

Risk factors for severe systemic reactions to Hymenoptera Venom in children

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SUMMARY

Sensitization to Hymenoptera venom (HV) affects 3.7% of children with a risk of systemic reaction (SR) and fatalities, but little is known regarding the risk factors associated with severe reactions in paediatric patients. This paper provides a comprehensive summary of recent findings on personal risk for developing SRs in children after Hymenoptera stings. However, much remains to be explored and concluded in this area, leaving room for further research and discovery.

KEYWORDS: Hymenoptera venom allergy, Anaphylaxis, Pediatrics, Children

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INTRODUCTION

Sensitization to Hymenoptera affects 3.7% of children ¹, but the prevalence of systemic reactions (SR) in Italian children is lower than 1% ², reaching 6.5% in an Israeli study based on questionnaires ³. In general, the overall prevalence of SR or anaphylaxis in children ranges from 0.15% to 0.8%; however, children younger than five years have a low risk of SR ⁴.

Patients with SR should be investigated for Hymenoptera venom allergy (HVA) by performing skin tests and measuring specific IgE levels ⁵. Moreover, tryptase levels should be determined to exclude mastocytosis. A study by Yavuz et al. ⁶ compared the levels of serum baseline tryptase in children with a history of SR and LLR and found that tryptase levels were significantly higher in patients with previous SR. In this paper, logistic regression analysis revealed serum baseline tryptase > 4.8 µg/l, even in normally accepted ranges, as a significant risk factor for severe SR in children with venom allergy. Even if further studies are needed, the authors propose that this finding may help clinicians identify patients at risk of severe SR who may benefit from venom immunotherapy.

Children with proven HVA and a history of SR exceeding generalized skin symptoms should be treated with immunotherapy and provided with epinephrine ⁴.

Although fatalities mainly occur in adults, the potential risk of death due to HVA is also present in children. Understanding the natural history and epidemiology of HVA is essential

for improving preventive strategies. There are conflicting data in the literature regarding the predisposing factors for the development of SR in children. A recent review ⁷ described the following factors that influence the outcome and severity of reactions to insect stings, mainly in adults: genetic factors, atopy, venom sensitization, number of stings, old age, severity of previous reactions, sex (male more affected than female), and elevated tryptase levels.

This paper summarizes the risk factors for SR to Hymenoptera in children, as described in the literature.

METHODS

A systematic search of English literature on pediatric HVA was conducted using the Medline (PubMed) database in December 2023. Eight articles were included after a full-text review, representing 20097 patients, using the following combination of keywords: ("Hymenoptera venom allergy" OR "bee sting allergy" AND "child" OR "children" OR "pediatric"). Case reports were excluded. Three independent authors selected candidate studies. The bibliographies of the selected studies were checked for potential articles. To be included, studies had to be performed on patients younger than 18 years, and the demographic characteristics of the enrolled patients and types of reactions to Hymenoptera venoms were described. We excluded studies that reported both adult and pediatric cases without correctly specifying the characteristics of the pediatric population. The following information was obtained for the analysis: age, sex, ethnicity, atopic comorbidities, number of stings, severity of previous reactions, time latency between different stings, body site of stings, and allergy test results (serum-specific IgE levels and skin tests). A descriptive analysis was performed for all variables. The initial database search included 104 articles, and the bibliographic

review identified nine articles. Eighteen articles were included based on our inclusion and exclusion criteria. After a full-text article review, eight pediatric HVA papers analyzing risk factors were included⁷⁻¹⁴. All studies, except one, were questionnaire-based.

RESULTS

The risk factors for severe reactions to Hymenoptera stings are summarized in Table I ⁸⁻¹⁴. No agreement has been reached in pediatric age regarding sex (males are not more at risk for SR than females), and atopic disease (i.e. allergic rhinitis, atopic dermatitis) are not a predisposing factor for SR to Hymenoptera. Only asthma has been described as a risk factor for SR in the Hymenoptera. In addition, in a study by Novembre et al. ¹⁵, 1175 children were investigated using questionnaires and skin prick tests, and those positive for inhalants and food allergens were significantly associated with positivity to Hymenoptera venom, suggesting that sensitization to HV is linked to atopy-related humoral IgE hyperresponsiveness.

Few studies have correlated a high level of serum-specific IgE or positivity of skin testing with a higher risk for developing SR to Hymenoptera compared to less sensitized patients. One paper ⁹ reported an higher level of specific IgE in children with a history of SRs compared to those with a history of LLRs for both vespids and honey bees, but these findings were not confirmed in other pediatric studies, such as those published by Yavuz et al. ⁸, where no statistically significant correlations were found between the severity of the reaction and diagnostic test results. In particular, positive results of skin testing and venom-specific IgE that existed before subsequent stings were not predictive of sting outcome ¹⁴.

According to a study conducted on Irish schoolchildren, the risk

TABLE I. Risk factor for severe systemic reactions (SSR) to Hymenoptera stings in children.

Study	N. of patient: Gender (M/F)	Age group (years)	Specific IgE	Ethnicity	Rural area	Asthma	Males	Female	Atopic diseases	Head and Neck stings	Eosinophilia ($\geq 5\%$)	Median number of stings	Time latency between stings	Severity of the previous reactions
9	80; (58/22)	4-15	✓											
10*	10021; (4672/5349)	13-14		✓					✓					
11*	4112	7-8; 11-13			✓	✓								
12*	5602; (2482/3120)	12-14				✓	✓							
8*	76; (57/19)	9.8 (mean)						✓	✓	✓	✓			
13*	148; (41/107)	15.2 (mean)										✓		
14*	130; (93/37)	3-18											✓	✓

* Questionnaire-based studies.

of being stung by hymenoptera, and consequently the risk of sensitization, was high in boys, old subjects, and children living in rural areas. Although the study by Arıkan-Ayyıldız did not confirm this finding¹², similar results were reported in the population described by Graif¹⁰.

When comparing the demographic features of children allergic to wasp and bee venoms, some differences were found: the mean age of children with anaphylactic reactions was lower in children with bee allergy; moreover, those with bee allergy were at a higher risk for SR even if the frequency of SR did not reach a statistically significant difference between wasp and bee⁸.

DISCUSSION

This paper provides a comprehensive summary of the recent findings on personal risk for developing SRs in children after Hymenoptera stings. However, there is still much to be explored and concluded in this area, which increases the demand for further research and discovery. Attempting to summarise conclusions, we can assert that a history of previous severe reactions and the number of stings received are significant risk factors for developing future severe reactions. This underscores the importance of patient history in risk assessment. Furthermore, these findings suggest that increased exposure to a specific allergen, often due to lifestyle and environmental factors, increases the risk of sensitization and subsequent severe reactions. These insights could potentially inform preventive strategies in the clinical practice.

In contrast, no final data on genetic predisposition have been described in paediatric patients, and in this regard, ethnicity seems to affect the risk of SR more because of the lifestyle of the population studied than because of the genetic background. In addition, for sex, there were no concordant results: one study described male sex, and another described female sex as a risk factor for Hymenoptera SRs.

Moreover, as for food allergy, asthma represents a relevant risk factor for SRs^{11,12}. Asthmatic children with severe food allergies are at risk for SRs when exposed to the allergen, and death from food allergies occurs mainly in asthmatic adolescents. Asthma has been described in two studies as a risk factor for SRs to the Hymenoptera in children. In the Irish population described by Jennings et al.¹¹, children affected by asthma in the past were 2.8 times more likely to suffer an SSR than were non-asthma sufferers. Similarly, Arıkan-Ayyıldız et al.¹² reported that Turkish children with asthma were more likely to experience SSR (OR 3.3). Both studies were questionnaire-based, and no further information regarding disease severity or control was reported.

Regarding age, literature has reported that older children are more at risk for SRs¹⁶. This could be explained by the fact that sensitization increases with exposure to trigger allergens. So far, sensitization to airway or food allergens and sensitization to Hymenoptera without a history of reactions could not be considered a risk factor for developing SRs to Hymenoptera.

Only one study reported the site of sting (head and neck) as a risk

factor for SRs⁸, even though it is in conflict with that reported in studies on adult patients^{17,18}. Analysing the time interval between the sting, as for drug allergy, in which those intermittently receiving drugs (i.e., children affected by cystic fibrosis) are more at risk for developing drug hypersensitivity reactions, the same can occur in those stung within a recurrent time frame.

No conclusion regarding eosinophilia or other atopic diseases affecting the risk of SSRs to Hymenoptera venom has been reached. One and two articles reported a higher risk in patients with eosinophilia (blood eosinophils > 500/mm³) and atopic disease (i.e., rhinitis, atopic dermatitis), respectively, but these findings were not confirmed in other studies.

CONCLUSIONS

Our review had several limitations. Given the limited literature on paediatric risk of SR to Hymenoptera, the included studies were mainly based on questionnaires. Non-well-designed prospective studies were included, and the number of children enrolled in this review was low.

In conclusion, this study aimed to highlight the knowledge gap in HVA. In particular, the literature on this topic needs to be revised to agree on strategies to prevent SR to Hymenoptera in children.

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Ethical consideration

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Conflicts of interest statement

The authors declare no conflicts of interest in relation to this publication.

Authors' contributions

Conceptualization, FM and LT; Methodology, FM; Validation, FM and CI; Writing-Original Draft Preparation, LT, EDA and IB; Writing-Review & Editing, AK, FG, SM, AAS, and MMDG; Supervision, CI and FM.

References

- 1 Bilò M, Pravettoni V, Bignardi D, et al. Hymenoptera Venom Allergy: Management of Children and Adults in Clinical Practice. *J. Investig. Allergol. Clin. Immunol* 2019;29:180-205, <https://doi.org/10.18176/jiaci.0310>.
- 2 Quercia O, Incorvaia C, Marseglia GL, et al. Prevalence and Incidence of Reactions to Insect Stings in Children: A Reappraisal. *Minerva Pediatr* 2014;66:257-260.
- 3 Graif Y, Romanozelekha O, Livne I, et al. Allergic Reactions to Insect Stings: Results from a National Survey of 10,000 Junior High School

- Children in Israel. *J Allergy Clin Immunol* 2006;117:1435-1439. <https://doi.org/10.1016/j.jaci.2006.03.004>.
- ⁴ Sturm GJ, Varga E-M, Roberts G, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. *Allergy* 2018;73:744-764. <https://doi.org/10.1111/all.13262>.
- ⁵ Novembre E, Giovannini M, Mori F, et al. Allergia al veleno di imenotteri in età pediatrica. *Rivista di Immunologia e Allergologia Pediatrica* 2020;34(04):I-XX.
- ⁶ Yavuz ST, Sackesen C, Sahiner UM, et al. Importance of serum basal tryptase levels in children with insect venom allergy. *Allergy* 2013;68:386-391. <https://doi.org/10.1111/all.12098>.
- ⁷ Bilò MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. *Clin Exp Allergy* 2009;39:1467-1476. <https://doi.org/10.1111/j.1365-2222.2009.03324.x>.
- ⁸ Yavuz ST, Sahiner UM, Buyuktiryaki B, et al. Clinical Features of Children with Venom Allergy and Risk Factors for Severe Systemic Reactions. *Int Arch Allergy Immunol* 2013;160:313-321. <https://doi.org/10.1159/000341666>.
- ⁹ Pastorello EA, Borgonovo L, Piantanida M, et al. Higher venom-specific IgE levels differentiate children with previous local large reactions from children with previous systemic reactions of different severity. *Arch Asthma Allergy Immunol* 2021;5:017-021. <https://doi.org/10.29328/journal.aaai.1001025>.
- ¹⁰ Graif Y, Romano-Zelekha O, Livne I, et al. Increased Rate and Greater Severity of Allergic Reactions to Insect Sting among Schoolchildren with Atopic Diseases. *Pediatr Allergy Immunol* 2009;20:757-762. <https://doi.org/10.1111/j.1399-3038.2009.00863.x>.
- ¹¹ Jennings A, Duggan E, Perry IJ, et al. Epidemiology of Allergic Reactions to Hymenoptera Stings in Irish School Children. *Pediatr Allergy Immunol* 2010;21:1166-1170. <https://doi.org/10.1111/j.1399-3038.2010.01054.x>.
- ¹² Arıkan-Ayyıldız Z, Isık S, Babus S, et al. Allergic Reactions to Hymenoptera Stings in Turkish School Children. *Allergol. Immunopathol (Madr)* 2016;44:41-45. <https://doi.org/10.1016/j.aller.2015.04.009>.
- ¹³ Toyran M, Celik İK, Guvenir H, et al. Frequent Bee Stings May Promote More Severe Allergic Reactions in Children with Large Local Reactions. *Asthma Allergy Immunology* 2023;21:128-134. <https://doi.org/10.21911/aaai.041>.
- ¹⁴ Lange J, Cichocka-Jarosz E, Marczak H, et al. Natural History of Hymenoptera Venom Allergy in Children Not Treated with Immunotherapy. *Ann Allergy Asthma Immunol* 2016;116:225-229. <https://doi.org/10.1016/j.anai.2015.12.032>.
- ¹⁵ Novembre E, Cianferoni A, Bernardini R, et al. Epidemiology of insect venom sensitivity in children and its correlation to clinical and atopic features. *Clin Exp Allergy* 1998;28:834-838. <https://doi.org/10.1046/j.1365-2222.1998.00313.x>.
- ¹⁶ Bilò BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. *Curr Opin Allergy Clin Immunol* 2008;8:330-337. <https://doi.org/10.1097/ACI.0b013e32830638c5>.
- ¹⁷ Arzt L, Bokanovic D, Schwarz I, et al. Hymenoptera stings in the head region induce impressive, but not severe sting reactions. *Allergy* 2016;71:1632-1634. <https://doi.org/10.1111/all.12967>.
- ¹⁸ Sturm GJ, Schadelbauer E, Marta G, et al. Risk Factors for Severe Sting Reactions and Side Effects During Venom Immunotherapy. *J Allergy Clin Immunol Pract* 2025;13:17-23. <https://doi.org/10.1016/j.jaip.2024.08.025>.