Supplementary material

Cichocka-Jarosz E, Nittner-Marszalska M, Mól N, et al. Hymenoptera sting in the head and neck region is not a risk factor for grade IV systemic reactions in patients with venom allergy. Pol Arch Intern Med. 2019: 129; 160-166. doi:10.20452/pamw.4448

Appendix S1. Questionnaire used in the study for adults

Questionnaire regarding the place of sting site, severity of reaction, and exposure to sting

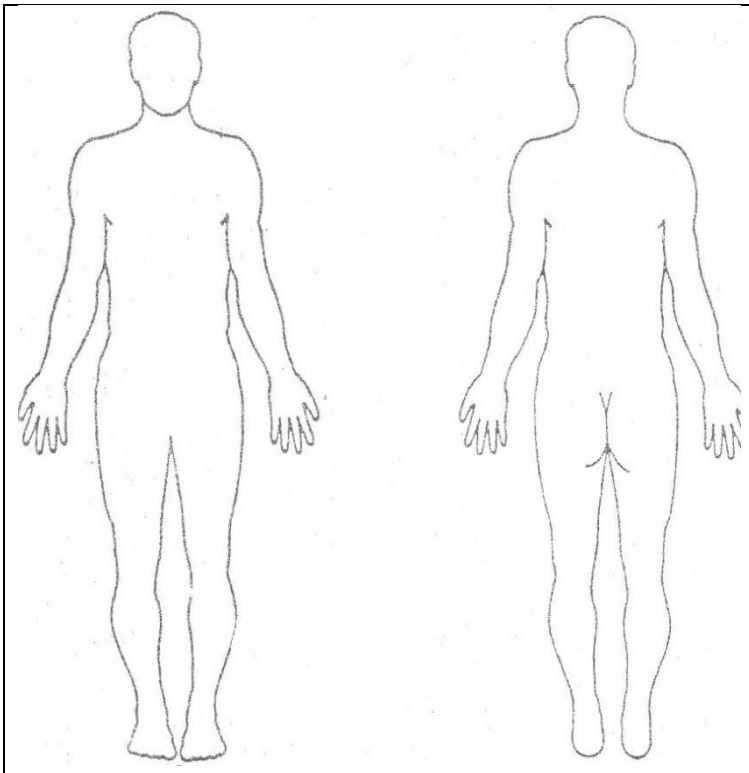
Please supplement the information concern the most severe sting reaction being a basis for qualifying your child to the Venom Immunotherapy.

Date of sting: Day: □□ Month: □□ Year: □□□□

(If You do not remember exact date, please estimate the month and year, please use Arabic numerals)

1. **Sting site.**

(Please point the place of sting site and describe it next to the scheme if it requires a more precise location determination, eg, the lip, tongue, finger)

	lips, tongue, oral cavity head neck abdomen (belly) / chest back right arm left arm right forearm, elbow right hand left forearm, elbow left hand right thigh left thigh right calf, knee right foot left calf, knee left foot

2. Please indicate the symptoms that occurred during the reaction after this sting:

Local skin reaction: □Large local reaction – redness and swelling larger than 10cm in diameter, last over 24 hours	**Skin:** □urticaria/ hives or redness □angioedema □flushing, □itch
Gastrointestinal system: □nausea, □vomit, □diarrhea, □spastic abdominal pain	**Respiratory tract:** □ dyspnea, chest tightness □ wheezing (inspiratory or expiratory) □ laryngeal edema, throat and tongue edema □ rhinorrhea
Cardiovascular system: □ dizziness, □ fainting, □ hypotension □ confusion □ loss of consciousness	**Others:** □ headache □ chest pain □ convulsions □ incontinence of urine or feces

1. **At which sting, in order, systemic symptoms described in points 1,2 appeared?**

   ……

2. **Are you able to identify the insect?**

   □ wasp

□ bee

□ hornet

□ I am not able to identify the insect

3. **How many insects sting caused reaction described in points 1 and 2?**

□ 1 insect

□ more insects – how many? _____

□ I cannot determine

4. **Is there an apiary in your neighborhood (home, vicinity)?**

□ yes, near the house/ farm

□ yes, in the vicinity

□ no

□ I don't know

5. **I am exposed due to the nature of the work / hobby that I perform:**

□ beekeeping

□ fruit growing, agriculture,

□ grocery store,

□ confectioner's trade

□ barman, waiter,

□ fireman

□ others –what?_____

Name: Surname:

Date of birth: Zip code of the place of residence:

Appendix S2. Results of multivariable analysis concerning grade IV systemic reactions (SRs) with respect to age

The risk of grade IV SRs was four times lower in children following a Hymenoptera sting (OR 0.26; 95%CI, 0.13–0.54; p<0.001), however it was almost two and a half times higher in the rural population (OR 2.34; 95%CI, 1.13–4.84; p=0.022). The analysis of the groups divided into six age categories that differed by 10-year intervals demonstrated that the risk of grade IV SRs due to IS increased with age, reaching its peak in the 30-40 years age group (OR 9.42; 95%CI, 2.30–38.5; p=0.002). It was still significantly higher in the 41-50 age group (OR 5.48; 95%CI, 1.69–7.0; p=0.005), and in the 50+ group (OR 4.77; 95%CI, 1.53–14.9; p=0.007), when compared to the youngest age group below 10 years. According to this model, living in a village increased the risk of grade IV SRs to a similar extent as in the previous one (OR 2.27; 95%CI, 1.9–4.72; p=0.029). There was no significant association between patient's age and his/her place of residence, which confirmed that the relationship between place of living and severity of reaction was similar in both age groups.

There was a predominant notion that HVA patients reported higher incidence of more severe clinical reaction due to IS in adults than children [32]. It was also the case in our selected population, as we observed grade IV SRs in adults two times more often than in children. Some authors indicated even 10 times more frequent grade IV reaction in adults in comparison to children [1]. According to the data published by some European and American authors both severity of systemic reaction and fatality rate due to IS, was the highest in the middle-aged men [33]. Similar data were obtained in Australia, where most of the IS-induced anaphylaxis deaths occurred in the patients between 35 and 84 years, almost exclusively in male subjects [25]. Our results corroborated previous findings since the highest odds ratio of grade IV SRs was observed in age group 30-40 years (OR 9.42; 95%CI, 2.30–38.5), followed by age groups 41-50 years (OR 5.48; 95%CI, 1.69–17.0) and over 50 years (OR 4.77; 95%CI,

1.53–14.9.). On the other hand, our data indicated that childhood period was a factor that reduced risk of grade IV SRs 4-times (OR 0.26; 95%CI, 0.13–0.54). In the European Anaphylaxis Registry, there were two factors identified as the most important predictors for increased risk of severe anaphylaxis, specifically advanced age (OR not given for age) and concomitant mastocytosis (OR 3.1; 95%CI, 2.6–3.7) [5]. The above registry confirmed earlier observations that indicated the significance of older age [34,35], as well as mast cells activation syndrome [36] in this particular group of patients. The authors suggested that the higher risk of severe, potentially fatal IS reaction in seniors might result from the high, increasing with age, upload and/or activity of the mast cells corresponding to increased baseline concentration of serum tryptase [37]. Mast cell activation syndromes might occur at any age, though indolent systemic mastocytosis, the most important risk factor for severe IS anaphylaxis, occurred mostly in adult population [38,39]. However, a more detailed evaluation of the mast cells activity was not a part of this study.

References:

32. Bilo, MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. Clin Exp Allergy. 2009; 39: 1467-76.
33. Turner PJ, Jerschow E, Umasunthar T, et al. Fatal Anaphylaxis: Mortality Rate and Risk Factors. Allergy Clin Immunol Pract. 2017; 5: 1169-1178
34. van der Linden PW, Hack CE, Struyvenberg A, et al. Insect-sting challenge in 324 subjects with a previous anaphylactic reaction: current criteria for insect-venom hypersensitivity do not predict the occurrence and the severity of anaphylaxis. J Allergy Clin Immunol. 1994; 94(2 Pt 1): 151-9.
35. Ruëff F, Przybilla B, Biló MB, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline

serum tryptase-a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. J Allergy Clin Immunol. 2009; 124: 1047-54.

36. Vos BJPR, van Anrooij B, van Doormaal JJ, et al. Fatal Anaphylaxis to Yellow Jacket Stings in Mastocytosis: Options for Identification and Treatment of At-Risk Patients. J Allergy Clin Immunol Pract. 2017; 5: 1264-1271.
37. Nguyen M, Pace AJ, Koller BH. Age-induced reprogramming of mast cell degranulation. J Immunol. 2005; 175: 5701-5707.
38. Niedoszytko M, Bonadonna P, Oude Elberink JN, et al. Epidemiology, diagnosis, and treatment of Hymenoptera venom allergy in mastocytosis patients. Immunol Allergy Clin North Am. 2014; 34: 365-81.
39. Nittner-Marszalska M, Cichocka-Jarosz E. Insect sting allergy in adults: key messages for clinicians. Pol Arch Med Wewn. 2015; 125: 929-37.