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Jörg Fischer, Ralf Wenninger, Lena Löffelad, Sebastian Volc

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Is the serological bee/vespula venom-specific IgE ratio supplemented by component-resolved diagnostics a reliable alternative to skin testing for hymenoptera venom allergy?

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Abstract
Background A reliable diagnosis of hymenoptera venom allergy is based on medical history, skin tests, and serological immunoglobulin E (IgE) determination. Over the past 10 years, component-resolved diagnostics (CRD) have gained in importance, and new strategies for interpreting serological double sensitization have been introduced with the bee/vespula venom-specific IgE ratio.
Objectives The aim was to examine whether the bee/vespula venom-specific IgE ratio supplemented by CRD can be a reliable alternative to skin testing.
Methods In a student project, the guideline algorithm for serological diagnostics was supplemented with the sIgE ratio (≥5:1) and tested in a simulation using anonymized data from a retrospective study (Fischer et al.). A partial data set of 375 cases with complete CRD and documented prick and intradermal test results was selected for the simulation. The performance of the algorithm was evaluated by a post hoc comparison of the algorithmic therapy recommendations with the allergen immunotherapies (AIT) actually implemented in the clinic.
Results The simulation yielded 48.5% monosensitizations and 49.9% double sensitizations. In 56.3% of the double sensitizations, the ratio ≥5:1 indicated a dominant sensitization, which was classified as a monoallergy. The therapies suggested by the algorithm corresponded to the clinically implemented AIT in 91% of cases; overall, the correspondence was 89.7%. While the algorithm predicted double AIT in 10% of cases, this was only clinically implemented in 2.7% of cases, with anamnestic details on sting circumstances and diagnostic certainty influencing the decision.
Conclusion Standardized serological diagnostics with bee/vespula venom-specific IgE ratio and CRD provide high diagnostic precision and comprehensively demonstrate the progress made over the last 10 years. Skin tests remain a medically useful and valuable part of diagnostics, especially in cases of double sensitization.

Keywords Componend-resolved diagnostic · Hymenoptera venom allergy · Anaphylaxis · Skin testing · Allergology

PD Dr. J. Fischer (✉)
Department of Dermatology and Allergology, Augsburg University Hospital, Sauerbruchstr. 6, 86179 Augsburg, Germany
joerg.fischer@uk-augsburg.de

R. Wenninger
Faculty of Medicine, University of Augsburg, Augsburg, Germany

PD Dr. J. Fischer · L. Löffelad · S. Volc
University Dermatology Clinic, Tübingen University Hospital, Eberhard Karls University of Tübingen, Tübingen, Germany

Abbreviations

BV	Bee venom
CCD	Cross-reactive carbohydrate-associated determinants
CRD	Component-resolved diagnostics
ELISA	Enzyme-linked immunosorbent assay
Ig	Immunoglobulin
IT	Venom immunotherapy
sIgE	Specific immunoglobulin E
VV	Vespula venom

Introduction

In allergology, an allergy is considered a confirmed diagnosis if a qualified medical history confirms an allergic systemic reaction in temporal connection with allergen exposure and allergological testing detects

sensitization to the suspected allergen [1, 2]. When applied to the diagnosis of an immediate-type allergy to hymenoptera venom, there are three independent sources of information: medical history, skin tests (prick and intradermal tests), and serological determination of specific IgE antibodies (sIgE) against whole venoms and recombinant allergen components [1, 2]. The medical history plays a prominent role in the diagnostic process, as it can significantly influence the choice of treatment in cases where skin test and serological diagnostic findings are inconsistent. In addition to the occurrence and severity of symptoms and the acute therapy administered, a qualified allergological medical history records situational aspects of the sting, information on the stinging hymenoptera species, and previous sting experiences, and checks them for their plausibility [1–3]. These detailed physician–patient consultations require increased medical resources. For high-quality medical histories, a sound knowledge of the biology and lifestyle of hymenoptera is helpful, which doctors acquire during their specialist training. In comparison, skin tests and serological procedures appear to be quicker to learn, more objective, and more reliable. However, skin tests with bee and wasp venom carry a risk of test-associated anaphylaxis and therefore require patient education and consent. In addition, pain, itching, and discomfort may occur during the prick test. Prick and intradermal tests are time-consuming, tie up consultation hours, and are further complicated by supply bottlenecks of histamine positive controls. Over the past 10 years, component-resolved diagnostics (CRD) with recombinant allergen components for bee and vespula venom have made significant progress [4–9]. It enables a clear separation of nonspecific cross-reactivities to carbohydrate-bound determinants (CCD) from true double sensitizations. Recently, the bee/vespula venom-specific IgE ratio was published as a new strategy for interpreting serological double sensitizations [10]. In personal exchanges with allergists at conferences and training courses, the impression is currently emerging that skin tests are being reduced in clinical routine or are only being performed in special diagnostic cases. This approach is justified by the statement in the current S2k guideline Diagnosis and Treatment of Bee and Wasp Venom Allergy: "If a clear diagnosis is

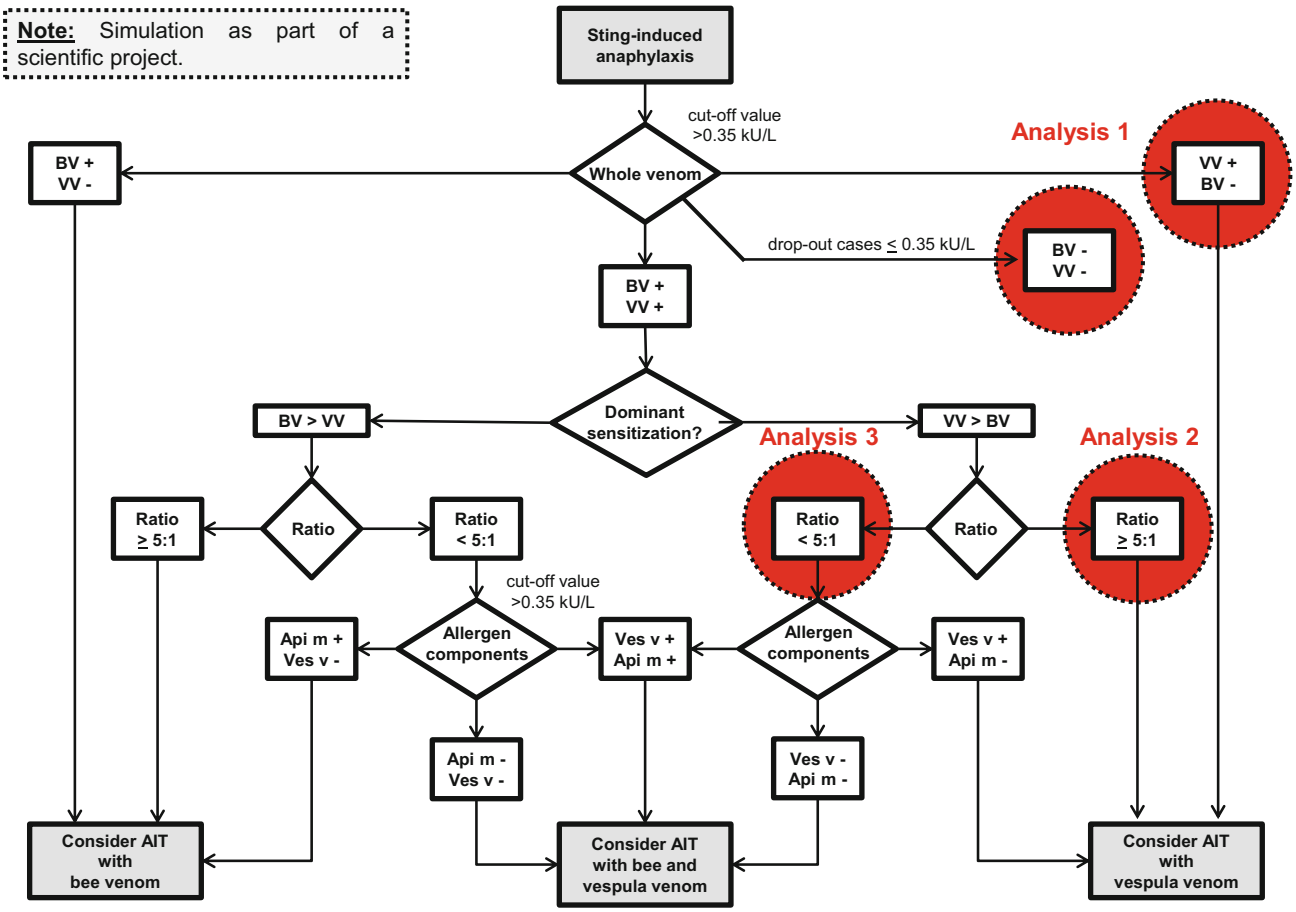

Fig. 1 Concept of the algorithm to be tested in the simulation for the serological diagnosis of hymenoptera venom allergy with an integrated intermediate step of the bee/vespula venom specific immunoglobulin (sIgE) ratio according to Tischler et al. [10]. The basis is the laboratory algorithm of the German S2k guideline with sequential evaluation of specific IgE against total venoms and recombinant allergen components [2]. *VIT* allergen-specific immunotherapy, *BV* bee venom, *VV* vespula venom, *AIT* allergen immunotherapy

achieved in the context of in vitro diagnostics, a skin test may be omitted" [2]. Against this background, the question arises as to whether standardized serological diagnostics using CRD and bee and wasp venom IgE ratio have now become so precise that they render skin testing unnecessary in the routine diagnosis of insect venom allergy.

Methods

As part of a student project (60 teaching units) in the longitudinal block internship in human medicine at the University of Augsburg, the diagnostic precision of a purely laboratory-based algorithm for clarifying hymenoptera venom allergy was investigated. The aim was to evaluate the predictive accuracy of a serological bee/vespula venom-specific IgE ratio according to Tischler et al., supplemented by component-resolved diagnostics (CRD) [10]. The algorithm for serological diagnostics of the S2k guideline Diagnosis and Therapy of Bee and Wasp Venom Allergy with sequential evaluation of specific IgE (sIgE) against whole venom and recombinant allergen components served as the basis. The bee/vespula venom-specific IgE ratio was integrated into this diagnostic concept as an intermediate step (Fig. 1). For the simulation, we used an anonymized partial data set from the retrospective study by Fischer et al. from the University Dermatology Clinic in Tübingen [11]. All cases in which both component-resolved diagnostics and documented prick and intradermal test results were available were selected from this data set. Information on sting circumstances, insect species, or anamnesis plausibility were not parameters of the original study and were therefore not available. In the clinical routine of the University Dermatology Clinic in Tübingen, all available CE-certified ImmunoCAP allergens were determined in cases of suspected insect venom allergy, regardless of anamnesis or skin test. Laboratory diagnostics included native bee and wasp venom; Api m1, m2, m3, m5, m10; Ves v1, v5; CCD/MUXF3; total IgE and tryptase. An sIgE value ≥ 0.35 kU/l was considered evidence of type I sensitization. The skin test findings included titrated prick tests in a concentration range of 1 µg/ml, 10 µg/ml, 100 µg/ml, and 300 µg/ml, as well as a supplementary intradermal test with 1 µg/ml bee and wasp venom in cases of negative prick tests. Based on current knowledge, it is known that irritative false-positive reactions are possible when bee venom is used in a concentration of 300 µg/L. This may possibly be included as an error in the analysis of the simulation and influence the rate of double sensitizations. The performance of the laboratory algorithm was determined by comparing the simulation results with the characteristics of the cases in clinical diagnostics (skin testing and component-based diagnostics). We evaluated the precision based on the percentage agreement between the therapy proposed by the algorithm and the venom immunotherapies (VIT) actually implemented. In the statistical analysis, the data were processed in a database derived from the SPSS software and analyzed using SPSS Statistics (version 29; IBM, Armonk, NY, USA). Qualitative variables are given as percentages, continuous variables as medians with minimum and maximum values or as means with standard deviations. All results of this student research project were checked and supplemented by the supervisor through independent calculations.

Results

The simulation of a serology-based indication was based on cases with complete information on skin testing and laboratory diagnostics, as well as the selected toxins for VIT from $N = 375$ cases in the study by Fischer et al. in anonymized form [11]. Following the concept of stepwise diagnosis, an initial assignment to groups was made based on the findings of specific IgE (sIgE) against total toxins (bee venom and wasp venom), with a cut-off value of > 0.35 kU/L defined as the decision limit (analysis 1). In 48.5% of cases ($n = 182/375$), there was sensitization to a single total toxin (monosensitization), with 15.4% sensitized to bee venom ($n = 28/182$) and 84.6% to wasp venom ($n = 154/182$; Fig. 2, step 1). The reliability of characterizing the groups as isolated specific reactivity to bee or wasp venom was verified using the information available in the data set on reactivity in skin tests (prick and intradermal tests) and component-resolved diagnostics (CRD). In 82.1% of bee venom monosensitizations ($n = 23/28$) and in 81.2% of wasp venom monosensitizations ($n = 125/154$), an isolated reaction was consistently observed in the skin test. At least one allergen component for bee venom (Api m1, Api m2, Api m3, Api m5) was detected in 89.3% of bee venom monosensitizations ($n = 25/28$) and one allergen component for vespula venom (Ves v1, Ves v5) in 95.5% of wasp venom monosensitizations ($n = 147/154$). Consistent findings between skin testing and CRD were found in 71.4% of bee venom monosensitizations ($n = 20/28$) and in 80.5% of vespula venom monosensitizations.

In skin testing for bee venom monosensitization, sensitization to vespula venom was also detected in 5 cases (17.9%), and in 27 cases (17.5%) of wasp venom monosensitization, sensitization to bee venom was detected. When applying a cut-off value of > 0.35 kU/L, 1.6% of cases ($n = 6/375$) are not included in the algorithm. These cases are classified as non-sensitized to hymenoptera venom in the simulation and excluded accordingly.

Serological double sensitization to bee and vespula venom was present in 49.9% of cases ($n = 187/375$) and was further investigated using the algorithm according to Tischler et al. with calculation of a bee/vespula venom-specific IgE ratio (analysis 2). Due to a higher measured titer, bee venom sIgE was used as

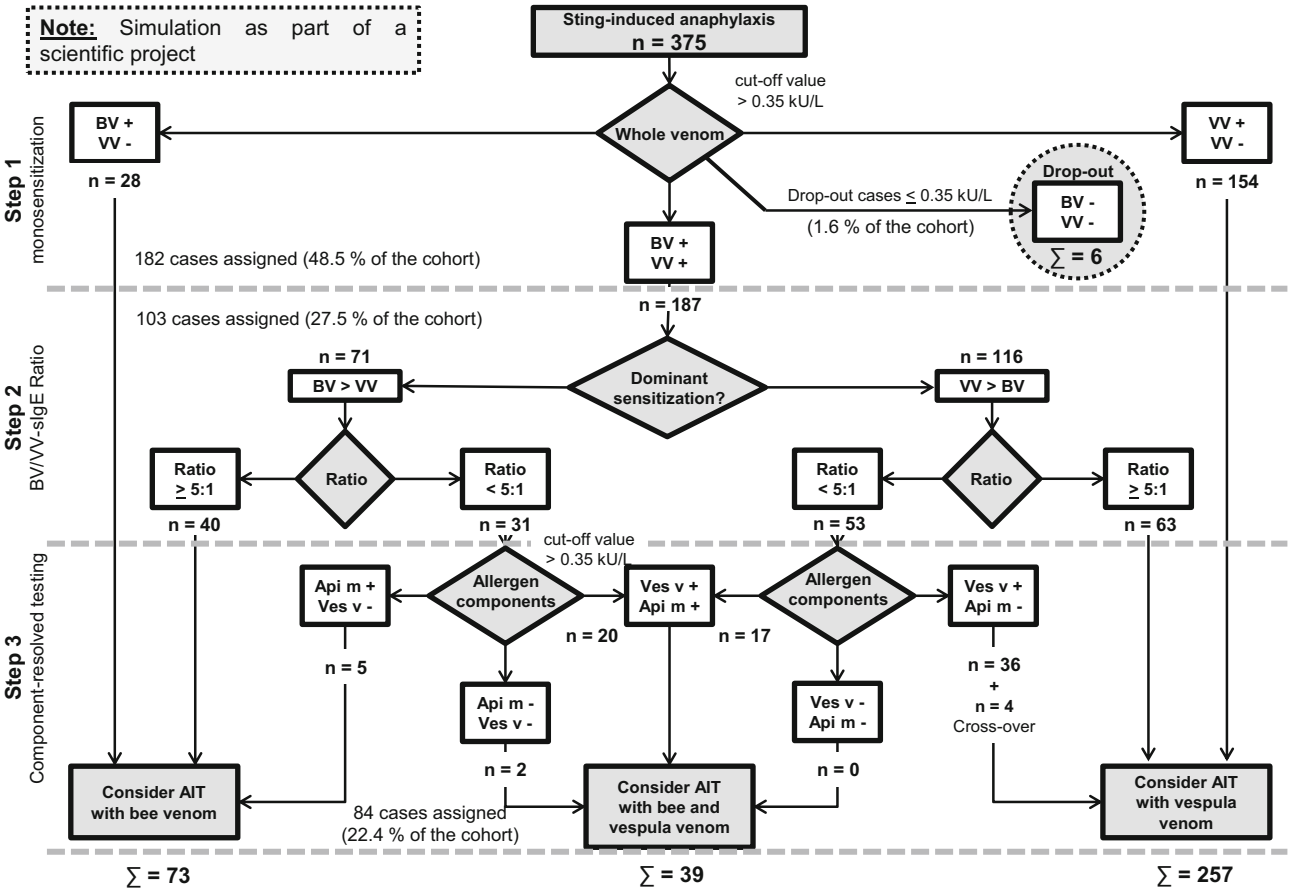

Fig. 2 Results of the simulation of the algorithm for serological diagnosis of hymenoptera venom allergy with the following steps: 1. Identification of monosensitization by determining sIgE against total venoms, 2. Calculation of a bee/vespula venom sIgE ratio according to Tischler et al. [10] with interpretation of cases with a ratio ≥5:1 as "mono-allergic" and 3. Breakdown of cases with a ratio <5:1 using component-resolved diagnostics. *VIT* allergen-specific immunotherapy, *BV* bee venom, *sIgE* specific immunoglobulin, *VV* vespula venom, *AIT* allergen immunotherapy

the numerator in the formula for calculating the ratio in 38% of cases (n=71/187) and vespula venom sIgE in 62% of cases (n=116/187), and the proportions with a ratio <5:1 and >5:1. A ratio value >5:1 was found in 56.3% of cases with bee sIgE dominance (n=40/71) and in 56.3% of cases with vespula sIgE dominance (n=63/116; Fig. 2, step 2). In accordance with the diagnostic strategy according to Tischler et al., in cases with a ratio >5:1, the nondominant sensitization was interpreted as "clinically irrelevant" and the cases were treated as "mono-allergy" [10]. The accuracy of this strategy was verified by comparing it with the information available in the data set on skin test reactivity, sIgE against cross-reactive carbohydrate determinants (CCDs), and the sIgE profile of the allergen components of dominant and nondominant sensitization. In the group of cases with a ratio >5:1, only 50.5% of cases (n=52/103) showed a reaction to bee and wasp venom in the skin test. In line with the dominant sensitization to the total venom, an isolated reaction was found in the skin test in 47.6% (n=49/103) of cases. There were clear differences in the results in cases with dominant sensitization to bee or vespula venom. In cases with dominant bee venom sensitization, the skin test showed double sensitization in 70% of cases (n=28/40), sensitization exclusively to bee venom in 25% (n=10/40), and no sensitization in 5% (n=2/40). In cases with dominant vespula venom sensitization, only 38.1% showed double sensitization (n=24/63) and 61.9% showed sensitization exclusively to vespula venom (n=39/63). Specific IgE against CCD was detectable in 62.5% (n=25/40) of bee venom-dominant cases with a mean value of 3.9 kU/L (standard deviation 5.9 kU/L) and in 39.7% (n=25/63) of vespula venom-dominant cases with a mean value of 2.1 kU/L (standard deviation 3.2 kU/L). No pattern between CCD-sIgE and monosensitization in the skin test was apparent. Analysis using allergen components confirmed the dominant sensitization to vespula venom in 100% of cases (n=63/63) and to bee venom in 97.5% of cases. In the investigation of nondominant sensitizations, additional sensitization to vespula venom was detected in 62.5% of bee venom-dominant cases. Conversely, only 9.5% of vespula venom-dominant cases showed sensitization to bee

venom. The results of CRD and skin tests with regard to nondominant sensitizations show a high degree of consistency. Overall, the skin test shows higher sensitivity in detecting additional sensitizations.

A ratio value <5:1 was found in 43.6% of cases with bee sIgE dominance (n=31/71) and in 45.6% of cases with vespula sIgE dominance (n=53/116). According to the diagnostic strategy described in Tischler et al., this constellation requires a differentiated allergological evaluation using skin testing and component-resolved diagnostics (CRD; analysis 3). In the group with a ratio <5:1, skin testing showed double sensitization in 69.0% of cases (n=58/84). An isolated reaction in skin testing corresponding to the dominant sensitization to the total venom was observed in 29.8% of cases (n=25/84). Even within this group, differences in skin test results occurred depending on the type of venom. In bee venom-dominant cases, double sensitization was observed in 90.3% (n=28/31), in 6.5% sensitization directed exclusively towards bee venom (n=2/31) and in 3.2% a group change with evidence of sensitization to vespula venom (n=1/31). In cases dominated by vespula venom, 56.6% showed double sensitization (n=30/53) and 43.4% showed isolated sensitization to vespula venom (n=23/53). Specific IgE against CCD was found in 41.9% (n=13/31) of bee venom-dominant cases with a mean value of 5.8 kU/L (standard deviation [SD] 7.4 kU/L) and in 52.8% (n=28/53) of vespula venom-dominant cases with a mean value of 4.0 kU/L (SD 4.7 kU/L). Analysis using allergen components (Fig. 2, step 3) confirmed the dominant sensitization to vespula venom in 100% of cases (n=53/53) and to bee venom in 80.6% of cases (n=25/31). In the investigation of nondominant sensitizations, additional sensitization to vespula venom was detected in 77.4% of bee venom-dominant cases (n=24/31). Conversely, 32.1% of vespula venom-dominant cases (n=17/53) showed additional sensitization to bee venom. When comparing the characteristics of the skin test and CRD results between the two ratio groups, it is noticeable that the rate of confirmed double sensitizations is higher in the group with a ratio <5:1. Apart from this, both groups show comparable characteristics, so that in this simulation, the 5:1 ratio as a decision limit does not reveal any clear difference between the groups.

To evaluate the accuracy of the algorithm, the therapy recommendations for allergen immunotherapy (VIT) were compared with the therapies actually performed based on the recommendations of the treating allergists. In the six cases that were excluded by applying a cut-off value of >0.35 kU/L, VIT with bee venom was initiated in one case and vespula venom VIT in five cases. These cases were not included in the comparison, reducing the total population to 369 cases. The algorithm resulted in the initiation of 73 bee venom VITs (19.8%), 257 vespula venom VITs (69.6%), and 39 cases of dual treatment with bee and vespula venom VIT (10.6%). The overall percentage agreement with the actual clinical treatment decision was 89.7% (n=331/369). In the monosensitization group (analysis 1), the agreement was 100%, in the group with a ratio >5:1 (analysis 2), it was 96.1%, and in the group with a ratio <5:1 (analysis 3), it was only 59.5%. The main differences were seen in the indication for dual treatment. In the actual clinical situation, this indication was only given in 10 cases (2.7%). The analysis showed that only 6 cases were decided identically. In 33 of the dual therapies suggested by the algorithm, the physician decided on a single VIT. Conversely, in 4 cases, dual treatment was indicated by the physician, while the algorithm had suggested a single VIT. These deviations illustrate the role that patient-reported key circumstances collected during the medical history and the degree of certainty regarding the type of stinging insect can play in the treatment decision.

Discussion

Comparing the information from the simulation of a serology-based diagnostic process with a conventional allergological approach provides information on challenges and possible solutions in the diagnostic process for hymenoptera venom allergy. Serological determination of specific IgE against the total venoms of bees and vespulas allows cases of monosensitization to be identified (analysis 1). In line with literature data, these account for approximately 50% of all cases [8]. Further consideration and inclusion of the diagnostic options of skin testing and CRD shows that all three test procedures reliably detect monosensitization to bee or vespula venom and that only minor, methodologically related deviations between the procedures are apparent. As an individual method, CRD proves to be the most sensitive procedure on a descriptive level. These are the cases referred to in the current guideline under “if a clear diagnosis is achieved in the context of in vitro diagnostics, a skin test may be omitted” [2]. Guideline recommendations are standardized and formulated in a graded manner using “should/is recommended,” “may be considered/could be considered,” and “may/can.” The wording should therefore be understood to mean that it does not represent a deviation from generally accepted standards of allergological care if, in these unproblematic cases, confirmation by further diagnostic tests is omitted. Cases with evidence of sIgE to bee and vespula venom pose a greater diagnostic challenge and require additional procedures. According to literature data, these cases account for approximately 50% of all cases. In most patients’ medical histories, there is only one indication of sting-induced anaphylaxis. Therefore, as a rule, only one anaphylaxis-triggering hymenoptera venom should be assumed [13]. If, at the end of the diagnostic process and after considering all available sources of information, it is not possible to identify a single allergenic hymenoptera

venom, allergen-specific immunotherapy with bee and vespula venom should be indicated [2]. These cases should be minimized through a high-quality diagnostic process. From the era before the introduction of CRD, it has been known for decades that skin tests can regularly detect reactivity to only one hymenoptera venom. This method is still used today to identify the allergenic venom and narrow down the group of double-sensitized cases. In the cohort used in this simulation, this is possible in 39.6% of cases. Before the availability of the CRD, double sensitization in the determination of total venoms was predominantly interpreted as nonspecific reactions to cross-reactive carbohydrate determinants on insect venom proteins or as reactivity to allergen components with related homologous proteins in the respective corresponding venom (e.g., hyaluronidase) [14, 15]. Since the analysis of these cases with CRD, this assessment has been relativized [4, 8]. As shown in this simulation (analysis 2 and analysis 3), there are regularly two independent type I sensitizations. Interestingly, in cases with dominant bee venom sensitization, nondominant sensitization to vespula venom was found more frequently than vice versa, where dominant vespula venom sensitization was detected with bee venom sensitization. It can be assumed that this inequality reflects the general risk of bee stings in the general population. This leads to the challenge of differentiating between clinically relevant type I sensitization and latent type I sensitization. The bee/vespula venom sIgE reaction was developed for this situation. A ratio is formed based on the consideration that prolonged contact with hymenoptera venom is associated with a higher titer of specific IgE. These considerations are not fundamentally new; with the establishment of a cut-off value of ≥5:1, a standardized procedure and the indication of existing algorithms are possible. As the post hoc comparison between the simulation and the actual treatment decisions showed, valid group differentiation is possible using a ratio of ≥5:1. The original aim of the student project was to analyze how group differentiation works with this ratio and how it correlates with other parameters such as CCD sIgE and skin test reactivity. The original working hypothesis that CCD sensitization plays a relevant role was found to be false on the basis of the analyses. How the bee/vespula venom sIgE ratio ultimately works mechanically remains unclear. However, it is functionally capable of reducing the group of double-sensitized cases by a further 50%, similar to a skin test. When compared with a conventional approach, it should be noted that a skin test is at least an equivalent diagnostic option. The absence of a reaction to a tested venom is more intuitive as a marker for clinically irrelevant type I sensitization and can be projected onto the affected patients. Based on these observations, the question posed in the introduction can be answered by saying that, even with the current state of knowledge, allergological skin testing with prick and intradermal testing is a medically useful and valuable diagnostic tool and should continue to be used in the routine diagnosis of insect venom allergy. The double-sensitized cases represented by the ratio <5:1 group pose the greatest diagnostic challenge both in simulation and in actual clinical diagnostics and are also the group in which it is most often impossible to identify a single allergy-triggering hymenoptera venom. In these cases, it is possible to determine a differentiated sensitization profile using CRD. This allows for a further reduction of diagnostically unclear cases by 53% using a process of elimination. At the end of the simulation algorithm, double VIT with bee and vespula venom was recommended in only 10% of the analyzed cohort. The high percentage of agreement between the simulation and the actual clinical treatment decision was not expected a priori by the authors. These results reflect the increased recognition of serological diagnostics among experts as a central element in the investigation of insect venom allergy. The deviations regarding the decisions for a double VIT can be attributed to the inclusion of information from the medical history. This shows the importance of a thorough medical history taken by an allergist for high-quality diagnostics.

In summary, the results of this simulation show the progress that serological allergy diagnostics has made over the last 10 years. At the same time, the analysis shows that the diagnostic standards established over decades, involving medical history and skin tests, remain medically useful and valuable components of diagnostics. The time when artificial intelligence (AI) integrated into an automated ELISA platform will render a trained allergist superfluous has not (yet) arrived.

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Author Contribution J. Fischer conceived, designed, and supervised the student project. R. Wenninger worked on the project. L. Löffelad collected the data used for the simulation as part of her doctoral thesis. J. Fischer and S. Volc were involved in the retrospective study in a responsible capacity. J. Fischer wrote the manuscript in collaboration with the co-authors.

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Statement on data availability All data collected or analyzed in this study are included in this article and in the supplementary materials. For further inquiries, please contact the corresponding author.

Conflict of interest J. Fischer received lecture fees from ALK-Abelló, Bencard, Bristol Myers Squibb, Novartis, Janssen-Cilag, Sanofi-Aventis, AeDA (Association of German Allergologists), and GEKA (Society for Experimental and Clinical Respiratory Research), consulting fees from Bencard and Sanofi-Aventis, and travel grants from Pierre Fabre Oncology outside the scope of the submitted paper. He is a member

of the AeDA and the DGAKI (German Society for Allergology and Clinical Immunology) and is deputy spokesperson for the DGAKI's Working Group on Insect Venom Allergy. S. Volc received consulting fees from AbbVie, Almirall Hermal, Amgen, Leo Pharma, Novartis, and Pfizer, as well as support for conference attendance and/or travel from AbbVie, Amgen, Almirall Hermal, and Pfizer. In addition, he received payments or fees for lectures and presentations from Almirall Hermal, Leo Pharma, Novartis, and Pfizer. R. Wenninger and L. Löffelad declare that they have no competing interests.

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