

# Current practices in diagnosis of Hymenoptera venom allergy in Poland

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Adv Dermatol Allergol 2021; XXXVIII (2): 222–229

DOI: <https://doi.org/10.5114/ada.2021.106200>

## Abstract

**Introduction:** Hymenoptera venom allergy (HVA) is associated with a high risk of anaphylaxis. Effective treatment of HVA patients requires allergologists' familiarity with the latest HVA recommendations.

**Aim:** Evaluation of current practices in HVA diagnosis in Poland.

**Material and methods:** A survey questionnaire was conducted in 32 HVA centres in Poland.

**Results:** The response rate was 97%. There were 1829 patients evaluated due to HVA in 2015. Sixty six percent ( $n = 21$ ) of the centres used skin prick tests, out of which 90% ( $n = 19$ ) used 100 µg/ml of the venom extract as the highest concentration. All the centres performed intradermal tests (IDT) and serum specific IgE (sIgE), an initial diagnostic tool in 91% ( $n = 29$ ). The highest venom concentration in IDT was 1 µg/ml in 75% ( $n = 24$ ), 0.1 µg/ml in 16% ( $n = 5$ ), 0.01 µg/ml in 3% ( $n = 1$ ) and 10 µg/ml in 6% ( $n = 2$ ). Baseline serum tryptase was assessed in 84% of the centres ( $n = 27$ ), out of which 53% ( $n = 17$ ) tested all their patients, whereas 31% ( $n = 10$ ) checked only those with life-threatening reactions. In case of negative IDT/sIgE, 59% of the centres ( $n = 19$ ) performed components evaluation, while 19% ( $n = 6$ ) did the basophil activation test. In case of no identification of the culprit insect and sensitization to both venoms, VIT employed venom with higher sIgE.

**Conclusions:** Most allergology centres in Poland follow HVA guidelines. We identified two inaccuracies in their HVA management including non-adequate venom concentration in IDT and a false belief in correspondence between sIgE concentration and severity of allergic reactions.

**Key words:** guidelines, adherence, venom allergy, diagnostics.

## Introduction

Almost everybody is at least once in his/her life stung by a Hymenoptera insect [1, 2]. The majority of individuals develop a local reaction, which resolves by itself within several hours. Some experience extensive and long-lasting local reaction due to the late phase of IgE-dependent allergic reaction, while 0.3–7.5% of adults and about 3.4% of children develop an immunoglobulin E (IgE)-dependent systemic reaction [1, 3–5]. HVA systemic

symptoms may vary in their intensity ranging from mild symptoms such as urticaria and angioedema, through moderate ones like dizziness, dyspnoea and nausea, to life-threatening reactions such as anaphylactic shock, loss of consciousness, and/or cardiac or respiratory arrest. The latter develop in 1–3% of the adult population, and they are ten times less common in children [4]. Current American and European epidemiological data based on registration of anaphylaxis events indicate that HVA is

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**Received:** 11.07.2019, **accepted:** 12.08.2019.

one of the most common causes of anaphylaxis in adults and children [6–10].

The latest 2018 guidelines on Hymenoptera venom allergy formulated by the experts from 16 European countries [11] recommend diagnosis of HVA only in patients evaluated to potentially receive venom immunotherapy due to a moderate to severe systemic reaction to insect sting. Venom immunotherapy (VIT) is a safe and highly effective treatment, recommended in these patients, and it might also be considered in patients with a systemic skin reaction that seriously impairs their quality of life. It is important to confirm IgE sensitization to venom extract or venom components. However it is the reaction following insect sting that is crucial as the prevalence of sensitization to Hymenoptera venoms is high, up to 40% adults in Polish general population [12].

It is recommended that every patient who experienced sting-induced HVA systemic reaction is instructed how to avoid stings and to use prescribed rescue medications, including adrenaline autoinjector (AAI) when indicated [13]. Such patients require allergological diagnostic evaluation to qualify for VIT.

The latest EAACI position paper on the diagnostic recommendations was published 14 years ago [14]. The new EAACI position paper on diagnosis of HVA is under preparation. However, there is a recent algorithm/document summarizing current recommendations on the diagnosis of Hymenoptera venom allergy [15].

The HVA allergological assessment including skin testing and analysis of sIgE specific to selected venom preparations constitute the core of the diagnostic procedure [14, 16, 17].

The last EAACI recommendations propose a stepwise HVA evaluation starting from skin prick testing (100 µg/ml or 300 µg/ml of venom extract concentration), if negative then followed by intradermal testing (IDT) with up to 1 µg/ml of venom concentration, and/or analysis of serum venom-specific IgE (sIgE) by the most sensitive available method [14, 16, 17]. Currently these three methods are regarded equivocal, while their combination increases sensitivity [15].

In selected and ambiguous cases, diagnostic management of HVA employs sIgE specific for particular allergic components of insect venom (component-resolved diagnosis – CRD), and basophile activation test (BAT) [18–20]. Both methods are still of limited use [21].

Another important test is concentration of serum baseline tryptase (BT), a specific marker of the mast cells which reflects their number and resting state activity. An elevated BT value requires broadening of the evaluation scope to include mast cell activation disorders (MCAD); in case of such diagnosis confirmation, then VIT application is modified accordingly in such patients [22, 23].

Two elements critical in proper care of the patients with systemic reaction to insect sting include easy access to specialist treatment as well as state-of-the-art

management. A guarantee of treatment accessibility is based on the sufficient number and uniform distribution of the centres that specialize in diagnostic and therapeutic management of HVA [24]. A guarantee of state-of-the-art management depends on up-to-date recommendations based on the current knowledge, but reality of the “actual life” is often different. Evaluation of the existing disparity between everyday practice and recommendations is important for improving the quality of medical services.

## Aim

The principal objective of the present study was an assessment of patients’ accessibility to diagnostic and therapeutic management of HVA, evaluation of the patient care and implementation of worldwide recommendations in everyday practice of Polish allergy specialists.

## Material and methods

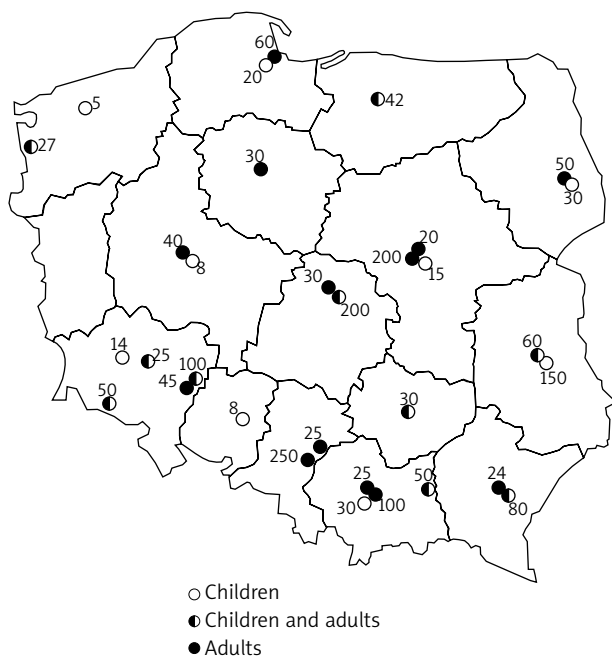
The study included 33 Polish allergology centres specializing in diagnostic and therapeutic management of HVA. The survey was carried out employing a questionnaire developed by the author (Appendix 1 – English version), based on the original British questionnaire which had been used in evaluating the practice of diagnostic and therapeutic management of HVA in the United Kingdom [25] and employed with the same purpose in Poland in 2009 [26]. The present study’s questionnaire was modified by adding new questions and reformulating several of the original questions.

The survey presented in this paper was conducted employing the computer assisted web interview (CAWI) method, using the Lime Survey software installed on the www server of the Jagiellonian University Medical College. An email with an invitation to the study, containing a personalized link to the questionnaire, was sent to the head of each study centre. In case of lack of an answer, two email reminders were sent 2 and 3 weeks later, then a phone reminder was employed in case of further lack of response. Finally, 32 answers (97% of all the diagnostic centres for HVA in Poland; one centre did not respond to the survey) were collected. The presented results and conclusions were not supported by any statistical tests because the paper presented real data.

## Results

### Availability (of diagnostics and treatment)

The distribution of the centres providing diagnostic management of HVA in Poland was not uniform; on the average there were two such centres in each province (voivodship), but the number of centres in particular provinces ranged from 0 to 5. There were over 38 million inhabitants in Poland, thus there were 1 201 thousand inhabitants from



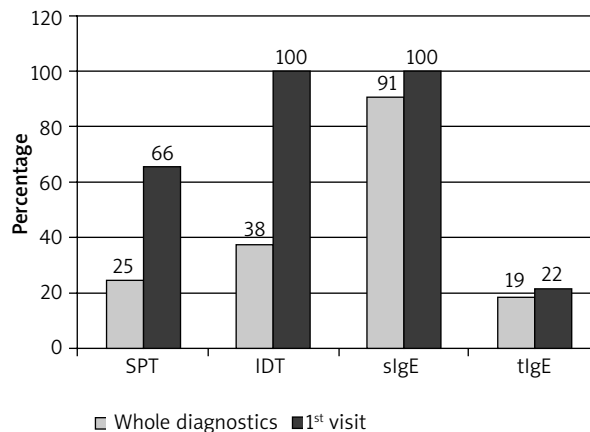
**Figure 1.** Location of HVA diagnostics centres and number of patients diagnosed in each centre in 2015

all age groups per centre, while in particular provinces, the number oscillated between 580 thousand and 2 285 thousand [27]. There were two provinces where one provided diagnostic management only for adult patients, and the other was available for children only (Figure 1). Given the estimated incidence of allergy to insect venom, 9% in adults and 3% in children (who account for 15% of the population), the likely number of individuals with HVA in both age groups was 2 837 884 and 173 547, respectively, taking into consideration children above 2 years of age [27].

In 2015, the total number of patients diagnosed with HVA in Poland was 1843; adults outnumbered children about three to one (Figure 1). The majority of Polish centres provided diagnostic and therapeutic management of HVA for adults only (41%,  $n = 13$ ), whereas there was a similar number of centres that either assisted children only (28%,  $n = 9$ ) or both adult and paediatric groups (31%,  $n = 10$ ), in which the same approach was declared regardless the age. The majority of HVA diagnostics in Poland was done as in-patient procedures (56%,  $n = 18$ ), the other cases were done either partially in in-patient and out-patient settings (22%,  $n = 7$ ), or solely in out-patient setting (22%,  $n = 7$ ).

### Skin testing

More than a half of the centres used skin prick testing (66% ( $n = 21$ ), out of which 90% ( $n = 19$ ) used the highest venom concentration of 100  $\mu\text{g/ml}$ , while the remaining 10% used 300  $\mu\text{g/ml}$  ( $n = 2$ ). All the centres performed intradermal tests (IDT) in a step-wise regimen with the highest



**Figure 2.** Tests used as a first-line procedure and during the whole diagnostic procedure (% of total)

concentration applied of 1  $\mu\text{g/ml}$  (75%,  $n = 24$ ), whereas the others used 0.1  $\mu\text{g/ml}$  (16%,  $n = 5$ ), 0.01  $\mu\text{g/ml}$  (3% of the centres,  $n = 1$ ) or even 10  $\mu\text{g/ml}$  (6%,  $n = 2$ ), respectively. The allergen extracts employed for diagnostic purposes were provided by two manufacturers, each of them supplying their products to about 60%-70% of the centres.

### Serum specific IgE

All the centres quantified serum specific IgE antibodies, the majority of them using the product of the same manufacturer (ImmunoCAP) (84%,  $n = 27$ ), whereas the rest used (in equal proportions) other methods provided by four different manufacturers (Immulite, Elisa Nexter Omega, Euroline Autoimmune, Polychex). Usually, the detection limit for a given sIgE analysis is 0.35 kU/l (66%,  $n = 21$ ). A significantly smaller number of the centres used methods characterized by lower detection limit equal 0.01 kU/l (31%,  $n = 10$ ) and rarely 0.1 kU/l (3%,  $n = 1$ ). Only 22% ( $n = 7$ ) of the centres evaluated total IgE levels.

### Diagnostics complexity

At the first visit, almost all the centres evaluated serum sIgE, whereas about one third of the centres performed *in vivo* skin tests (Figure 2). In 6% ( $n = 2$ ) of the centres, the first visit was devoted only to taking the patient's history. Forty seven percent ( $n = 15$ ) of the centres performed only one diagnostic test during the first visit, either sIgE (44%,  $n = 14$ ) or SPT (3%,  $n = 1$ ), 34% ( $n = 11$ ) of the centres performed two diagnostic tests during the first visit, either sIgE and IDT (25%,  $n = 8$ ) or sIgE together with SPT (9%,  $n = 3$ ), while 13% ( $n = 4$ ) of the centres performed all the three diagnostic tests during the first visit.

### Additional tests

When standard diagnostic tests did not identify a culprit insect; then either CRD was carried out or VIT with

venom of higher values of specific IgE was initialized (Table 1). In case of strong clinical recommendations for VIT due to sting-induced severe reaction and negative results of standard diagnostic tests, similar procedures were used regardless of the baseline serum tryptase (bsT) level. The most common approach was to repeat the standard evaluation after a few months (almost two thirds of the centres), supply the patient with AAI, and perform CRD (almost one-half of the centres) (Table 1). Basophil activation test was the third up to the fifth diagnostic strategy in problematic situations of HVA (Table 1). The majority of the centres (84%,  $n = 27$ ) evaluated baseline serum tryptase, out of which 53% ( $n = 17$ ) tested all the patients regardless of the severity of systemic reaction, whereas almost one third (31%,  $n = 10$ ) performed the above analysis only in those with life-threatening reactions.

#### Tests performed before VIT introduction

Sixty nine percent of the centres ( $n = 22$ ) performed the following primary diagnostic procedures to determine general health status prior to the VIT initiation. The typical tests included standard diagnostic blood and urine tests (31%,  $n = 10$ ), screening test for thyroid diseases (19%,  $n = 6$ ), ECG, chest X-ray and spirometry (22%,  $n = 7$ , respectively), or SPT with inhalant allergens (13%,  $n = 4$ ).

#### Discussion

The first standardized assessment of the practices in diagnostic and therapeutic management of HVA, and

their adherence to the international guidelines was conducted in the United Kingdom in 2006/2007 [25]. The results of audit provided the basis for the first BSACI (British Society of Allergy and Clinical Immunology) guidelines on HVA. British authors repeated the study in 2016 using the same version of the questionnaire with two additional questions concerning CRD and safety [28]. Polish authors obtained the British author's and publisher's consent, translated the questionnaire and used it to evaluate the practices in Polish allergological centres for the first time in 2009 [26], then in 2015, and the collected data on VIT practices were already published [24]. The present report demonstrates the results of the most extensive questionnaire survey aiming at analysis of the accessibility of diagnostic procedures for individuals suspected of HVA and evaluation of Polish allergologists in the diagnostic management of HVA. Table 2 compares the data of British and Polish original studies and their follow-ups (Table 2).

The analysis of the questionnaire responses demonstrates that patient accessibility to the centres specializing in HVA treatment is good and it improved as compared to the time 6 years earlier. The number of the centres offering diagnostic management to patients suspected of HVA increased by 27%, and presently there is at least one such centre in every province except one. The ongoing process of decentralization of medical care provided to HVA patients is important both in diagnostic and therapeutic management. Venom immunotherapy

**Table 1.** Diagnostic strategies in ambiguous diagnosis of HVA

<b>Lack of possibility to identify the culprit insect and positive results of serum IgE specific to both venoms</b>	<b>%</b>
Component-resolved diagnosis	59
Treatment using venom with sIgE higher results	44
Basophil activation test	19
Treatment with both venoms	9
Discharge the patient with epinephrine (AIA)	3
<b>Moderate to severe systemic reaction and negative results of standard diagnostic tests</b>	<b>%</b>
Repeat standard diagnostic procedures after a few months	63
Discharge the patient with epinephrine	59
Component-resolved diagnosis	47
Discharge the patient with recommendation to be in touch after subsequent sting	28
Basophil activation test	22
<b>Systemic reaction, negative results of standard diagnostic tests and elevated bsT concentration</b>	<b>%</b>
Repeat standard diagnostic procedures after a few months	63
Discharge the patient with epinephrine	63
Component-resolved diagnosis (CRD)	47
Basophil activation test (BAT)	22
Diagnostics of mastocytosis	22
Discharge the patient with advice concerning prophylactics	19

**Table 2.** Comparison of Polish and British studies' results on availability and practice of diagnostic procedures in patients with HVA

Variable	Poland		UK	
	2009	2015	2007	2016
Availability of HVA centres % (n):				
Adults	69 (18)	41 (13)	–	58 (37)
Children	31 (8)	28 (9)	–	19 (12)
Adults and children	0	31 (10)	–	23 (15)
Allergy specialist	100 (26)	100 (32)	100 (53)	44 (64)
Procedure				
Skin testing				
SPT frequency	100 (26)	66 (21)	87 (46)	66 (42)
SPT venom conc.:				
100 µg/ml	84 (22)	90 (19)	43 (23)	36 (23)
300 µg/ml	0	10 (2)	55 (29)	62 (40)
IDT frequency	88 (23)	100 (32)	80 (42)	80 (51)
IDT venom conc. 1 µg/ml	69 (18)	75 (24)	45 (24)	81 (52)
slgE	100 (26)	100 (32)	55 (29) (first line)	
Baseline serum tryptase	39 (10)	84 (27)	53 (28)	88 (56)

HVA – Hymenoptera venom allergy, SPT – skin prick test, IDT – intradermal test, slgE – specific IgE.

requires systematic treatment and physician visits every 4 to 8 weeks for 3 to 5 years. It was shown that shortening the distance to the closest specialist centre definitely improved compliance with the treatment [29].

Particular improvement is noted in children's accessibility to HVA treatment, at present, more than one-half of the centres provides care to either solely children or adult and paediatric population together [26]. A similar distribution of the HVA care centres is currently observed in the UK [28], which may reflect a general tendency to discontinue a rigid division into age categories especially in face of a relatively low incidence of severe allergic symptoms that require diagnostic management in children.

In Poland, diagnostic evaluation of HVA is carried out exclusively by allergy specialists, mainly as an in-patient procedure. By comparison, in the United Kingdom, HVA diagnostics are conducted by allergology specialists in less than half cases [28]. Transferring the competencies in management of British patients with HVA to GP physicians may be explained by differences in the health system organization. In Poland, such a shift in management would require an extensive educational process to be carried out among GPs according to the results of the questionnaire that evaluated knowledge on HVA-related issues among Polish physicians [30].

The results of our study demonstrate that the majority of Polish allergologists follow the international guidelines principles in the diagnostic approach to HVA. The "real-life" study of the management of HVA patients shows two tendencies: first that there are deviations from the suggested diagnostic procedures and second

that the diagnostic algorithm is modified, both of which, in our opinion, result from ambiguity or lack of detailed recommendations.

An example of the vague recommendations can be found in the skin test procedures. The recommendations dictate the IDT test to be preceded by the SPT test, but they do not ultimately define the maximum venom concentration in SPT, suggesting two acceptable concentration values of 100 µg/ml and 300 µg/ml. Only approximately two thirds of Polish and British physicians perform the SPT as their first-line diagnostic test [28]. As compared to the previous studies, it appears that there is a decrease in the frequency of performing the test by one third in Poland and by one fourth in the UK [25, 26]. The reason for such an approach in both countries might be their belief in the low diagnostic value of SPT. Neither current European, or the newest American recommendations address the above issue [14, 16, 17]. The new EAACI algorithm of diagnostic management of HVA makes SPT, IDT and slgE equivocal [15].

A great majority of the Polish allergologists use 100 µg/ml as the highest venom concentration employed in SPT. In the UK, the number of practitioners using the concentration of 100 µg/ml decreased, while those who used venom extract concentration equal to 300 µg/ml increased [25, 28]. There are no data comparing diagnostic properties of SPTs performed with these two concentrations of venom extract.

Nowadays, the Polish allergologists more frequently perform the IDT test in contrast to the previous questionnaire in which IDT was described as "confirmatory only"

after the use of SPT or serum sIgE [26]. In the UK, the number of centres using IDT as a confirmatory test remains on the same level [25, 28]. Moreover, there is an increased use of IDT with the highest venom concentration equal to 1 µg/ml in line with recommendations both in Poland and in the UK [25, 28]. The more frequent application of the IDT test appears to result from the physicians' trust in safety of the procedure, confirmed by the report of the Mayo Clinic as well as the previous publications of the present authors [31, 32]. In the cited American study, the prevalence of complications occurring during the SPT- and IDT-type tests was 0.03% and 0.06%, respectively, and none of the complications was severe [31, 32]; similarly, no complications were noted during SPT and IDT in the Polish study [33]. There were two substantial irregularities in performing IDT demonstrated by 25% of Polish physicians. Those errors resulted from use of either too high (10 µg/ml) or too low venom concentrations. We believe that the former error may lead to a potential overestimation of HVA diagnoses due to falsely positive test results caused by the toxic effect of the venom, while the latter may result in HVA diagnosis underestimation since the extract concentration < 1 µg/ml.

Another problem with the IDT test identified in our survey is difficulty with interpretation of the skin tests when both wasp and bee venom tests are positive and no culprit insect can be determined. It was previously shown that belief that the size of the skin test reaction correlated with its severity was not justified [34]. A consequence of such a false belief might be use of the venom that evoked more extensive reaction in IDT or showed a higher serum sIgE level. Such a strategy does not reflect the recommendations [14, 16, 17]. It is worrisome that the number of centres which implement such unjustified approach increased since the previous study (44% vs. 27%), whereas the number of the centres undertaking treatment with both venoms decreased (9% vs. 27%) [26]. This might be due to economic reasons as treatment with both venoms doubles the costs [35]. In fact, there are also some data confirming that single venom-based immunotherapy continuing for over 3 to 5 years provides effective and long-lasting protection in the vast majority of both mono-sensitized and double-sensitized Hymenoptera venom allergic patients [36]. Hence, double venom immunotherapy is indicated in clinically double allergic patients reporting systemic reactions to stings of both Hymenoptera species and in those with equal reactivity to both venoms in diagnostic tests without reliable identification of the culprit stinging insect [14, 16]. It is worth noting that in the same clinical situation more than half of the centres recommend the latest clinical tests, such as component-resolved diagnostics (CRD) and basophile activation testing (Table 2). The British allergologists more frequently than their Polish counterparts employ the above molecular diagnostics (87%), which not necessarily indicates a better knowledge of these

methods but rather their better availability in the United Kingdom (Table 2). On the other hand, almost the same percentage of centres (3% vs. 4% previously) prescribed epinephrine and did not start treatment [25].

All the centres in Poland evaluate serum specific IgE (according to the results of both audits). It is not possible to compare sensitivity of the methods due to different assays used [26]. The threshold of 0.35 kU/l remains the cut-off point for the positive results despite increased sensitivity of the newest methods. The same threshold sIgE value of 0.1–0.35 kU/l remains true even in case of low total IgE [15]. In contrast to the Polish diagnostic approach, only 55% of practitioners in the UK use solely sIgE as the initial test in investigation prior to VIT, whereas the others used only SPT [25]. We should remember that *in vivo* tests present higher specificity compared to an *in vitro* test in HVA evaluation. The new European Medical Agency regulations recognize the extracts for skin testing as drugs, what may limit their accessibility and may shift the diagnostic balance towards increased use of *in vitro* tests [37]. In comparison to our previous study, the extract manufacturers either retained its position on the market (69% vs. 77% previously), increased its market share (from 38% to 62%) or withdrew from the Polish market due to loss of registration [26]. In the UK in 2008, the extracts of one European manufacturer (available also in Poland) were used almost exclusively (95%) [25], while trademarks of venom extracts were not evaluated in the latest British study [28].

The number of centres performing BST test increased more than two-fold in comparison to 2009 [26]. However, the percentage of those that evaluated tryptase only in patients with life-threatening reactions remained constant [26]. In the UK, previously 53% of practitioners evaluated BST in the patients with the life-threatening symptoms and 80% of them did it in all the patients, compared to current 88% of physicians who analysed BST in all the patients with a history of systemic reactions. The practice of evaluating BST in patients with severe systemic HVA reactions is dictated by more common occurrence of mast cell activation disorders in HVA patients as it was recently reported [38, 39].

## Conclusions

The results of the survey indicate that the organization of care of HVA patients is improving due to better accessibility of specialist care and high competences of physicians providing such care. The noted irregularities are common in the situations where unambiguous guidelines of diagnostic management are lacking or no current recommendations are available. The update of US guidelines has been just published, while the European guidelines on diagnostic management in HVA are still evaluated and most likely will refer to problems of irregularities demonstrated in the present survey. Since

the phenomenon appears universal, and most probably is also encountered in other European and non-European countries, we recommend performing a similar questionnaire-based survey in other countries, where HVA poses a significant clinical problem.

## Acknowledgments

We would like to express our gratitude to all members of the Immunotherapy Section of Polish Society of Allergology Working Group that carried out the questionnaire: Zbigniew Bajor, Zbigniew Bartuzi, Anna Bodzenta-Łukaszyk, Elżbieta Borucka, Piotr Z. Brewczyński, Anna Bręborowicz, Andrzej Dąbrowski, Radostaw Gawlik, Grzegorz Gąszczyk, Marek Jutel, Marek Kowalski, Jerzy Kruszewski, Piotr Kuna, Michał Kurek, Artur Kwaśniewski, Joanna Lange, Teresa Małaczyńska, Elżbieta Matusz, Marek Niedoszytko, Katarzyna Olejniczak, Marek Józef Paśnicki, Jolanta Pietraszek-Mamcarz, Grażyna Pulka, Marta Rachel, Barbara Rogala, Magdalena Rzeszutko-Grabowska, Marcin Stobiecki, Ewa Świebocka, Ewa Trębas-Pietraś, Magdalena Zakrzewska, Aleksander Zakrzewski, Janusz Zaryczański, Małgorzata Żurowska-Gębała  
English proofreader – Anna Knapp MD, PhD.

## Conflict of interest

The authors declare no conflict of interest.

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