

EDITORIAL

Hymenoptera venom hypersensitivity: an update

Systemic allergic reactions to hymenoptera stings occur worldwide and severe anaphylaxis as a result of such stings is thought to cause more than 40 fatalities a year in the United States [1] and near 100 in Europe [2]. In the late 1970s diagnosis and treatment of this allergy were greatly improved by the introduction of hymenoptera venoms instead of the formerly used hymenoptera whole body extracts (WBE): in a number of studies [3–6] venoms were found to be highly superior to WBE in skin testing. Other authors observed a close association between a history of systemic sting reactions and the presence of venom specific serum IgE antibodies [7,8]. Finally, in the late 1970s immunotherapy with hymenoptera venoms was shown to be highly superior to treatment with WBE in two controlled studies [9,10]. Absence of a systemic reaction during re-exposure to a sting was observed in 80 to more than 90% of venom treated patients but only in a quarter to one-third of WBE or placebo treated patients. Hymenoptera venom allergy was then (and is still today) by many considered to be a nearly perfect model of IgE-mediated allergy, both owing to the availability of reliable diagnostic tests and almost invariably effective immunotherapy.

During the following years and with more widespread experience with diagnosis and treatment of this allergy, a number of remaining problems have, however, been identified: diagnostic tests, both skin tests and detection of venom specific serum IgE-antibodies, although distinguishing reliably between individuals with and without a history of systemic hymenoptera sting reactions [2,4], are of a limited predictive value with regard to the reaction to a subsequent sting. In a number of prospective studies [11–14], it was shown that only between 20 and 50% of test and history positive individuals will develop a systemic reaction when restung. For this reason, a diagnostic sting challenge was recommended by some Dutch groups [11,14] for the selection of patients for immunotherapy. This procedure is, however, rejected by most allergists in Europe and the United States because they feel that it is unethical to perform provocation tests in untreated patients with a potentially fatal allergy [15] and a more recent study has revealed the limited reproducibility of a negative sting challenge. Among 63 wasp venom allergic patients with a first negative sting challenge, 23% developed a systemic reaction to a subsequent challenge within 6 months, and some of these reactions were severe [16]. As a consequence, the indication for venom immunotherapy is still most often based on a history of a severe systemic reaction, including cardiovascular and/or

respiratory symptoms following a hymenoptera sting, together with positive diagnostic tests [17] (Table 1).

In this issue, Egner *et al.* [18] address another diagnostic problem which is of relevance for immunotherapy, that of double positivity of diagnostic tests. Double positivity, that is reactivity to both honey bee and *Vespula* venom may be due to actual sensitization to both venoms or to cross-reactivity between allergens of the two venoms. In the first case immunotherapy should obviously be performed with both venoms, in the second the venom of the insect causing sensitization will suffice. The major honey bee venom allergen phospholipase A₂ does not crossreact with the major *Vespula* venom allergen phospholipase A₁ B nor is there a counterpart to the second major *Vespula* allergen, antigen 5, in honey bee venom. The crossreactivity between *Vespula* and honey bee venom is limited and largely confined to hyaluronidase [19]. While a number of patients can positively identify the responsible insect (the number of 82% is much higher than what we find in our patients), many may not be able to do so. RAST inhibition procedures may help to distinguish between double sensitization and cross-reactivity [20], but are cumbersome and expensive. The problem of double-positivity has been accentuated by the introduction of the highly sensitive CAP procedure, which has greatly increased the sensitivity as compared to the previously used RAST procedure, especially for *Vespid* specific IgE [21–23]: with the RAST procedure only about 60% of patients with a history of a systemic allergic reaction to a *Vespula* sting during the last year were found to be positive, with the CAP this number increased to 90% [23]. On the other hand, the specificity of venom specific IgE as estimated by CAP is reduced, since up to 20% of history and skin test negative individuals have detectable venom specific IgE. Finally, the percentage of hymenoptera allergic patients with double positivity is greatly increased, as shown in the paper by Egner *et al.* from around 10 up to 30%. In another study [23] even more than 50% of sera from venom allergic patients were found to react with both venoms. The majority of these double-positive reactions are most likely due to detection of trace amounts of cross-reacting hyaluronidase specific IgE, owing to the very high allergen binding capacity of the allergosorbent used in the CAP. Superficial interpretation of CAP results might therefore lead to considerable and costly overtreatment of hymenoptera venom allergic patients with both honey bee and *Vespula* venom. As the authors stress, it is most important to base the selection of venoms for treatment on a careful history, skin tests and estimation of specific IgE

Table 1. Indications for venom immunotherapy [according to 17]

Type of reaction	Diagnostic tests		Decision regarding venom immunotherapy
	ST and sIgE		
<i>Severe systemic</i>			
Respiratory and cardiovascular symptoms	Positive	Yes	
	Negative	No	
<i>Mild to moderate</i>			
Urticaria, angioedema, etc.	Positive	Usually not; only in heavily exposed patients with repeated reactions	
	Negative	No	
Large local	Positive	No	
	Negative	No	
Unusual	Positive	No	
	Negative	No	

ST, skin test; sIgE, venom-specific IgE.

antibodies in serum to both venoms. If the situation remains unclear, we would rather recommend the RAST inhibition procedure instead of a challenge, which as mentioned above, is neither safe nor reliable and not inexpensive as well.

A further remaining problem in hymenoptera venom allergy is related to the safety, especially of honey bee venom immunotherapy, which may cause systemic allergic reactions in up to 20–40% of patients so treated [17]. Different approaches to improve the safety of venom immunotherapy by changing protocols [17], by pretreatment with antihistamines [24] or bee-keeper gamma globuline [25] or by the use of chemically modified honey bee venom [26] have met with variable success, but on the whole were rather disappointing. Preliminary clinical studies using T-cell peptides of major venom allergens for immunotherapy are promising [27].

Finally, the question of how long venom immunotherapy should be continued, is still unsettled. Most authors agree, that immunotherapy of 3–5 years duration will protect 90% or more of the patients when restung 1 or 2 years after stopping treatment [17,28,29]. Data concerning a longer observation period after stopping treatment are still scarce but indicate, that relapses may occur more frequently, especially following repeated stings [29,30].

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