

# Sex Differences in Adults with Insect Venom Allergy regarding Psychological Distress, Attitudes toward the Emergency Medication, and Factual Knowledge about the Disease

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## Keywords

Anaphylactic reaction · Emergency medication · Insect venom allergy · Gender differences

## Abstract

**Background:** Hymenoptera venom allergy (HVA) has a prevalence of 3% in adults. Although patients have no ongoing symptoms, they often suffer from an impairment of their psychological well-being and quality of life. **Objective:** The aim of this study was to analyze sex-specific differences regarding the psychological burden caused by this allergy and handling of the emergency medication. **Method:** Study participants filled out a questionnaire including sociodemographic and disease-specific characteristics, the Hospital Anxiety and Depression Score (HADS), and theoretical knowledge about the emergency medication set (EMS). Additionally, an objective structured clinical examination was used to assess practical knowledge and handling of the EMS. **Results:** Fifty-six patients were included (55.4% females). Female patients showed higher subjective anxiety levels due to HVA compared to men (mean 7.2 vs. 4.6,  $p = 0.0003$ ). Furthermore, the HADS revealed that women had a significant higher anxiety level, especially after Mueller grade I–II anaphylactic reactions (mean 6.3 vs. 2.8,  $p = 0.0134$ ). This was

associated with a higher theoretical but not practical knowledge about their disease. On the other hand, males were less inclined to carry the emergency medication “always” or “almost always” (56 vs. 87.1%,  $p = 0.0015$ ) but showed higher self-assurance in using it (mean 7.3 vs. 6.1,  $p = 0.0446$ ). **Conclusions:** This clinical study provides evidence for sex differences in coping with HVA. The results suggest that females should be monitored more closely for allergy-associated anxiety symptoms, while men need more encouragement to carry the emergency medication.

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## Introduction

Hymenoptera venom allergy (HVA) can manifest anywhere from cutaneous symptoms, including generalized urticaria, angioedema, flushing, and itching, to hypotension and shock [1]. Symptoms may develop within minutes and in some cases can be fatal [2].

Approximately 60% of patients who suffered a first incident are at risk for a second systemic allergic reaction

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[3]. Some patients feel traumatized by the anaphylactic reaction, holding self-imposed debilitating beliefs even after a long time [4]. Thus, it is not surprising that patients may suffer from psychological distress even without permanent symptoms. Avoiding further stings may cause limitations in everyday activities, may result in a decrease in Health-Related Quality of Life (HRQL), and may lead to social restrictions [5, 6].

All patients with a history of a systemic allergic reaction to a Hymenoptera sting are routinely prescribed an emergency medication set (EMS) consisting of an adrenaline autoinjector, oral antihistamines, and oral corticosteroids. Even though patients are advised to carry this set with them at all times, compliance is often low [3]. Additionally, blunders in using the emergency medication have also frequently been reported [3, 7]. Studies investigating for an association between HVA and quality of life as well as patients' compliance with the prescribed EMS are sparse. Thus, in our previous study, we investigated the disease burden, psychological well-being, and attitudes regarding the set of emergency medication in 55 HVA patients [8]. Here, HVA was associated with a moderate disease burden and good compliance with carrying the emergency medication. However, several HVA patients demonstrated borderline or significant anxiety and depression disorders. These results incited us to further analyze for sex-specific differences in HVA patients as it is known that sex distinctions regarding anxiety and depression exist even though public awareness for this fact is low [1, 9, 10]. The aim of this study was to assess sex-specific differences regarding the psychological burden in HVA patients and distinctions in the attitudes toward the EMS. In addition, theoretical and practical knowledge about the EMS was analyzed.

## Materials and Methods

All outpatients  $\geq 18$  years who met the inclusion criteria of (a) a positive diagnostic test for venom-specific sensitization by skin test and in vitro test [1, 11] and received a venom immune therapy (VIT) or (b) presented for the first time with a history of an anaphylactic reaction to a Hymenoptera sting at the Department of Dermatology, Venerology, and Allergology at the University Medical Center Mannheim, Germany, between April 2016 and January 2017 were asked to participate. The exclusion criteria was age  $< 18$  years or being unable to consent. The study was approved by the Ethics Committees of the Medical Faculty Mannheim, Heidelberg University (2016580N-MA), and performed according to the principles of the Declaration of Helsinki.

Every participant was required to fill out a paper-based questionnaire including sociodemographic and disease-specific characteristics, the Hospital Anxiety and Depression Score (HADS)

[12], and the patient's subjective anxiety level because of the venom allergy, and subjective self-assurance in using and willingness to always carry the EMS. Age, disease duration (in years), and VIT duration (in months) were assessed through open questions, whereas questions about sex (male, female), venom involved (wasp, honeybee, wasp, and honeybee), severity of reaction (Muller grade I [slight general reaction] to IV [shock reaction]) [13], VIT (currently ongoing, completed, intended, and not intended), and compliance with carrying the EMS (always, almost always, often, infrequently, and never) were closed-ended multiple-choice questions answered with a single selection. Additionally, the questionnaire included a semi-closed multiple-response question about reasons for not always carrying the EMS, where participants could choose several predetermined answers (too big, too heavy, forgetfulness, fear of overheating the medication, I do not need it, or storage in the car is sufficient) or check "other reasons" and fill in their answer.

Furthermore, patients were asked to state their subjective anxiety level on a visual analog scale (VAS) from 0 (not anxious at all) to 10 (extremely anxious) and their subjective self-assurance in using the EMS (0 = very unsure how to use EMS, 10 = very self-confident in using the EMS). The questionnaire contained the HADS to evaluate the presence of depression and anxiety in our cohort. As previously confirmed by Bjelland et al. [14], the HADS is highly efficient in screening for anxiety and/or depression disorders in patients from nonpsychiatric hospital clinics. The scale consists of 14 items (7 each for the depression and anxiety subscales) with 4 possible answers for every item, which are valued from 0 to 3. The total score is added for depression and anxiety separately and interpreted as follows: 0–7 = normal, 8–10 = borderline abnormal, and 11–21 = abnormal.

We tested the patients' factual knowledge concerning the EMS, conduct in the event of an anaphylactic reaction following an insect sting, and storage of the medicine with 5 questions. The patients were asked which components their "emergency set" consisted of (open question, max. 3 points), what they had to do after using the EMS in case of an anaphylactic reaction from an insect sting (open question, max. 1 point), which drugs they should not take during a VIT (open question, max. 2 points), which active substance the emergency pen contains (open question, max. 1 point), and what one has to keep in mind concerning the storage of the individual substances (closed multiple-response question, max. 5 points).

We used an objective structured clinical examination (OSCE) to evaluate patients' handling of the emergency medication in a fixed setting. The evaluation criteria were "immediately looking for/unpacking EMS" (1 point), application and order of drugs (max. 3 points), proper use of EpiPen (max. 2 points), time until completion (max. 3 points), and further actions, for example, call an ambulance (max. 3 points).

Statistical analyses were performed with GraphPad software (GraphPad Software, Inc., La Jolla, CA, USA). Descriptive statistics were calculated for all parameters, including mean, standard deviation, median, and percentiles. Gaussian distribution was assessed with the d'Agostino and Pearson omnibus normality test. If Gaussian distribution was confirmed, statistical correlations were performed using the unpaired *t* test; otherwise, the Mann-Whitney test was applied for all continuous parameters. Categorical parameters were analyzed using the  $\chi^2$  test or the Fisher exact test as indicated. *p* values  $< 0.05$  were treated as statistically significant.

**Table 1.** Characteristics of the study cohort (*n* = 56)

Group	Total	Female	Male
Total, <i>n</i> (%)	56 (100)	31 (55.4)	25 (44.6)
Age, years			
Mean±SD	54.1±12.3	52.5±11.8	56.1±12.8
Median (25th; 75th percentile)	54.0 (45.3; 61.8)	52.0 (45.0; 61.0)	60.0 (47.5; 62.5)
Disease duration, years			
Mean±SD	5.1±6.1	5.8±7.7	4.1±3.1
Median (25th; 75th percentile)	3.0 (2.0; 5.0)	3.0 (1.0; 7.0)	3.0 (2.0; 5.0)
Venom involved, <i>n</i> (%)			
Honeybee	7 (12.5)	3 (9.7)	4 (16.0)
Wasp	46 (82.1)	26 (83.9)	20 (80.0)
Honeybee and wasp	3 (5.4)	2 (6.5)	1 (4.0)
Severity of reaction, <i>n</i> (%)			
Mueller grade I	6 (10.7)	3 (9.7)	3 (12.0)
Mueller grade II	26 (46.4)	15 (48.4)	11 (44.0)
Mueller grade III	20 (35.7)	11 (35.5)	9 (36.0)
Mueller grade IV	4 (7.1)	2 (6.5)	2 (8.0)
VIT, <i>n</i> (%)			
Currently ongoing	46 (82.1)	23 (74.2)	23 (92.0)
Completed	2 (3.6)	2 (6.5)	0 (0)
Intended	3 (5.4)	2 (6.5)	1 (4.0)
Not intended	5 (8.9)	4 (12.9)	1 (4.0)
VIT duration, months			
Mean ± SD	27.6±26.1	26.4±24.5	28.8±28.2
Median (25th; 75th percentile)	23.0 (7.0; 48.0)	21.5 (6.3; 47.3)	23.0 (7.0; 48.0)

VIT, venom immune therapy; SD, standard deviation.

## Results

### Participants

Fifty-seven patients agreed to participate in this study and filled out the questionnaire. One patient had to be excluded based on testing negative for the specific IgE. In total, 56 patients were included in the study. Thirty-one patients were female (55.4%) with a mean age of 52.5 years, and 25 patients were male (44.6%) with a mean age of 56.1 years. The mean disease duration in the female cohort was 5.8 years, while in men it was slightly shorter with a mean disease duration of 4.1 years. The most frequently reported allergen in females and males was wasp venom with 83.9 and 80%, respectively. No statistically significant difference in the severity of the anaphylactic reaction classified in Mueller grades I–IV between females and males was noted. In all, 74.2% of females were currently receiving a VIT with a mean VIT duration of 26.4 months, and 6.5% had completed the VIT. In 6.5% of women a VIT was intended, while no VIT was planned in 12.9%. At that time, nearly all men were under a VIT (92%) with a mean VIT duration of 28.8 months, while

none of the male patients had completed their treatment (0%). In 4% of men, a VIT was intended and in 4% not intended. All descriptive data of the study population are listed in Table 1.

Female HVA patients have a higher subjective anxiety level than male patients and are more inclined to carry the EMS “always” or “almost always” with them, but have lower self-assurance in using it. In our previous analysis of our study data, we did not find significant differences regarding anxiety and depression levels between female and male HVA patients in the HADS-A and HADS-D [8]. Interestingly enough, when asked to define their subjective anxiety level due to the venom allergy on a VAS (0 = not anxious at all, 10 = extremely anxious), female patients had a mean value of 7.2, while the mean score in men was 4.6. This difference was significantly different ( $p = 0.0003$ ) (Table 2). This higher anxiety score was associated with a better compliance in carrying the EMS with them; 87.1% of the female study patients declared to carry the EMS “always” or “almost always,” while only 56% of the male study patients did. Hence, 36% of men stated to carry the EMS “often,” “infrequently,” or “nev-

**Table 2.** Subjective anxiety level due to the venom allergy in adults with insect venom allergy

Group	Total, n (%)	Female	Male	p value
Subjective anxiety level due to the venom allergy (analog scale from 0 [not at all] to 10 [extremely anxious])	(n = 53)	(n = 28)	(n = 25)	
Mean ± SD	5.9±2.8	7.2±2.5	4.6±2.5	<b>0.0003<sup>a</sup></b>
Median (25th; 75th percentile)	6.0 (4.0; 8.0)	8.0 (5.0; 9.0)	4.0 (3.0; 6.5)	

Bold type denotes significance. SD, standard deviation. <sup>a</sup> Unpaired *t* test.

**Table 3.** Attitudes regarding the emergency medication

Group	Total	Female	Male	p value
Compliance with carrying the emergency medication, n (%)	(n = 56)	(n = 31)	(n = 25)	
Always	15 (26.8)	13 (41.9)	2 (8.0)	<b>0.0015<sup>a</sup></b>
Almost always	26 (46.4)	14 (45.2)	12 (48.0)	
Often	8 (14.3)	2 (6.5)	6 (24.0)	
Infrequently	3 (5.4)	0 (0)	3 (12.0)	
Never	0 (0)	0 (0)	0 (0)	
Just when I plan to do outdoor activities	4 (7.1)	2 (6.5)	2 (8.0)	
Willingness to carry the emergency medication always (scale from 0 to 10)	(n = 55)	(n = 30)	(n = 25)	
Mean ± SD	7.7±2.8	8.6±2.1	6.6±3.1	<b>0.0057<sup>b</sup></b>
Median (25th; 75th percentile)	8.0 (7.0; 10.0)	9.5 (8.0; 10.0)	8.0 (4.0; 9.0)	
Subjective self-assurance in using the emergency medication (scale from 0 to 10)	(n = 55)	(n = 30)	(n = 25)	
Mean ± SD	6.7±2.3	6.1±2.4	7.3±1.9	<b>0.0446<sup>c</sup></b>
Median (25th; 75th percentile)	7.0 (5.0; 8.0)	6.5 (5.0; 8.0)	8.0 (6.0; 9.0)	
Reasons for not always carrying the emergency medication, n (%)	(n = 56)	(n = 31)	(n = 25)	
Too big	10 (17.9)	6 (19.4)	4 (16.0)	0.5 <sup>d</sup>
Too heavy	6 (10.7)	4 (12.9)	2 (8.0)	0.4 <sup>d</sup>
Forgetfulness	20 (35.7)	8 (25.8)	12 (48.0)	0.07 <sup>d</sup>
Fear of overheating the medication	6 (10.9)	2 (6.5)	4 (16.0)	0.24 <sup>d</sup>
I do not need it	1 (1.8)	0 (0)	1 (4.0)	0.45 <sup>d</sup>
Storage in the car is sufficient	5 (8.9)	1 (3.2)	4 (16.0)	0.12 <sup>d</sup>
Other reasons <sup>e</sup>	10 (17.9)	5 (16.1)	5 (20.0)	0.49 <sup>d</sup>

Bold type denotes significance. <sup>a</sup>  $\chi^2$  test. <sup>b</sup> Mann-Whitney test. <sup>c</sup> Unpaired *t* test. <sup>d</sup> Fisher's exact test. <sup>e</sup> Stated other reasons: "unhandiness," *n* = 2; "no handbag to store it today," *n* = 2; "I do not need it for short trips," *n* = 2; and "only in summer," *n* = 4.

er," while only 6.5% of women chose those answers in the questionnaire ( $p = 0.0001$ ,  $\chi^2$  test,  $2 \times 5$  contingency table), and 8% of men and 6.5% of women declared to carry the EMS with them but only when they plan to do outdoor activities (Table 3).

When asked to rate their subjective self-assurance in using the EMS on a VAS (0 = very unsure how to use the EMS, 10 = very self-confident in using the EMS), the mean score in women was 6.1 and in men 7.3. This difference was statistically significant ( $p = 0.0446$ ) (Table 3). A semi-closed multiple-response question about reasons for not always carrying the EMS was offered to all pa-

tients. Here, no statistically different answers were given by women and men, with "forgetfulness" being the main reason (25.8% in women, 48% in men), followed by "too big" (19.4% in women, 16% in men) and "other reasons" (16.1% in women, 20% in men) (significance assessed with the Fisher exact test) (Table 3). "Other reasons" included "unhandiness," "no handbag to store it today," "I do not need it for short trips," and "only in the summer." Female HVA patients with an anaphylactic reaction Mueller grades I–II have a significantly higher anxiety degree associated with higher theoretical but not practical knowledge about anaphylactic reactions than men.

**Table 4.** Correlation of Mueller grade and gender, depression, anxiety, points scored in an OSCE, and knowledge regarding the emergency medication

Group	Total	Female	Male	<i>p</i> value
<b>Depression</b>				
Mueller grade I–II ( <i>n</i> = 31)	( <i>n</i> = 31)	( <i>n</i> = 17)	( <i>n</i> = 14)	
Mean ± SD	3.5±3.2	4.5±3.6	2.3±2.3	0.0590 <sup>a</sup>
Median (25th; 75th percentile)	3.0 (1.0; 5.0)	4.0 (1.5; 7.0)	1.5 (0; 5.0)	
Mueller grade III–IV	( <i>n</i> = 24)	( <i>n</i> = 13)	( <i>n</i> = 11)	
Mean ± SD	3.6±4.7	4.4±5.9	3.1±2.8	0.9764 <sup>b</sup>
Median (25th; 75th percentile)	2.0 (0; 5.8)	1.0 (0; 7.0)	3.0 (0; 6.0)	
<b>Anxiety</b>				
Mueller grade I–II	( <i>n</i> = 31)	( <i>n</i> = 17)	( <i>n</i> = 14)	
Mean ± SD	4.7±4.0	6.3±3.8	2.8±3.3	<b>0.0134<sup>b</sup></b>
Median (25th; 75th percentile)	4.0 (1.0; 7.0)	7.0 (3.0; 10.0)	2.0 (1.0; 4.0)	
Mueller grade III–IV	( <i>n</i> = 24)	( <i>n</i> = 13)	( <i>n</i> = 11)	
Mean ± SD	5.8±5.0	6.6±6.3	4.7±2.9	0.3714 <sup>a</sup>
Median (25th; 75th percentile)	4.0 (1.0; 9.8)	4.0 (1.0; 12.0)	4.0 (2.0; 7.0)	
<b>OSCE</b>				
Mueller grade I–II	( <i>n</i> = 32)	( <i>n</i> = 18)	( <i>n</i> = 14)	
Mean ± SD	7.7±3.1	7.5±3.5	7.9±2.6	0.7042 <sup>a</sup>
Median (25th; 75th percentile)	8.0 (5.0; 10.0)	8.5 (4.0; 10.0)	8.0; (5.8; 10.0)	
Mueller grade III–IV	( <i>n</i> = 24)	( <i>n</i> = 13)	( <i>n</i> = 11)	
Mean ± SD	8.3±2.6	8.8±2.5	7.7±2.8	0.3476 <sup>a</sup>
Median (25th; 75th percentile)	8.5 (7.0; 10.0)	7.0 (7.0; 10.5)	9.0 (5.0; 10.0)	
<b>Knowledge</b>				
Mueller grade I–II	( <i>n</i> = 31)	( <i>n</i> = 17)	( <i>n</i> = 14)	
Mean ± SD	7.4±1.7	8.7±1.4	6.4±1.6	<b>0.0023<sup>a</sup></b>
Median (25th; 75th percentile)	8.0 (6.0; 9.0)	8.0 (7.5; 9.0)	6.5 (4.8; 8.0)	
Mueller grade III–IV	( <i>n</i> = 24)	( <i>n</i> = 13)	( <i>n</i> = 11)	
Mean ± SD	7.4±2.1	7.3±2.1	7.5±2.3	0.8715 <sup>a</sup>
Median (25th; 75th percentile)	8.0 (5.0; 9.0)	8.0 (5.0; 9.0)	8.0 (5.0; 10.0)	

Bold type denotes significance. SD, standard deviation; OSCE, objective structured clinical examination. <sup>a</sup> Unpaired *t* test. <sup>b</sup> Mann-Whitney test.

Next, the severity grade of the anaphylactic reaction was correlated with the HADS-D/-A and the practical as well as theoretical knowledge regarding the anaphylactic reaction of female and male patients (Table 4). There was a tendency toward a higher depression score ( $p = 0.059$ ) and a highly significant difference in the anxiety level ( $p = 0.0134$ ) assessed by the HADS-D and HADS-A in female compared to male patients with a Mueller grade I–II anaphylactic reaction. No significant difference between women and men with a Mueller grade III–IV anaphylactic reaction was noticed. Also, no significant difference in the OSCE performance was noted between women and men with Mueller grade I–II ( $p = 0.7$ ) and grade III–IV ( $p = 0.37$ ) anaphylactic reactions. There was, however, a statistically significant higher factual knowledge in women than men with a history of an anaphylactic reaction Mueller grade I–II to an insect venom allergen con-

cerning the administration of the EMS and conduct in the event of an anaphylactic reaction (8.7 in women, 6.4 in men;  $p = 0.0023$ ), which again could not be demonstrated in patients with an anaphylactic reaction Mueller grade III–IV ( $p = 0.8715$ ) (Table 4).

## Discussion

Our results show that females with a Mueller grade I–II anaphylactic reaction have a higher disease-associated anxiety level than men. The female patients' higher level of anxiety is associated with a higher theoretical but not practical knowledge about the disease. Male patients on the other hand seem to be less compliant in carrying the emergency medication but revealed a higher self-assurance in handling it.



Female HVA patients showed a higher subjective anxiety level on a VAS and a highly significant difference in the anxiety level assessed by the HADS-A after a Mueller grade I–II anaphylactic reaction. These results indicate that female HVA patients have a significantly impaired psychological well-being when compared to their male counterparts, especially those with a previous anaphylactic reaction of Mueller grades I and II. This finding is consistent with previous studies of other dermatological diseases such as psoriasis. Compared to males, female patients reported greater decrease in HRQL despite having a similar self-reported severity of the disease [15]. Although not yet fully understood, sex differences regarding mood disorders might be related not only to hormonal differences but also to diversities in the immune system [16]. Women show higher numbers of innate and adaptive immune cells and have a higher incidence of disorders associated with an increased immune response such as autoimmune diseases and allergies [17, 18]. They show a distinct reaction to acute stress with higher secretion of pro-inflammatory mediators and decreased glucocorticoid sensitivity [19]. Evidence exists that women respond to systemic inflammation with greater behavioral changes, such as an impaired mood and affective behavior. Patients who have experienced anaphylactic reactions following yellow jacket stings have a reduced HRQL, mostly due to emotional distress [20]. It is conceivable that this chronic emotional distress might lead to a higher anxiety level in our female patient cohort via induction of a low-grade, generalized inflammatory state in the body and brain [19]. More scientific evidence for such a hypothesis is needed.

Against expectations and the results of Cichočka-Jaroszyk et al. [5], who were able to show a significant association between Mueller grade of anaphylactic reaction and anxiety [6], the Mueller grade of the last anaphylactic reaction did not seem to influence the degree of depression or anxiety in our female study subgroup. The males' grade of anaphylactic reaction correlated at least partly with the depression and anxiety level, which explains why we identified significantly higher anxiety levels in females with an anaphylactic reaction Mueller grade I–II than in males, but not in females with an anaphylactic reaction Mueller grade III–IV than their respective subgroup. The reason for such a discrepancy in data can only be suspected. When HVA patients present at our Department of Dermatology, Venerology and Allergology, we always provide information about the possibility of a more serious anaphylactic reaction after a second yellow jacket sting. This information might lead to correspond-

ing anxiety levels in female HVA patients independent of their previous degree of anaphylactic reaction, while men with a history of mild anaphylactic reaction to HVA might remain unimpressed by this fact. In line with this hypothesis is also our finding that women have significantly better theoretical knowledge about the disease than men after a Mueller grade I–II anaphylactic reaction.

Higher anxiety scores thus correlate with higher theoretical knowledge, but we could not find an association with practical knowledge. OSCEs have been described to be a feasible, valid, and reliable tool to examine clinical skills in undergraduate and postgraduate medical students [21–23] and have been used for more than 40 years, first introduced by Harden et al. [21]. Overall, patients with Mueller grade I–II anaphylactic reactions performed worse than those with Mueller grade III–IV, and in general, their practical and theoretical knowledge could only be classified as being moderate, with an average of 61 and 62% right actions/answers, respectively. Cohen et al. [7] found inadequate education of patients and providers and uncertainty of when or how to administer the EpiPen to be some of the most common pitfalls in administration of epinephrine [3, 4, 24]. We also observed this insecurity or lack of knowledge in our cohort.

Next, we asked patients about their willingness to always carry and their compliance with carrying the EMS. As shown in prior studies [3, 25, 26], overall compliance to always carry the EMS was low: 41.9% of female HVA patients stated they would carry the EMS always compared to only 8% of the male patients. A very recent study by Warren et al. [26] from the USA also asked patients at risk for anaphylaxis about their compliance in carrying the EMS with them; 42% of the patients stated they would carry the EpiPen with them at all times and 49% keep their EpiPen close (reachable within 5 min). In our cohort, 27% of the patients stated they would carry the EpiPen with them at all times, and 46% almost always. Sanchez [25] noted that recurrent instructions have a positive impact on patients' compliance with the medication, and it seems reasonable to give instruction repeatedly on how and when to use epinephrine, H1-antagonists, and steroids and thus constantly reinforce patients' self-confidence in using the medication correctly.

Naturally, our study has limitations. Due to our small study group size, generalizability is limited, and we may have failed to show any differences between subgroups. Almost all of our included patients received a VIT, which

might have made the group more consistent. We had a monocentric setting and mainly asked patients to fill out the questionnaires during fall and winter (July–January). One might hypothesize that insect season influences answers including, but not limited to, anxiety and compliance in carrying the EMS.

Concluding, we can say that there are sex differences regarding psychological burden and handling of the EMS in HVA patients. Female patients should be monitored more closely for allergy-related psychological problems as they have a higher degree of HVA-associated anxiety, while men need more encouragement and reminders to carry the EMS more consistently. Altogether, we also found that there is a need to raise more awareness and that regular education and training for both female and male patients, for instance during waiting periods after VIT administration, is needed.

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## Statement of Ethics

The study was approved by the Ethics Committees of the Medical Faculty Mannheim, Heidelberg University (2016580N-MA), and performed according to the principles of the Declaration of Helsinki.

## Disclosure Statement

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