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Antigen 5–spiked *Vespula* and *Polistes* venom extracts for Vespid allergy diagnostics: A French multicenter study



Vespula and *Polistes* spp venom extracts (VEs) for ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) platforms have been spiked, that is, enriched, with group 5 allergens since 2012. Limited information was available from the manufacturer, but small cohorts have reported altered performance for in vitro diagnostics.^{1,2} Herein we present the results of a French multicenter study on antigen 5–spiked *Vespula* and *Polistes* VEs compared with nonspiked VEs.

Data on Vespid venom immunoglobulin E (IgE) were collected for outpatients attending allergy clinics after recent experience with *Hymenoptera* sting–induced anaphylaxis. IgE workup was done with conventional (2008–2012, $n = 1,314$) or spiked (2013–2015, $n = 725$) VEs. Each patient was assayed for IgE directed against at least 2 VEs or molecular allergens. Geographic distribution, gender, and age did not differ (2008–2012: 62% males; median age, 48 years; range, 1–85 years; 2013–2015: 58% males; median age, 50 years; range, 2–83 years). The study was a retrospective, noninterventional review of IgE data under the French laws on the protection of persons and confidentiality as approved by the Reims Ethics Committee. IgE to *Vespula* conventional and Ves v 5–spiked VE (i3), North American *Polistes* conventional and Pol d 5–spiked VE (i4), European *Polistes dominulus* VE (i77), and to recombinant Ves v 5 (i209), Pol d 5 (i210), and Ves v 1 (i211) were measured with ImmunoCAP. A multicenter, interlaboratory comparison of IgE has been described elsewhere.³

Results are expressed as prevalence rates in Table 1. Statistical analysis was done using the Student t test and χ^2 test as appropriate. Statistical significance was set at $P \leq .05$.

Vespula and *Polistes* VE double-positive results were more prevalent with spiked VE ($P = .0001$), and discordant *Vespula*-positive, *Polistes*-negative findings diminished after spiking ($P = .01$). Most of these discordant samples displayed IgE to Ves v 1 or Ves v 5, supporting true *Vespula* sensitization (80% with spiked extracts and 95% with conventional extracts, $P = .01$). Ves v 5 spiking of *Vespula* VE resulted in less discordant *Vespula* VE–negative sera with detectable IgE to Ves v 5 ($P = .005$) or to Ves v 1 ($P = .0003$), suggesting improved diagnostic sensitivity of spiked VE. Likewise, Pol d 5 spiking of *Polistes* VE decreased prevalence of discordant *Polistes* VE–negative, Pol d 5–positive samples ($P = 10^{-6}$), whereas concordant

Polistes VE and Pol d 5 double-positive results increased ($P = .005$). Spiking was also associated with more *Polistes* VE–positive, Ves v 1–negative results and fewer *Polistes* VE–negative, Ves v 1–positive results ($P = .02$, for both). Most of these discordant results with spiked VE were resolved through further assays of IgE to Pol d 5 and *Vespula* VE: (i) all *Polistes* VE–negative, but Ves v 1–positive sera displayed IgE to *Vespula* VE; and (ii) most *Polistes* VE–positive, but Ves v 1–negative sera displayed IgE to Pol d 5.

Among 257 sera assayed for *P dominulus* and conventional *Polistes* VE, 27 samples (10.5%) were discordant, with 23 of 27 displaying IgE to *P dominulus*, but not to *Polistes* spp (data not shown).

We confirmed a small increase in the sensitivity of the Ves v 5–spiked *Vespula* VE, in line with most previous studies.^{2,4} However, sensitivity was strikingly improved for Pol d 5–spiked *Polistes* VE. Improved sensitivity presented as fewer VE–negative, antigen 5–positive results: from 2.7% to 0.7% for *Vespula* and from 20.6% to 4.2% for *Polistes*. Thus, antigen 5 spiking led to a significant decrease in the prevalence of discordant–extract–negative, antigen 5–positive results.

Spiking of *Polistes* spp (American species) VE with Pol d 5 of the European *P dominulus* improved sensitivity to autochthonous European species. Indeed, in our hands, as in an earlier study,⁵ conventional *Polistes* VE lacked sensitivity when compared with *P dominulus* VE and Pol d 5.

Improved sensitivity of the spiked *Vespula* VE diminished the usefulness of Ves v 1 as a second-line diagnostic assay. IgE to Ves v 1 was found in 0.3% of sera without detectable IgE to spiked *Vespula* VE, as compared with a previous rate of 4.5% in our previous work and up to 10% in other earlier studies.^{1,6,7} Ves v 1 was not informative in *Polistes* sensitization workup, as all *Polistes* VE–negative (spiked and conventional), Ves v 1–positive samples demonstrated IgE to *Vespula* VE. This finding suggests some Ves v 1 specificity for *Vespula*. However, antigen 5 spiking led to an increased prevalence of double-positive *Vespula* and *Polistes* sera, meaning more efforts to distinguish between single and double sensitization would be needed.

The main strengths of our study is that it included a large sample of 2,039 patients, spanned a large portion of France, and utilized a single, standardized method. Multicenter involvement allowed data collection within a limited time frame, minimizing population, climate, insect, and medical practice variations. The lack of clinical feedback is a limitation of our study; however, at this stage, we

Table 1Sensitivity and Specificity of Antigen 5–spiked *Vespula* and *Polistes* spp Venom Extracts vs Conventional Venom Extracts and Vespid Molecular Allergens

Comparison	Venom extract or molecular allergen	Sample size (n)	Double-positive	Double-negative	Discordant	Discordant
Antigen 5–spiked and conventional extracts	Antigen 5–spiked <i>Vespula</i> spp and <i>Polistes</i> spp extracts	242	70.7% ^a (171)	12.4% (30)	<i>Vespula</i> -positive, <i>Polistes</i> negative	<i>Polistes</i> -positive, <i>Vespula</i> -negative
	Conventional <i>Vespula</i> spp and <i>Polistes</i> spp extracts	843	57.5% ^a (485)	13.6% (115)	16.1% (39), of which 80% was confirmed by Ves v 1 or Ves v 5 27.2% (229), of which 95% was confirmed by Ves v 1 or Ves v 5 <i>Vespula</i> -positive, component-negative	0.8% (2) 1.7% (14) <i>Vespula</i> -negative, component-positive
Components and <i>Vespula</i> extracts	Ves v 5–spiked <i>Vespula</i> spp extract and rVes v 5	573	81.7% (468)	8.4% (48)	9.6% (55)	0.7% ^a (4)
	Conventional <i>Vespula</i> spp extract and rVes v 5	599	81.6% (489)	6.3% (38)	9.3% (58)	2.7% ^a (16)
	Ves v 5–spiked <i>Vespula</i> spp extract and rVes v 1	328	60.9% ^a (198)	7.3% (24)	32% (105)	0.3% ^a (1)
	Conventional <i>Vespula</i> spp extract and rVes v 1	154	70.8% ^a (109)	4.5% (7)	24.7% (38)	4.5% ^a (7)
Components and <i>Polistes</i> extracts	Pol d 5–spiked <i>Polistes</i> spp extract and rPol d 5	167	70.1% ^a (117)	21.6% (36)	<i>Polistes</i> -positive, component-negative	<i>Polistes</i> -negative, component-positive
	Conventional <i>Polistes</i> spp extract and rPol d 5	330	58.2% ^a (192)	13.6% (45)	4.2% (7)	4.2% ^a (7)
	Pol d 5–spiked <i>Polistes</i> spp extract and rVes v 1	114	47.4% ^a (54)	19.3% (22)	7.6% (25)	20.6% ^a (68)
	Conventional <i>Polistes</i> spp extract and rVes v 1	138	52.9% ^a (73)	15.9% (22)	26.3% (30)	7% ^a (8)
					15.9% (22)	15.2% ^a (21)

For discordant *Vespula* vs *Polistes* venom extract results, further assays of immunoglobulin E directed to Vespid molecular allergens are presented.^aSignificant difference ($P < .05$).

have deliberately focused on technical aspects of IgE determination, aiming at improving characterization of spiked VE as tools for in vitro diagnostics.

The positivity threshold was set at 0.10 kUA/L because: (i) even though 0.35 kUA/L was the historical threshold of the radioallergosorbent test, the 0.10-kUA/L cut-off has been employed for more than 10 years for contemporary immunofluorometric IgE assays in major clinical laboratory autoanalyzers; (ii) this cut-off has been accepted by the United States Food and Drug Administration⁸ and is recommended by a consensus document⁹; (iii) it has proven utility in patients with low IgE to VE but true *Vespula* allergy¹⁰; and (iv) IgE assays between 0.10 and 0.35 kUA/L on ImmunoCAP platforms have demonstrated good repeatability and interlaboratory coefficients of variation.³

In conclusion, we have shown that antigen 5 spiking resulted in more sensitive but also more cross-reactive *Vespula* and *Polistes* VEs, and that IgE assays of Ves v 5, Pol d 5, or Ves v 1 in sera without detectable IgE to spiked VE resulted in minimal diagnostic sensitivity improvement.

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Skin testing and desensitization outcomes among platinum-sensitive oncology patients



Platinum-based, immediate hypersensitivity reactions (HSRs) are relatively common, with incidences ranging from 6.5% to 44% for carboplatin and from 10% to 19% for oxaliplatin.¹ Platinum hypersensitivity potentially leads to patient anxiety, delayed chemotherapy administration, or switches to less-preferred regimens. Platinum skin tests (STs) confirm immediate-type reactions in upward of 66%–98% of patients.^{2–5} False-negative results may occur if ST is performed shortly after a platinum-based HSR.⁴ Although breakthrough reactions occur during desensitization, success rates range from 71% to 99% for carboplatin and from 80% to 100% for oxaliplatin.^{1–3,5,6}

We conducted an institutional review board–approved, retrospective review of adult patients (≥18 years old) with a recent history (≤3 months) of platinum immediate-type HSRs. These patients were evaluated by allergist-immunologists at our institution from 2009 to 2016 and identified through a query of Current Procedural Terminology and *International Classification of Disease*—9th/10th revision codes. Patients with physician-documented initial reactions consistent with immediate-type HSRs who received subsequent cycles utilizing desensitization were included in the analysis. Patients' demographics and clinical characteristics reviewed included age, sex, cancer type, self-reported atopic disease history, and/or reported drug allergy. Index platinum HSR details were recorded, including cycle number, symptoms/signs observed, treatments received, and reaction severity.

Skin prick (SP) and/or intradermal (ID) platinum ST results were reviewed. Skin testing was performed (as previously described²), with either carboplatin (Teva Pharmaceuticals USA, Fairfield, New Jersey) or oxaliplatin (Winthrop US-Sanofi SA, Bridgewater, New Jersey), depending on the history, along with histamine-positive and saline-negative controls. If SP testing was positive (wheal >3 mm

compared with the negative control), ID testing was not performed. A single-repeat ST (SP with or without ID) was performed in a subset of patients who had initial negative results. Each practitioner determined the number of desensitization steps based on clinical history, modifying the standard 12-step desensitization protocol² if considered clinically appropriate. All patients received premedication with a combination of systemic corticosteroid, antihistamine, leukotriene-receptor antagonist, and/or aspirin. In cases of desensitization reactions, the severity grade, treatments administered, and infusion status (discontinued or restarted/completed) were reviewed. The platinum index reaction and subsequent desensitization reaction severities were classified using the Brown classification.⁷

Patients' clinical characteristics and history details were summarized using descriptive statistics with mean, median, and frequency. ST results and desensitization outcomes were summarized by identifying frequency. Data were compared using Fisher's exact test, independent two-sample *t* test, Wilcoxon rank sum test, Pearson χ^2 test, and Cochran-Armitage trend test, with exact *P* values computed. Desensitization outcomes were analyzed using a generalized estimating equation to account for the repeated data measurements. *P* ≤ .05 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Thirty-six patients (age, 63.6 ± 10.1 years; 89% women; carboplatin, *n* = 34; oxaliplatin, *n* = 2) who underwent a total of 146 desensitizations (carboplatin, *n* = 137; oxaliplatin, *n* = 9) were identified. The patients were predominantly Caucasian (83%) and afflicted with gynecologic malignancies (89%). Most index reactions were grade 1 or 2 severity (72%), occurring around the eighth cycle (median, 8; interquartile range [IQR], 6.5–9.5). Patients who tolerated all of their desensitization infusions were classified as desensitization-tolerant, whereas those with at least 1 reaction were