**The increasing cases of allergy to *Vespa velutina* in Europe: which immunotherapy?**

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*Vespa velutina nigrithorax* (VVN), accidentally introduced in France in 2004 from South-East Asia and rapidly spread across Europe (1), may cause relevant health problems to humans due to its venom: indeed, the proteins contained in VVN's venom are able to act both as toxins and allergens, and deaths due to organ dysfunction induced by toxins in venom and to fatal allergic reactions were both reported (2-5).

The two most dangerous groups of toxins identified are the hemostasis-impairing toxins, that participate in the blood coagulation cascade with a distinct hemolytic effect, probably representing the main lethal factor of the multiple organ failure produced by VVN stings, and neurotoxins, that can induce varying degrees of nerve degeneration and paralysis (2).

About the allergenic components, according to the serum samples from patients who had experienced allergenic reactions, two most common allergens have been identified: Vesp v 5, corresponding to antigen 5, and Vesp v 1, corresponded to A1-phospholipase (one of whose most interesting features is its glycosylated nature) (4, 6, 7). Despite this, only Vesp v 5 may be considered a dominant allergen, with more than 85% of patients having IgE against it, while Vesp v 1 has been detected in less than 50% of patients (6-8) Additionally, IgE against Vesp v 5 also resulted higher than IgE against VVN whole venom (9, 10). Other two components purified in the venom of VVN specimen, Vesp v 2A and 2B (two hyaluronidase isoforms) have been characterized as potential allergens, but specific IgE against these isoforms has not yet been demonstrated (4, 11, 12).

Since there is no specific available VIT for VVN yet, several studies focused on the importance of finding out if VVN stung patients with severe systemic reactions may be treated with actual Hymenoptera commercially available extracts.

By studying the degree of similarity with respect to antigen 5 and $A_1$-phospholipase from *Vespula* spp., *Vespa crabro* and *Polistes dominula*, it was found that both VVN antigen 5 and $A_1$-phospholipase show a very high homology with *Vespa crabro* and *Vespula* spp. Instead, a lower percentage of structural identity has been found with antigen 5 and $A_1$-phospholipase present in *Polistes dominula* (12).

According to studies conducted so far on patients with anaphylaxis due to VVN, fewer than 25% recalled previous stings from the same insect, although they reported previous stings to other Hymenoptera (especially common wasps) (4). Furthermore, different studies results show that patients who experienced anaphylaxis to Hymenoptera venom with and without previous VVN stings have similar sensitization patterns, suggesting that sensitization in patients allergic to VVN may come through a different species (10). Specifically, most patients with anaphylaxis due to VVN show a very high predominance of *Vespula s*pp. allergic sensitization, with Ves v 5 as the most frequently recognized allergen (4, 7, 9). Other components showing > 50% positivity in patients with anaphylaxis to VVN are Api m 5 (the dipeptidyl peptidase IV, equivalent to Ves v *3* in *Vespula* spp. venom) and Pol d 5, pattern similar to that of *Vespula* spp. anaphylaxis but different from that of *Apis mellifera* anaphylaxis (4). This fact suggests a high level of cross-reactivity between VVN and other *Vespidae*, potentially being relevant for diagnostic and therapeutic purpose.

All these findings, particularly the similar sensitization profile shared by patients with reported VVN allergy, with positive IgE to *Vespula* spp. and Ves v 5, and the strong correlation demonstrated between IgE to Ves v 5 and Vesp v 5, suggest that *Vespula* spp. immunotherapy may be a valid option for patients allergic to VVN venom (13). Actually, an available immunotherapy regimen based on *Vespula* spp. used to treat VVN stung patients with severe systemic reactions has proven to be efficacious and able to induce both a significant decrease in IgE and a significant increase in $sIgG_4$ against VVN in the majority of patients after 12 months of immunotherapy (11). Moreover, real-life observations confirmed that no anaphylaxis episode developed after spontaneous stings by VVN in patients treated with *Vespula* spp. venom immunotherapy. Taken together, all these evidences suggest clinical and immunological efficacy of immunotherapy with *Vespula* spp. venom in patients with VVN anaphylaxis.

Nevertheless, the conclusion of a recent study conducted on four patients with a clinical history of systemic reactions after VVN sting suggests that VIT with *Vespa crabro* venom, compared to *Vespula* spp. venom, may be more effective in patients allergic to VVN venom: according to this study, even if both *Vespula* spp. and *Vespa crabro* venoms are able to inhibit the specific IgE for VVN, *Vespa crabro* venom showed a higher inhibition rate (14).

In fact, from a systematic point of view, cladistic analyses performed using morphological and molecular data (15, 16) point out that, phylogenetically, VVN is closer to *Vespa crabro* than to *Vespula* sp. and *Polistes* sp.

In conclusion, as there is no specific available VIT for VVN, VVN stung patients could be treated with *Vespula* venom or, when available, *Vespa crabro* venom, that may be more effective according to recent data. For this reason, it may be appropriate to use the same extract of *Vespa crabro,* if available, also for diagnostic purposes. Nevertheless, the differences highlighted in the composition and structure of the VVN venom compared to *Vespa crabro* and *Vespula* spp. venoms suggest that a specific venom for VVN could be relevant for a diagnostic and therapeutic use (14). In particular, a specific VVN immunotherapy in patients with anaphylactic reactions after Hymenoptera sting, documented IgE sensitization to VVN and a high risk of being re-stung in view of their professional and leisure activities should be carefully considered (10).

**Key points**

- The main allergen components identified in the venom of *Vespa velutina nigrithorax* (VVN) are Vesp v 1 (Phospholipase A1) and Vesp v 5 (antigen 5), but only Ves v 5 may be considered a dominant allergen.
- Both allergens Vesp v 5 and Vesp v 1 share a high level of cross-reactivity with their counterparts in Vespula spp and Vespa crabro (VC).
- Sensitization in patients allergic to *Vespa veluthina nigrithorax* may come through different species.
- Since there's no specific available VIT for VVN yet, *Vespula* spp. immunotherapy may be a valid option for patients allergic to VVN; when available, VIT with VC venom may be more effective.

**References**


1. Quaresma A, Henriques D, Godinho J, Maside X, Bortolotti L, Pinto MA. Invasion genetics of the Asian hornet Vespa velutina nigrithorax in Southern Europe. Biol Invasions. 2022;24(5):1479-94. doi: 10.1007/s10530-022-02730-9.
2. Liu Z, Chen S, Zhou Y, Xie C, Zhu B, Zhu H, et al. Deciphering the venomic transcriptome of killer-wasp Vespa Velutina. Sci Rep. 2015;5:9454. doi: 10.1038/srep09454.
3. Xie C, Xu S, Ding F, Xie M, Lv J, Yao J, et al. Clinical features of severe wasp sting patients with dominantly toxic reaction: analysis of 1091 cases. PLoS One. 2013;8(12):e83164. doi: 10.1371/journal.pone.0083164.
4. Vidalc C, Armisén M, Monsalve R, González-Vidal T, Lojo S, López-Freire S, et al. Anaphylaxis to Vespa velutina nigrithorax: Pattern of Sensitization for an Emerging Problem in Western Countries. J Investig Allergol Clin Immunol. 2021;31(3):228-35. doi: 10.18176/jiaci.0474.
5. Bazon ML, Silveira LH, Simioni PU, Brochetto-Braga MR. Current Advances in Immunological Studies on the Vespidae Venom Antigen 5: Therapeutic and Prophylaxis to Hypersensitivity Responses. Toxins (Basel). 2018;10(8):305. doi: 10.3390/toxins10080305.
6. Chugo S, Lizaso MT, Alvarez MJ, Arroabaren E, Lizarza S, Tabar AI. Vespa velutina nigritorax: A New Causative Agent in Anaphylaxis. J Investig Allergol Clin Immunol. 2015;25(3):231-2. Available at: https://www.jiaci.org/summary/vol25-issue3-num1237.
7. Vidal C, Armisén M, Monsalve R, Gómez-Rial J, González-Fernández T, Carballada F, et al. Vesp v 5 and glycosylated Vesp v 1 are relevant allergens in Vespa velutina nigrithorax anaphylaxis. Clin Exp Allergy. 2020;50(12):1424-7. doi: 10.1111/cea.13738.
8. Vidal C. The Asian wasp Vespa velutina nigrithorax: Entomological and allergological characteristics. Clin Exp Allergy. 2022;52(4):489-98. doi: 10.1111/cea.14063.
9. Rodríguez-Vázquez V, Gómez-Rial J, Monsalve RI, Vidal C. Consistency of Determination of sIgE and the Basophil Activation Test in Vespa velutina nigrithorax Allergy. J Investig Allergol Clin Immunol. 2022;32(2):143-5. doi: 10.18176/jiaci.0716.
10. Esteves Caldeira L, Silva MIT, Pedro E, Cosme J. Hypersensitivity to Vespa velutina nigrithorax: an emerging problem in Portugal? Eur Ann Allergy Clin Immunol. 2023;55(4):xx-xx. Online version: Eur Ann Allergy Clin Immunol. 2023;55(4):xx-xx. doi: 10.23822/EurAnnACI.1764-1489.279.

11. Rodríguez-Vázquez V, Armisén M, Gómez-Rial J, Lamas-Vázquez B, Vidal C. Immunotherapy with Vespula venom for Vespa velutina nigrithorax anaphylaxis: Preliminary clinical and immunological results. Clin Exp Allergy. 2022;52(2):345-47. doi: 10.1111/cea.14039.
12. Monsalve RI, Gutiérrez R, Hoof I, Lombardero M. Purification and molecular characterization of phospholipase, antigen 5 and hyaluronidases from the venom of the Asian hornet (Vespa velutina). PLoS One. 2020;15(1):e0225672. doi: 10.1371/journal.pone.0225672.
13. Hoffmann HJ, Santos AF, Mayorga C, Nopp A, Eberlein B, Ferrer M, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. Allergy. 2015;70(11):1393-405. doi: 10.1111/all.12698.
14. Grossi V, Severino M, Massolo A, Infantino M, Laureti F, Macchia D, Meucci E, Francescato E, Pantera B, Ebbli A, et al. Vespa Velutina Nigrithorax venom allergy: inhibition studies approach for the choice of specific immunotherapy. Eur Ann Allergy Clin Immunol. 2023;55(4):xx-xx. Online version: Eur Ann Allergy Clin Immunol. 2023;55(4):xx-xx. doi: 10.23822/EurAnnACI.1764-1489.277.
15. Perrard A, Pickett K, Villemant C, Kojima JI, Carpenter J. Phylogeny of hornets: a total evidence approach (Hymenoptera, Vespidae, Vespinae, Vespa). JHR. 2013;32:1-15. doi: 10.3897/JHR.32.4685.
16. Perrard A, Lopez-Osorio F, Carpenter JM. Phylogeny, landmark analysis and the use of wing venation to study the evolution of social wasps (Hymenoptera: Vespidae: Vespinae). Cladistics. 2016;32(4):406-25. doi: 10.1111/cla.12138.