, varying from mere cutaneous to severe organ symptoms [3]. The only causal therapy is Hymenoptera venom immunotherapy (IT) [4]. In affected patients, it is important to distinguish between honeybee and *Vespula* (yellow jacket) stings. This requires a detailed medical history that frequently requires photographic evidence. Individual sensitization profiles are determined by

measuring specific IgE (sIgE) to venom extracts and single allergens as well as by conducting intradermal testing (IDT). However, in cases of double sensitization to *Vespula* and bee venom allergens, identification of the eliciting insect to confirm the final diagnosis can be difficult. Furthermore, medical history and sensitization profiles often do not match. Here we report two clinical cases. The first patient's history suggested a honeybee venom allergy, but sensitization was more pronounced for *Vespula* venom, leading to in-depth investigation of the sting photograph. In the second case, the patient's report and his mobile phone photograph of the corresponding insect were inconclusive to his sensitization profile.

A 53-year-old male patient reported a bee sting on the leg during a hike in Germany in August. The stinger remained in the skin and was later removed. A photograph of the site was taken. Approximately 15 to 20 minutes later, the patient developed generalized pruritus, urticaria, and angioedema of the face. Symptoms resolved after intravenous antihistamine administration by emergency medical services. Thus, no further antiallergic treatment nor hospitalization was required.

sIgE-antibodies (ImmunoCAP, Phadia, Uppsala, Sweden) were positive (≥ 0.1 kUA/l) for *Vespula* venom (25.3 kUA/l), rVes v5 (36.6 kUA/l), bee venom (0.29 kUA/l) and rApi m10 (0.33 kUA/l), with total IgE adding up to 515 kU/l. IDT was positive for *Vespula* venom at 0.1 µg/ml (Venomil, Bencard, Germany) and negative for bee venom. Due to the discrepancy between the sensitization profile and the patient's history, we consulted an entomologist for interpretation of the photograph. Analysis of the photograph revealed a *Vespula* sting. Consequently, the indication for *Vespula* venom IT as demonstrated by the sensitization profile was secured.

A 15-year-old boy reported generalized urticaria with pruritus 5-10 minutes after a sting in the first digit of the foot by an unspecified Hymenoptera. This was followed by nausea, emesis, dizziness and progressive asthenia. There was no remaining stinger. A photograph of the insect was taken by the father. Therapy with antihistamines and glucocorticosteroids led to symptom regression. Diagnostics revealed both honeybee and *Vespula* venom reactivity. sIgE to bee venom extract in the serum (13.0 kUA/l) was higher than that to *Vespula* venom (8.42 kUA/l). Reactivity to bee venom in the IDT was observed at lower concentrations (positive from 0.0001µg/ml) than reactivity to *Vespula* venom (IDT positive from 0.01µg/ml, respectively). Several recombinant molecular allergens to bee and *Vespula* were positive (rVes v1 0.50 kUA/l and rApi m10 0.82 kUA/l, rApi m1 0.42 kUA/l), with highest values for rVes v5 (3.65 kUA/l). Total IgE was 154 kU/l. The patient reported multiple bee stings in the past that were tolerated without systemic reaction. Based on the discrepancy between the sensitization profile and the photograph of the insect, the same specialized entomologist was consulted for interpretation.

Analysis of the photograph revealed a hornet that could be identified to the species level as a European hornet (*Vespa crabro*, Linnaeus, 1758) based on taxonomic features and the geographic area in which the sting occurred (Tsagkarada, Greece). Thus, the diagnosis of hornet venom allergy was made, and IT with *Vespula* venom was initiated.

If medical history reveals a singular event of anaphylaxis following a single Hymenoptera sting, the diagnosis of either a honeybee or *Vespula* (hornet) venom type-I allergy should be made so that the corresponding IT can be chosen. Initiating double venom IT, which is associated with increased healthcare costs and adverse

events, should be the exception but may be necessary in case of sensitization to both venoms in the absence of circumstantial evidence for one type of Hymenoptera.

Indeed, when the first patient was questioned again based on the results of the IgE-analyses and IDT, he admitted to having reported a 'definitive bee sting' purely because of the remaining stinger in the skin after having read that this was indicative of a bee sting. There are clues to differentiate between bee and *Vespula* stings (Table 1) [5]. A common misconception is that a remaining stinger always characterizes a bee sting. Shear forces, e.g., from clothing, can also cause a remaining stinger from *Vespula*. Furthermore, some species, like *V. maculifrons*, are more likely to leave a remaining stinger in the skin. [5, 6]

Diagnostics in our second case showed sensitization to both bee and *Vespula* venom as well as showing higher sIgE levels to bee venom and reactivity to lower concentrations of bee venom in IDT. However, despite a marked sensitization to bee venom, the photograph of the insect and the geographic location where the sting occurred helped to identify *Vespa crabro* as the culprit and secure the correct diagnosis of hornet venom allergy. The sensitization to bee venom was without clinical significance due to previously tolerated bee stings.

Overall, knowledge of the exact circumstances under which a sting happened may help to correctly identify the insect. Additionally, documenting the season in which the sting took place can also be helpful.

The diagnosis of venom allergy is routinely based on the patient's history and sensitization profile, consisting of a) sIgE to total venom extract, b) sIgE to single

venom allergens and c) skin test results [7]. Our report demonstrates in two patients that history and sensitization profile were not conclusive and may have led to incorrect diagnoses. In both cases, photographs taken by the patient or family members were available and used to obtain additional information from an expert entomologist. Thus, asking whether photographs were taken should be added to routine questioning and consecutive analyses to secure diagnosis and choice of treatment.

Table 1. General clues differentiating honeybees from social *Vespula*. Adapted from [5].

Criterion	Honeybee	Vespula
Sting	Sting apparatus and abdominal tip detached from the rest of the body, remaining anchored in the sting canal.	Stinger often does not remain at the sting site (<i>Vespula</i> stinger and abdominal tip may be found if the <i>Vespula</i> is compressed and sheared), but exceptions with certain <i>Vespula</i> species, e.g. <i>V. maculifrons</i> , exist.
Lancets	Long barbs.	Short barbs.
Color	Brownish with lighter banding on metasoma.	Striking black and yellow.
Surroundings	Immediate vicinity of a bee colony, beehive, or foraging site, i.e. richly flowering lawns, meadows, bushes, trees, or water sites.	Close to an aerial or ground nest made of <i>Vespula</i> paper or at foraging sites, i.e. near human food sources, bins, windfall.
Typical activity	Mechanical interference/irritation of a bee worker while it is visiting flowers i.e. on clover bloom meadows or collecting water near garden ponds or	Mechanical interference/irritation of <i>Vespula</i> worker while drinking or eating anthropogenic food outside, e.g. sugary drinks, cake, fruits and

	swimming pools, especially on hot summer days.	berries. Also near bakeries, barbecues, or butchers where workers forage for fresh food. Vespula, especially hornets, are also highly sensitive to vibration.
Frequently reported sting circumstances	Often when walking barefoot.	Often while emptying trash receptacles, as Vespula often forage in bins and composts, or during lawn and garden activities, especially those that disturb insects or nests.

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