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Honeybee and wasp venom allergy: Sensitization and immunotherapy

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In Europe, 0.3 % to 7.5 % of adults and up to 3.4 % of children experience systemic sting reactions.

Based on current European guidelines, VIT is indicated even for grade I anaphylactic reactions (Ring and Meßmer classification) if patients experience impairment in quality of life and if there is evidence of IgE-specific sensitization.

The classification by Ring and Meßmer has proven useful for classifying the severity of anaphylaxis.

It allows for the distinction between mild, moderate, and severe reactions.

If the classic sequence of anaphylactic symptoms is missing, other diseases that may mimic anaphylactic reactions – such as carcinoid syndrome, pheochromocytoma, and others – must be included in the differential diagnosis.

A stinger remaining in the skin is no reliable criterion for distinguishing between honeybee stings and wasp stings.

The order of Hymenoptera includes the families of bees (Apidae), wasps (Vespidae), and ants (Formicidae). The bumblebee (*Bombus*) and honeybee (*Apis*) genera are part of the Apidae family. The genera of hornets (*Vespa*), yellowjackets *(Vespula* and *Dolichovespula)*, and paper wasps *(Polistes)* belong to the Vespidae family.

Simultaneous intradermal testing with said concentrations (serial dilution, 0.2 mL each) is safe and effective.

The optimal time window for skin testing is one to six weeks after the sting. A long interval between sting and skin testing may be associated with negative test results.

Cross-reactive carbohydrate determinants in HV can be measured by ImmunoCAP assays directed against horseradish peroxidase (HRP) or pineapple stem bromelain (MUXF3). However, their detection does not rule out genuine sensitization.

Wasp venom extract spiked with Ves v5 has increased the diagnostic sensitivity from 83 % to 97 %.

Cross-reactivity between *Vespula* spp. and *Polistes* spp. is usually caused by homologous proteins, such as hyaluronidases (Ves v2-homologous *Polistes* protein) and dipeptidyl peptidases IV (Ves v3-Pol d3). Measurement of antibodies against phospholipase A1 (Ves v1-Pol d1) and antigen V (Ves v5- Pol d5 is used to identify the respective sensitization.

An established method, the basophil activation test (BAT) should not be used in the routine diagnostic workup of HVA. It is particularly useful, if there is a positive history of HVA but no evidence of IgE-mediated sensitization (using laboratory tests and the above-mentioned skin tests).

Based on the prevalence of hypersensitivity to the various Hymenoptera venoms in different countries, therapeutic venom preparations for honeybees, *Vespula* spp., and *Polistes* spp. are available throughout Europe, as well as for ant (Formicidae) species in certain regions worldwide.

The reported efficacy of VIT is up to 84 % for honeybee venom, up to 96 % for wasp venom, and up to 98 % for ant venom.

The Paul Ehrlich Institute expresses no concerns about the risk of accumulation of aluminum-containing depot preparations in case of a three-year treatment regimen.

Api m10 is underrepresented in the therapeutic HBV extracts currently available. This may explain the lower efficacy of honeybee venom immunotherapy.

If VIT is not tolerated, tolerability may be achieved with omalizumab.

VIT is indicated for grade II anaphylactic sting reactions (Ring and Meßmer classification) and evidence of IgE-mediated sensitization. A grade I anaphylactic sting reaction in combination with an increased risk of re-exposure and impairment in QoL is also an indication for VIT.

The new EAACI guidelines do not consider the use of beta blockers and ACE inhibitors a contraindication.

MAO inhibitors may cause a hypertensive crisis and pronounced tachycardia in combination with epinephrine administered in an emergency.

Based on EAACI recommendations, VIT may be initiated in children younger than five years of age if there was a grade II anaphylactic sting reaction.

To date, no in-vitro markers for the effectiveness of VIT have been established. Although not standardized, sting challenge testing (while on VIT) with a live insect is still the preferred method.

Patients who did not tolerate the sting challenge during VIT should receive continued treatment using twice the maintenance dose. Treatment duration will be 3–5 years, starting from the time of dose increase.

Diagnostic sting challenge testing is not recommended in Germany as it is associated with a high risk and considered to be unreliable.

In Germany, epinephrine autoinjectors are available from three different manufacturers. They are designed for single use and differ significantly in terms of needle length. The price ranges from € 81.99 to € 118.45.

Summary

Hymenoptera venom allergy is the most common cause of anaphylactic reactions in adults. In children, it is the second most common cause after food-related anaphylaxis. Such reactions are primarily due to stings by honeybees (*Apis*) and certain social wasps (*Vespula vulgaris* and *Vespula germanica* in particular). Especially in adults, stings are frequently associated with severe anaphylaxis. Established diagnostic methods including molecular tests allow for greater success rates in terms of determining the insect actually responsible for triggering the anaphylactic reaction. Sensitization to both venoms, or a history of systemic sting reaction without any evidence of sensitization, complicate the decision regarding treatment. Venom immunotherapy (VIT) is a safe and effective causal treatment.

Introduction

The prevalence of sensitization to Hymenoptera venoms (HVs) in the general population is high, with 27 % to 40 % among adults and up to 50 % among children 1. The majority of sensitizations is clinically irrelevant. According to European epidemiological studies, the frequency of systemic sting reactions is 0.3 % to 7.5 % in adults and up to 3.4 % in children 2. In Central Europe, stings of the wasp species *Vespula vulgaris* and *Vespula germanica* as well as the honeybee *Apis mellifera* are the primary cause of anaphylactic reactions. Stings by other Hymenoptera, such as yellowjackets (*Dolichovespula* spp.), paper wasps (*Polistes* spp.), hornets (*Vespa crabro*), bumblebees (*Bombus* spp.), and ants (Formicidae), are much less common. While the documented fatality rate following Hymenoptera stings is low (0.03–0.48 cases per 1,000,000 population), the actual number is likely higher, given that undetected anaphylactic sting reactions are not included in these statistics 2.

Experts from 16 European countries participated in the development of new European guidelines on Hymenoptera venom allergy (HVA) published in July 2017 2. A guideline update is scheduled for 2022.

Based on current European guidelines, treatment with HV is indicated for ≥ grade II anaphylactic reactions (Ring and Meßmer classification) and evidence of IgE-mediated sensitization; such treatment is also warranted for grade I anaphylaxis if patients experience impairment in quality of life (QoL).

Affected individuals are strongly advised to always carry an emergency kit consisting of an epinephrine autoinjector (EAI), an oral corticosteroid, and an antihistamine. For correct usage in case of emergency, it is recommended that affected individuals and their families regularly participate in training courses. Insect venom allergy is – in particular due to fear of another sting – associated with significant impairment in disease-specific quality of life, which is not improved by carrying an EAI. Venom immunotherapy (VIT) is the only causal and preventive treatment with respect to potential future sting reactions; it leads to significant improvement in patients' quality of life 3. Success rates in terms of protective

effects range from 77 % to 84 % for honeybee venom allergy and from 91 % to 96 % for wasp venom allergy 2.

Clinical presentation

With a reported prevalence of 2.4 % to 26.4 % in the general population, increased local reactions are the most common manifestation of HVA 2. It is defined as localized erythematous edema (>10 cm in diameter) that persists for more than 24 hours.

Systemic sting reactions are characterized by symptoms that occur at sites distant from the actual sting site. The severity scale (as proposed by Ring and Meßmer) has proven useful for classifying anaphylactic reactions (Table 1) 4, 5.

Table 1. Severity scale for the classification of anaphylactic reactions (Ring and Meßmer 4, 5; modified after 4)

Grade	Skin and subjective general symptoms	Abdomen	Respiratory tract	Cardiovascular system
I	– Pruritus – Flushing – Urticaria – Angioedema	–	–	–
II	– Pruritus – Flushing – Urticaria – Angioedema	– Nausea – Cramps	– Rhinorrhea – Hoarseness – Dyspnea	– Tachycardia (increase ≥ 20/min) – Hypotension (decrease ≥ 20 mmHg systolic) – Arrhythmia
III	– Pruritus – Urticaria – Flushing – Angioedema	– Vomiting – Defecation	– Laryngeal edema – Bronchospasm – Cyanosis	– Shock
IV	– Pruritus – Flushing – Urticaria – Angioedema	– Vomiting – Defecation	– Respiratory arrest	– Cardiac arrest

Mild symptoms of a systemic sting reaction present as cutaneous reactions including flushing, urticaria, and/or angioedema (grade I anaphylaxis according to Ring and Meßmer). Moderate symptoms of grade II anaphylaxis are characterized by additional involvement of

at least one other organ besides the skin (e.g., nausea, dyspnea, hypotension, and tachycardia). Severe systemic sting reactions present as grade III and IV anaphylaxis. Important symptoms are urinary and fecal incontinence as sign of cardiovascular dysregulation and shock (including respiratory and cardiac arrest). Following a sting, the onset of symptoms – initially frequently cutaneous symptoms – is usually within 30 minutes. Symptoms that predominantly involve organs other than the skin should raise suspicion for a clonal mast cell disorder 1. While measurement of basal serum tryptase levels may be useful in such cases, normal levels do not rule out a clonal mast cell disorder.

If the classic sequence of anaphylactic symptoms is missing, other diseases that may mimic anaphylactic reactions must be included in the differential diagnosis (Table 2) 1, 6.

Table 2. Differential diagnosis of anaphylaxis

Disorders that may mimic anaphylactic reactions (guidelines for acute treatment and management of anaphylaxis 6, 21).	
Cardiovascular disorders	– vasovagal syncope – cardiogenic shock – cardiac arrhythmia – hypertensive crisis – pulmonary embolism – myocardial infarction
Endocrine disorders	– carcinoid syndrome – pheochromocytoma – thyroid storm – hypoglycemia
Neuropsychiatric disorders	– hyperventilation syndrome – anxiety and panic disorders – dissociative disorders and conversion (e. g. globus hystericus) – psychosis – artifacts (e. g. Munchausen syndrome) – somatoform disorders (e. g. psychogenic dyspnea *vocal cord dysfunction*) – seizures – coma (e. g. metabolic, traumatic)
Respiratory disorders	– status asthmaticus – acute stenosing laryngotracheobronchitis – tracheal/bronchial obstruction (e. g. foreign body)

“Unusual sting reactions”, which may, for example, occur after multiple stings, comprise serum sickness, vasculitis, thrombocytopenic purpura, as well as neurologic or renal toxic

symptoms. These patients require no further diagnostic workup 4.

Responsible insect

Identification of the stinging insect is essential in terms of diagnostic and therapeutic planning. However, the information patients provide is not always reliable and thus of limited value in this regard. In a study, nearly one-third of the participants could not accurately identify wasps; roughly 10 % could not identify honeybees; and approximately 50 % could not distinguish paper wasps (*Polistes*) 1. It is commonly believed that the distinctive feature of a honeybee sting is the fact that bees leave their stinger behind. Although – compared to wasps – the stinger apparatus of honeybees does remain in the skin more frequently, this is no reliable criterion. Other factors, too, such as the skin texture at the sting site or the patient's attempt to forcefully remove the wasp, may result in the stinger apparatus remaining in the skin. Important distinguishing criteria between honeybees and wasps are summarized in Table 3 4. In Central Europe, roughly 15 social bee and wasp species are primarily responsible for Hymenoptera stings 7. Taxonomically, the order of Hymenoptera comprises the Apidae (true bees), Vespidae (social wasps), and Formicidae (ants) families. The Apidae family includes the genera *Apis* (honeybee) and *Bombus* (bumblebee); the Vespidae family encompasses the genera *Vespa* (hornet), *Vespula* and *Dolichovespula* (yellowjacket), as well as *Polistes* (paper wasp) (Figures 1-5). In Germany, stings are predominantly caused by honeybees and two species of the genus *Vespula* (*Vespula germanica* and *Vespula vulgaris)*. *Polistes* species are common in Mediterranean countries as well as tropical and subtropical regions (especially South America) 8. Phylogenetically, the Formicidae (ants) family appears to be more closely related to bees than to wasps 8. In Germany, ant bites are virtually irrelevant as trigger factors of allergic reactions. Outside of Europe, the American fire ant (*Solenopsis* spp, *Myrmicinae*) and the Australian bulldog ant (*Myrmecia* spp., *Myrmicinae*) play a rather significant role in terms of triggering allergic reactions 2; this circumstance should be observed when traveling abroad.

Table 3. Clues for distinguishing honeybees and wasps (modified after 4)

Honeybee	Wasp
Rather calm (except around the hive)	Rather aggressive
Flying season mainly spring to late summer	Flying season mainly summer to fall
Stinger usually remains in the skin	Stinger does usually not remain in the skin
Near hives, flowers and clover	Near food and waste

Figure 1

Open in figure viewer | PowerPoint

Vespa (hornet) (© pixabay.com).

Figure 2

Open in figure viewer | PowerPoint

Vespula (yellowjacket) (© pixabay.com).

Figure 3

Apis mellifera (honeybee) (© pixabay.com).

Figure 4

Bombus (bumblebee) (© pixabay.com).

Figure 5

Polistes (paper wasp) (© pixabay.com).

Diagnostic workup

Skin tests

In Europe, standardized, dialyzed venom preparations available for skin testing include honeybee, bumblebee, *Vespula* spp., hornet, *Polistes*, and *Dolichovespula* venom 2. Given that *Polistes* or *Dolichovespula* stings are less frequent in Germany, it is common practice to run tests with honeybee and *Vespula* spp. venom, using positive (histamine 0.1 % solution) and negative controls (albumin solution or normal saline). In Mediterranean countries and America, *Polistes* and/or *Dolichovespula* stings are common. In these regions, affected individuals should therefore be tested with other venoms as well 2.

Skin prick testing (SPT) is an established, rapid test method. To determine the threshold for triggering a reaction, venom concentrations of 1.0 µg/mL, 10 µg/mL, 100 µg/mL, and, if necessary, 300 µg/mL can be used. If SPT is negative, it may be followed by intradermal testing (IDT), with a maximum venom concentration of 1.0 µg/mL. It is also possible to only do IDT, using venom concentrations of 0.001 µg/mL 0.01 µg/mL, 0.1 µg/mL, and 1.0 µg/mL. A study has shown simultaneous intradermal testing with these concentrations (serial dilution, 0.2 mL each) to be safe and effective, too 9. Some experts consider IDT to be more sensitive than prick testing. In a recent publication, it was shown that SPT had a high specificity for WV (90 %) – but not for HBV (51.9 %) – at a concentration of 300 µg/mL 10. For

patients with severe anaphylactic sting reactions or individuals at a particularly high risk, the German guidelines recommend an incremental approach with increasing venom concentrations 4. A long interval between sting and skin testing may be associated with negative test results. Loss of sensitization must be expected in 12 % of the cases per year (33 % after 2.5 years) 1. An interval of one to six weeks after the sting is recommended as the best time window for skin testing 1. As the booster effect is still insufficient, skin testing prior to the optimal time window may give rise to false-negative results. Frequently used drugs, such as corticosteroids, antihistamines, and psychotropic drugs, may affect skin tests and cause false-negative results (Table 4) 1, 11.

Table 4. Recommended interval between skin tests and the intake of frequently used drugs 1, 11

Drug group	Suppression*	Interval
First generation H1 antihistamines.	+++	> 3 days
New-generation H1 antihistamines	+++	> 7 days
H2 antihistamines	–/+	2 days
Ketotifen	+++	> 5 days
Prednisolone < 10 mg	–	–/+
Prednisolone > 10 mg	0	> 3 weeks
Benzodiazepines	+++	> 7 days
Omalizumab	+++	4–8 weeks
Tricyclic antidepressants	+++	> 14 days
Promethazine	++	> 5 days

*Suppression of skin tests: – negative; 0 no evidence; + low; ++ moderate; +++ high.

In vitro test methods

Specific IgE (sIgE) against HV

Various systems are available for measuring sIgE using venom preparations (fluid- and solid-phase systems; single or multiplex measurements). The internationally accepted cutoff is 0.35 kU/L. Other assays use a cutoff of 0.10 kU/L for the detection of sIgE 1, 12. In case of low total IgE levels, sIgE levels between 0.10 kU/L and 0.35 kU/L may be clinically relevant. This is particularly true for patients with mastocytosis. A recent study among patients with

mastocytosis and anaphylactic reactions to wasp stings showed the highest sensitivity for a cutoff of 0.17 kU/L sIgE 13.

Due to the aforementioned booster effect, measurement of sIgE should be performed one to six weeks after the sting (as with skin testing) 1.

Specific IgE (sIgE) against recombinant marker allergens and CCD

Twelve honeybee and six wasp venom allergens have so far been detected and described in detail (http://www.allergen.org: WHO/IUIS Allergen Nomenclature Subcommittee). Marker allergens specific for honeybee venom (HBV) are Api m1 (phospholipase A2), Api m3 (acid phosphatase), Api m4 (melittin), and Api m10 (icarapin). Ves v1 (phospholipase A1) and Ves v5 (antigen V) are considered specific marker allergens for wasp venom (WV). These allergens are currently commercially available for sIgE measurement.

Apart from marker allergens, HBV and WV also contain homologous, potentially cross-reactive allergens with highly similar peptide sequences. These are hyaluronidases (Api m2 and Ves v2), dipeptidyl peptidases IV (Api m5 and Ves v3), as well as vitellogenins (Api m12 and Ves v6) (Table 5).

Table 5. Marker allergens of honeybee and wasp venoms, as well as potentially cross-reactive allergens 1

HBV marker allergens	Potentially cross-reactive allergens	WV marker allergens
Api m1	Api m2 ↔ Ves v2	Ves v1
Api m3	Api m5 ↔ Ves v3	Ves v5
Api m4	Api m12 ↔ Ves v6	
Api m10		

Abbr.: HBV, honeybee venom; WV, wasp venom.

The majority of HBV and WV allergens have oligosaccharide side chains bound to their protein structure. Known as cross-reactive carbohydrate determinants (CCD), they are also commonly found in plants. With respect to insect venom hypersensitivity, cross-reactive carbohydrate determinants are thought to play a clinically insignificant role. By contrast, they are highly relevant in food allergies, especially in the context of IgE-mediated sensitization to α-gal (galactose-α-1,3-galactose). Cross-reactive carbohydrate determinants in HV can be measured by ImmunoCAP assays directed against horseradish peroxidase (HRP) or pineapple stem bromelain (MUXF3). However, their detection does not rule out

genuine sensitization.

Since October 2012, a test system spiked with Ves v5 has been available for the diagnosis of WV allergy, which has increased the diagnostic sensitivity from 83 % to 97 % 14.

The diagnostic success rate regarding HBV hypersensitivity can be significantly increased by measuring IgE antibodies to Api m1, Api m3, Api m4, and Api m10 (marker allergens). Compared to sole measurement of anti-Api m1, this will increase the diagnostic sensitivity from 72 % to almost 90 % 15.

HBV and WV marker allergens are particularly useful in patients who are sensitized to both types of venom and for those who cannot name the exact insect responsible.

Distinguishing between sensitization to *Vespula* spp. and *Polistes* spp. continues to be a challenge; the latter species are more prevalent in Mediterranean countries and America. Currently, routine diagnostic tests allow for the measurement of sIgE directed against two marker allergens related to *Polistes*: Pol d1 (phospholipase A1) and Pol d5 (antigen 5). As these allergens are characterized by high cross-reactivity with Ves v1 and Ves v5 (www.allergen.org), differences in antibody levels directed against the various marker allergens may be useful in identifying the insect in question 16. Cross-reactivity between *Vespula* spp. and *Polistes* spp. is usually caused by homologous proteins, such as hyaluronidases (Ves v2-homologous *Polistes* protein) and dipeptidyl peptidases IV (Ves v3-Pol d3). Measurement of antibodies against phospholipase A1 (Ves v1-Pol d1) and antigen V (Ves v5-Pol d5 is used to identify the respective sensitization.

Basal serum tryptase (bST)

Basal serum tryptase (bST) is an indicator of mast cell activity. It is measured using a commercial assay, with the 95th percentile generally used as normal value (11.4 µg/L according to the manufacturer). In adults with HVA, highly severe sting reactions are associated with elevated bST levels 4. Persistently elevated levels > 11.4 µg/L are indicative of mastocytosis. Patients with systemic mastocytosis often have bST levels > 20 µg/L. Cutaneous mastocytosis with bST levels < 20µg/L is usually also associated with bone marrow involvement 17. The German guidelines recommend determining bST levels in adults with systemic immediate-type reactions to Hymenoptera stings and in children with severe reactions 4.

Cell-based tests

An established test method, the basophil activation test (BAT) involves incubation of the patient's blood (EDTA blood) with insect venom. This results in expression of activation markers (CD203c and CD63) on the surface of basophils, which can then be quantified by flow cytometry. The CD63-based BAT is commonly used. Activation of 15 % of basophils is considered a positive test result, with negative controls showing activation of up to 10 % 1. If there is an unequivocal history of insect venom-related anaphylaxis but no evidence of sIgE

against HV (respectively, negative skin testing), BAT will provide evidence of IgE-mediated sensitization in 80 % (respectively, 60 %) of cases. Though an established method, BAT should not be used in the routine diagnostic workup of HVA. It is particularly useful, if there is a positive history of HVA but no evidence of IgE-mediated sensitization (using laboratory tests and the above-mentioned skin tests).

The histamine release test is another cellular test that has been largely replaced by BAT. Given that platelets release histamine, too, it has proven to be more expensive and time-consuming and less reliable.

The leukotriene release test (cellular antigen stimulation test, CAST) measures the release of sulfidoleukotrienes by activated basophils and may be useful in certain cases 1.

The routine diagnostic workup should include skin tests and measurement of sIgE. Molecular in vitro tests may be useful, if there is evidence of sensitization to both venoms. In case of a positive history of Hymenoptera venom allergy without any evidence of IgE-mediated sensitization, BAT may provide useful additional information.

Venom immunotherapy (VIT)

In Europe, the venoms of honeybees and *Vespula* spp. are available for therapeutic purposes. In Mediterranean countries, the venom of *Polistes* spp. is also available, including *Polistes dominula* venom preparations in Spain and Italy. In some European countries, for example Italy, bumblebee venom preparations are also available. The latter should preferentially be used in patients with primary bumblebee allergy, which is occasionally seen in greenhouse workers in the vegetable-growing industry, where bumblebees are used for pollination. Within the Apidae family, approximately 70 % of individuals allergic to honeybee venom also react to bumblebee venom 16. Both honeybee and bumblebee venoms contain phospholipase A2, hyaluronidase, serine protease, and acid phosphatase, which exhibit limited cross-reactivity due to low sequence homologies 16. In affected regions worldwide (such as Australia), ant venom preparations (for example, *Myrmecia pilosula*) are also available 2.

In Europe, purified and nonpurified aqueous venom preparations, as well as purified preparations adsorbed with aluminum hydroxide (depot preparations), are available for subcutaneous VIT. Purified aqueous preparations are associated with fewer systemic reactions than nonpurified preparations 2. The reported efficacy of VIT is up to 84 % for honeybee venom, up to 96 % for wasp venom, and up to 98 % for ant venom.

Purified aqueous preparations can be used for updosing following rush, ultra-rush, cluster, and conventional protocols. Depot preparations are preferably used for conventional or cluster protocols and for maintenance therapy. Once the therapeutic standard dose has been reached during the updosing phase, aqueous preparations may be switched to depot preparations; this is also possible during maintenance therapy. Depot preparations seem to

be associated with fewer local side effects than aqueous preparations 2.

Possible updosing schedules can be found in the summary of product characteristics (provided by the various manufacturers). Table 7 shows the ultra-rush protocol most frequently used at our own department.

The maintenance dose is 100 µg. In case of insufficient efficacy as evidenced by intolerance to sting challenge testing or to a field sting, the dose may be increased to 200 µg. High-risk patients, such as beekeepers, should initially be treated with twice the standard dose 3.

It is recommended to administer the subcutaneous injections every four weeks during the 1st year, every six weeks during the 2nd year, and at eight-week intervals during the 3rd–5th year. In patients who require continued or even lifelong treatment, injection intervals may be extended to twelve weeks 2. Extending the interval to more than eight weeks in mastocytosis patients (high-risk group) requires special caution. If injections are given at three-month intervals, the expiration date of the therapeutic venom may be reached before it is completely used up, which is a negative aspect in terms of cost efficiency 18. Moreover, the summaries of product characteristics of the various preparations specify a maximum injection interval of eight weeks for the dose of 100 µg. Exceeding that interval must therefore be considered off-label use.

Based on the assessment of the Paul Ehrlich Institute (PEI), a three-year treatment regimen is not associated with an increased risk of accumulation of aluminum contained in therapeutic venom extracts (8 injections/year; https://www.pei.de/DE/arzneimittelsicherheit-vigilanz/archiv-sicherheitsinformationen/2014/ablage2014/2014-01-21-sicherheitsbewertung-von-aluminium-in-therapieallergenen.html). If an increased dose is required, current EAACI guidelines recommend the injection of 100 µg of an aqueous formulation in combination with 100 µg of a depot preparation. For lifelong VIT, only aqueous preparations are recommended 2.

The reported efficacy of VIT is 77 % to 84 % for HBV; 91 % to 96 % for WV; and 97 % to 98 % for ant venom 2. Potential reasons proposed with respect to the lower response rate to HBV immunotherapy include higher and more consistent amounts of venom introduced into the skin by a real-life honeybee sting and sensitization to a wide variety of allergens contained therein. Some patients, for example, are only sensitized to Api m10, whose amount may be too low in therapeutic venom extracts available today. The Robert Koch Institute (RKI) is currently planning regulatory reviews of the concentrations of allergen components in the context of batch quality checks 13.

If VIT is not tolerated, use of modern antihistamines (AH) may reduce the rate of systemic and local reactions. There is no evidence that this has a negative impact on the efficacy of VIT 13. In case of repeated intolerance to VIT, tolerability may be achieved with omalizumab. Administration of omalizumab five, three, and one week(s) prior to VIT initiation has been shown to be effective 13.

Omalizumab can usually be discontinued after six months 13.

Based on EAACI guidelines, the duration of VIT depends on the severity of the anaphylactic sting reaction (Table 6). For mild-to-moderate anaphylaxis (corresponding to grade I to II anaphylaxis according the classification by Ring and Meßmer), patients should be treated for three years 4, 5. In case of severe anaphylactic reactions (corresponding to grade III to IV anaphylaxis according to the classification by Ring and Meßmer), VIT should be performed for at least five years 4, 5. Lifelong treatment should be considered for individuals allergic to HBV and exposed to a high risk of being stung. According to the EAACI, other indications that warrant lifelong treatment include very severe sting reactions, systemic reactions to VIT, and renewed anaphylactic sting reactions following VIT.

Table 6. Duration of venom immunotherapy according to 2017 EAACI recommendations 2

Severity of anaphylactic sting reactions	Clinical presentation	Duration of VIT
Increased local reaction	> 10 cm, > 24 h persistence	None
Grade I anaphylactic sting reaction* (mild)	Flushing, urticaria, angioedema etc.	3–5 years
Grade II anaphylactic sting reaction* (moderate)	(Grade I) + nausea and/or dyspnea and/or cardiovascular dysregulation	3–5 years
Grade III anaphylactic sting reaction III* (severe)	(Grade I) + vomiting and/or laryngeal edema and/or shock	≥ 5 years to lifelong
Grade IV anaphylactic sting reaction* (severe)	(Grade I) + vomiting and/or respiratory arrest and/or cardiac arrest	≥ 5 years to lifelong
Systemic reactions during VIT	Grade I to grade IV	≥ 5 years to lifelong
Risk factors		
Individuals allergic to HBV with high risk for honeybee stings	e. g. beekeepers, gardeners, bakery sales assistants etc.	≥ 5 years to lifelong
Mastocytosis and/or elevated bST levels (> 11.4 µg/l)		≥ 5 years to lifelong

*Anaphylactic sting reactions grade I–IV (Ring and Meßmer classification) 4, 11

Abbr.: VIT, venom immunotherapy; HBV, honeybee venom; bST, basal serum tryptase.

Table 7. Ultra-rush protocol for venom immunotherapy (© Helios HSK)

Initiation of specific immunotherapy, ultra-rush protocol								
	Honeybee				Wasp			
Day 1								
Concentration	mL	Date	Time	Injection site	Local reaction	Systemic reaction	Treatment	Physician
Vial 1, lyophilized (0.1 µg/mL)	0.1							
Vial 2, lyophilized (1.0 µg/mL)	0.1							
Vial 3, lyophilized (10.0 µg/mL)	0.1							
Vial 4, lyophilized (100.0 µg/mL)	0.1							
Vial 4, lyophilized (100.0 µg/mL)	0.2							
Vial 4, lyophilized (100.0 µg/mL)	0.4							
Vial 4, lyophilized (100.0 µg/mL)	0.8							

There is some data on the effectiveness of VIT up to ten years after its discontinuation. Persistent sting reactions (recurrences) have been reported in 0 % to 10 % of the cases after one to five years after cessation of wasp venom immunotherapy 2. Other publications showed recurrence rates of 7 % to 7.5 % seven to ten years after wasp venom immunotherapy and of 15.8 % after honeybee venom immunotherapy 2. In children, long-term results seem to be significantly more favorable than in adults, with recurrence rates of 5 % reported 20 years after the end of VIT 2.

Indication for VIT

Based on current EAACI guidelines, VIT is indicated in both adults and children who experienced grade II anaphylactic reactions (Ring and Meßmer classification) following Hymenoptera stings and evidence of IgE-mediated sensitization to the insect implicated.

VIT may also be recommended in adults with grade I anaphylaxis, if there is an increased

risk of re-exposure and/or impairment in QoL. Furthermore, VIT may be considered as a therapeutic option in patients with recurrent, markedly increased local reactions.

At the same time, measures to prevent Hymenoptera stings should be instituted 4.

Contraindications for VIT

German guidelines distinguish between temporary and permanent contraindications. The former group includes intercurrent infection, insufficiently treated asthma, vaccination for infectious diseases, and noncompliance.

Permanent contraindications comprise cardiovascular disorders, current malignant neoplastic and immunological diseases, as well as use of beta blockers and ACE inhibitors. In case of stable remission of the aforementioned malignant neoplastic or immunological diseases, VIT may be carried out once the risk of progression has passed. If there is an absolute indication for treatment with beta blockers, VIT may be performed with appropriate precautions. If possible, cardioselective beta blockers should be used 4.

Pregnancy is also a contraindication for VIT. According to German guidelines, a pregnancy occurring during ongoing, well-tolerated maintenance therapy is no contraindication.

The 2017 EAACI guidelines differ from the 2011 German guidelines, in particular with respect to the significance of beta blockers and ACE inhibitors. Neither beta blockers nor ACE inhibitors are listed as contraindications. However, affected patients should be informed about potential risks (increased risk of severe systemic reactions, use of epinephrine in an emergency may be less effective).

In addition, cardiovascular disorders are not considered contraindications, either. Patients with preexisting cardiovascular disorders in particular are at high risk for severe systemic sting reactions 2. It is important to bear in mind that some manufacturers of therapeutic venoms list beta blockers and ACE inhibitors as contraindications in their summary of product characteristics. The requirements for off-label use therefore need to be observed prior to initiating VIT, Since July 2018, the summary of product characteristics provided by one manufacturer has no longer listed the use of beta blockers and ACE inhibitors in the category “contraindications” but as a “warning for use”.

Acute malignant neoplasms are considered to be relative contraindication in the EAACI guidelines. In high-risk HVA patients, VIT may be initiated if the malignancy is stable or in remission.

VIT may also be recommended to patients with stable organ-specific autoimmune disorders.

The EAACI guidelines place a particular focus on MAO inhibitors. Given their sympathomimetic effect, use of MAO inhibitors in combination with epinephrine administered in an emergency may cause a hypertensive crisis and/or pronounced

tachycardia. Although their use is not considered a contraindication, special caution is warranted in the context of VIT and the use of epinephrine.

As regards children, the summaries of product characteristics of the various therapeutic venoms recommend VIT only in individuals five years and older. The European guidelines, on the other hand, recommend the same approach for children as for adults and do not express any concerns with respect to initiating VIT in children younger than five years of age if there is a history of a grade II anaphylactic sting reaction (Ring and Meßmer classification) or an increased risk profile.

Elevated bST levels > 11.4 µg/L and/or the presence of mastocytosis is a risk factor for both development of HVA and severe systemic reactions 2. A large study of patients with systemic mastocytosis showed VIT to be safe and effective in this patient group 2. For safety reasons, the EAACI supports VIT beyond the recommended duration of three to five years in these patients. It remains unclear whether patients should receive lifelong treatment or whether it is possible to limit the duration of VIT.

Risk factors for frequent exposure and severe anaphylaxis are listed in Table 8 4.

Table 8. Risk factors (modified after 4)

Risk of frequent exposure
– beekeepers, their relatives and neighbors
– occupations such as fruit and bakery salespersons, forest workers, gardeners, fire fighters, farmers, construction workers, truck drivers
– very frequent outdoor activities
Risk for severe anaphylaxis
– history of severe anaphylactic sting reaction (grade III/IV or grade II reaction with significant airway obstruction)
– age (approximately ≥ 40)
– cardiovascular disease
– asthma
– beta blocker, ACE inhibitor, possibly NSAIDs
– physical or psychological stress situation
– bST levels > 11.4 µg/L
– mastocytosis

Abbr.: bST, basal serum tryptase; ACE, angiotensin-converting enzyme; NSAID, non-steroidal antiinflammatory drugs.

Procedures for monitoring VIT

Various attempts aimed at establishing markers (sIgE, sIgG, blocking IgG antibodies, BAT, skin test sensitivity) for the effectiveness of VIT have been unsuccessful. The European guidelines recommend sting challenge testing as "gold standard" for identifying those patients who are insufficiently protected by VIT. If a sting challenge is not possible, a history of a tolerated field sting may also be used to assess VIT effectiveness.

Sting challenge testing is not standardized as neither the quantity nor the quality of the venom thus introduced into the skin can be determined. There is also the risk of using the "wrong insect" that was not responsible for the anaphylactic reaction. Sting challenge testing therefore requires both expertise in dealing with allergic emergencies and familiarity with the taxonomy of Hymenoptera. Moreover, the role of cofactors – such as physical exertion, alcohol, or acetylsalicylic acid – in insect venom anaphylaxis has not yet been sufficiently investigated.

German guidelines recommend sting challenge testing (with emergency equipment on standby) 6–18 months after reaching the maintenance dose. If the sting challenge is not tolerated, the dose of the HV used should be increased to twice the maintenance dose. Treatment duration will again be three to five years, starting from the time of dose increase. To reduce the exposure to aluminum, either 100 μg of the depot preparation plus 100 μg of the aqueous preparation or two times 100 μg of the aqueous preparation may be used 2, 13. Proposals regarding the implementation of sting challenge tests have been presented in various publications 4, 19.

The EAACI guidelines recommend sting challenge testing as early as possible during VIT, without specifying the exact point in time.

At the Department of Dermatology in Wiesbaden, we recommend sting challenge testing (during VIT) to our patients (Figures 6, 7). It has been shown that a tolerated sting challenge during VIT significantly increases the disease-specific quality of life of affected individuals 3.

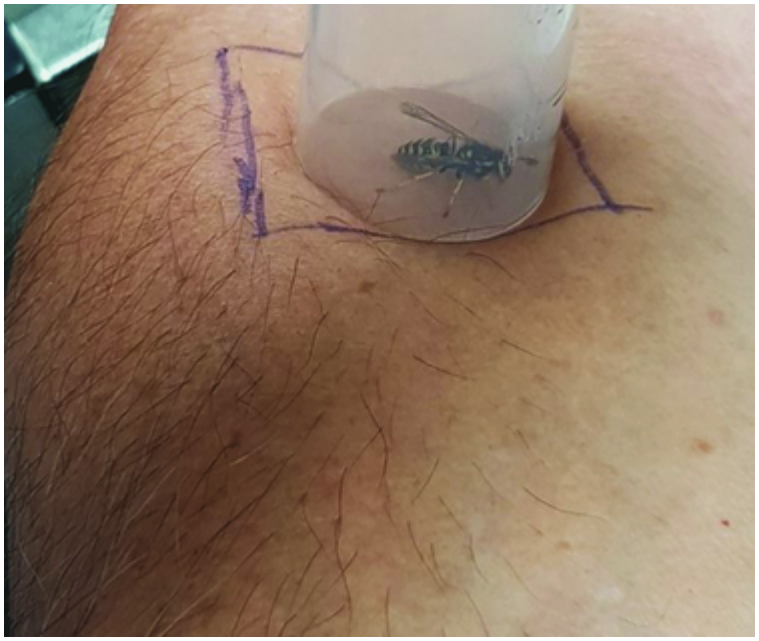

Figure 6

Sting challenge testing involves the placement of the insect onto the forearm using tweezers. The plastic tube allows the insect to remain on the forearm until the sting has occurred (©Helios HSK).

Figure 7

Sting challenge testing (© Helios HSK).

Diagnostic sting challenge testing is not recommended in Germany as it is considered to be unreliable. A study showed that 21 % of patients who had tolerated the first sting challenge subsequently developed anaphylaxis after the second challenge 1.

Epinephrine autoinjector (EAI)

During the development of the EAACI guidelines, no consensus was reached as to whether an EAI should be carried both during and after VIT. If there are risk factors for treatment failure, 100 % of the experts recommend carrying an EAI even after discontinuation of VIT 2. This suggests that, based on EAACI guidelines, physicians can exert some discretion when it comes to prescribing an EAI during and after VIT.

Apart from observing measures to prevent stings, German guidelines, too, recommend carrying an emergency kit after the end of VIT 4.

A 2016 position paper by the EAACI provides clear recommendations for carrying an EAI 20. Table 9 presents the absolute and relative indications for carrying an EAI stated therein.

Table 9. Absolute and relative indications for carrying an epinephrine autoinjector 20

Epinephrine autoinjector – absolute indication
– all patients with mast cell disease and/or bST ↑ and systemic sting reaction
– patients with more than cutaneous/mucosal sting reaction or high risk of being stung
– VIT-treated patients with systemic reaction + risk of VIT failure
– in case of recurrence risk after VIT discontinuation
– untreated patients with systemic reaction/increased risk of being stung
Epinephrine autoinjector – relative indication
– mild sting reaction, but difficulties in getting medical attention
– after VIT in case of previous systemic reactions
– risk of multiple stings
– after VIT carried out for less than 3 years
– no sting challenge/field sting during VIT

– in case of ACE inhibitor use

Abbr.: bST, basal serum tryptase; VIT, venom immunotherapy; ACE, angiotensin-converting enzyme.

In Germany, EAIs from three different manufacturers are available, with needle lengths between 13 mm and 23 mm. The price ranges from € 81.99 to € 118.45. However, there is only one manufacturer who, apart from the usual doses of 150 µg (15–30 kg) and 300 µg (> 30–60 kg), also offers an EAI for patients heavier than 60 kg (500 µg).

Another manufacturer permits the use of the EAI (150 µg) even in individuals with a body weight of 7.5–25 kg.

Patients for whom an EAI is indicated ought to be prescribed two such pens. Thus, if there is no clinical response after 10–15 minutes, a second dose can be administered.

Summary

In recent years, the options for the diagnostic workup of HVA have significantly improved, not least due to developments in molecular tests.

Spiking wasp venom extracts with Ves v5 (introduced in 2012), as well as the HBV marker allergens Api m1, Api m3, Api m4, and Api m10 now commercially available, have led to a significant increase in diagnostic sensitivity.

It should be kept in mind that different laboratories may provide different tests results (different sIgE levels) despite using the same test methods. It is therefore recommended – for better comparability – to have the sIgE measurements done at a designated institute for laboratory medicine.

The various test systems for measuring sIgE levels have not been sufficiently evaluated; future studies should be aimed at remedying this circumstance.

Despite the rapid development in molecular diagnostic tests, there is still a diagnostic gap, especially in challenging cases with sensitization to both wasp and honeybee venom, which is observed in 45–50 % of anaphylactic sting reactions [22]. While the majority of these cases involve clinically irrelevant sensitizations to CCDs, detection of sIgE against CCDs does not rule out a relevant sensitization.

VIT constitutes a highly effective, causal treatment for HVA. The tolerability of VIT may be improved by antihistamines. In addition, use of omalizumab may improve the tolerability of VIT, too. The requirements for off-label use have to be observed when using omalizumab.

In Europe, various manufacturers offer purified and nonpurified aqueous venom preparations for VIT, as well as depot preparations adsorbed with aluminum hydroxide. Various updosing schedules for initiating HVA treatment can be found in the summaries of product characteristics provided by the manufacturers. At 77 % to 84 %, VIT for HBV is less effective than VIT for WV, which is associated with success rates of 91 % to 96 % 2. Potential reasons proposed with respect to the lower response rate to HBV immunotherapy include higher and more consistent amounts of venom introduced into the skin by a real-life honeybee sting and sensitization to a wide variety of allergens contained therein, as well as the possible underrepresentation of Api m10 in therapeutic venom extracts. The detection of sIgE against Api m10 in individuals allergic to HBV may indicate a higher risk of treatment failure of VIT 13. In patients with hypersensitivity to honeybee venom and risk factors (Table 8), or a history of a honeybee sting challenge that was not tolerated, doubling of the standard dose (200 µg) may result in protection against HBV 2, 4.

The new EAACI guidelines on HVA published in July 2017 provide European allergists with updated treatment recommendations. These differ – especially with respect to contraindications – from the German guidelines currently valid.

An important example of these differences is the fact that beta blockers and ACE inhibitors are no longer considered to be contraindications. One manufacturer of therapeutic HV extracts has incorporated this information in their summary of product characteristics.

In case of discrepancies with regard to treatment recommendations between the European and German guidelines, the summaries of product characteristics should also be consulted.

In the future, it would be desirable to establish commercial methods for determining levels of sensitization to homologous HBV and WV allergens, which may be useful in detecting primary sensitizations.

Furthermore, it remains to be seen what role BAT will play when using of CCD-free cross-reactive allergens.

Finally, the results of the regulatory review (performed by the RKI) of allergen components in the context of batch quality checks of HV extracts are still pending.

Conflict of Interest

None.

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Fragen zur Zertifizierung durch die DDA

1. Welche der folgenden Aussagen zur Taxonomie der Hymenoptera trifft zu?
   a. Zur Ordnung der Hymenoptera gehören die Bremsen.
   b. Ameisen sind keine Hautflügler.
   c. Innerhalb der Familie der Apidae sind auch *Formicidae* zu finden.
   d. Die Gattung *Vespula* ist in Mitteleuropa heimisch.
   e. *Vespula vulgaris* zählt zu den Langkopfwespen.
2. Welche Antwort zur Epidemiologie der Hymenopterengiftallergie ist richtig?
   a. Die Wespengiftallergie ist bei Erwachsenen die zweithäufigste Form der Anaphylaxie.
   b. Die Häufigkeit systemischer Stichreaktionen liegt im Erwachsenenalter bei 0,3 % bis 7,5 %.
   c. Eine gesteigerte Lokalreaktion tritt in bis zu 48 % der Fälle auf.
   d. Bis zu 8 % der Kinder in Europa haben systemische Stichreaktionen.
   e. Bei Kindern ist die Hymenopterengiftanaphylaxie die häufigste Anaphylaxieform.
3. Welche Antwort bezüglich der Fähigkeit der Bevölkerung, Hymenoptera zu unterscheiden, ist richtig?
   a. Die Unterscheidung von Feldwespen (*Polistes* spp.) von gewöhnlichen Wespen (*Vespula vulgaris*) bereitet keine Probleme.
   b. 10 % der Bevölkerung erkennen keine Bienen.
   c. 90 % der Bevölkerung identifizieren Wespen korrekt.
   d. Aufgrund der großen Ähnlichkeit lassen sich Honigbienen von Wespen nicht unterscheiden.
   e. Hummeln werden häufig mit Honigbienen verwechselt.
4. Welche der Antworten zur allergologischen Hauttestung trifft zu?
   a. Der Hautpricktest ist bei der Diagnostik der Hymenopterengiftallergie dem Intrakutantest vorzuziehen, da er sensitiver ist.
   b. Die simultane Intrakutantestung mit unterschiedlichen Konzentrationen ist in der deutschen Leitlinie empfohlen.
   c. Der Intrakutantest wird in den Konzentrationen 0,001, 0,01, 0,1 und 1,0 µg/ml empfohlen.
   d. Der Pricktest kann in den Konzentrationen von 1,0, 10, 100, 300 und 1000 µg/ml durchgeführt werden.
   e. Bei negativem Pricktest darf kein Intrakutantest in der Konzentration 1,0 µg/ml durchgeführt werden.
5. Welche Antwort zum Monitoring der Hymenopterengiftimmuntherapie trifft zu?
   a. Der Nachweis von IgG4-Anitköpern ist ein sicherer Hinweis für die Wirksamkeit der

Hymenopterengiftimmuntherapie.
   b. Ein positiver BAT während der Hymenopterengiftimmuntherapie beweist ein Therapieversagen.
   c. Bisher konnten keine In-vitro-Marker zum Wirksamkeitsnachweis der Hymenopterengiftimmuntherapie etabliert werden.
   d. Die Stichprovokation sollte immer nach Beendigung der Hymenopterengiftimmuntherapie erfolgen.
   e. Die neue EAACI-Guideline rät ausdrücklich von der Stichprovokation zum Therapiemonitoring ab.
6. Welche der folgenden Aussagen zur In-vitro-Allergiediagnostik der Hymenopterengiftallergie ist richtig?
   a. Aktuell sind die Bienengiftmarkerallergene Api m1, Api m2, Api m3, Api m5 und Api m10 kommerziell erhältlich.
   b. Der Nachweis von sIgE gegen CCD schließt eine primäre Sensibilisierung gegen Hymenopterengift sicher aus.
   c. Die Markerallergene des Wespengifts sind das Ves v1 und das Ves v3.
   d. Bei klarer Anamnese einer Hymenopterengiftallergie und fehlendem Nachweis einer IgE-vermittelten Sensibilisierung ist der Histaminfreisetzungstest dem BAT vorzuziehen.
   e. Doppelsensibilisierungen findet man in ca. 60 % der Fälle.
7. Welche Aussage zur Hymenopterengiftimmuntherapie ist richtig?
   a. In Europa stehen lediglich therapeutische Giftpräparate für *Vespula* spp. und die Honigbiene zur Verfügung.
   b. Die protektiven Effekte der Bienengiftimmuntherapie überwiegen die Wespengiftimmuntherapie.
   c. Isolierte Hummelgiftallergiker sollten mit Bienengift behandelt werden.
   d. Hummelgiftpräparate werden in Europa nicht verordnet.
   e. Bei nachgewiesener Doppelsensibilisierung gegenüber Bienen- und Wespengiftextrakt und positiver Anamnese sollte mit beiden Giften behandelt werden.
8. Welche der Aussagen in Bezug auf die molekulare Allergiediagnostik trifft zu?
   a. Durch ein Ves v5-angereichertes Testsystem konnte die diagnostische Sensitivität auf nahezu 100 % gesteigert werden.
   b. Api m10 und Ves v6 sind homologe, potentiell kreuzreaktive Allergene des Bienen- und Wespengiftes.
   c. Bei Patienten, die gegenüber Bienengiftextrakt sensibilisiert sind, schließt der fehlende Nachweis einer Sensibilisierung gegenüber Api m1, eine Bienengiftallergie sicher aus.
   d. sIgE-Werte unterschiedlicher Anbieter sind direkt vergleichbar.
   e. Durch die Kombination der Markerallergene Api m1, Api m3, Api m4 und Api m10 konnte die diagnostische Sensitivität bei der Bienengiftallergie auf 100 % erhöht werden.

9. Welche der folgenden Aussagen in Bezug auf anaphylaktische Stichreaktionen ist zutreffend?
   a. Anaphylaxien mit vorwiegend zirkulatorischer Dysregulation ohne begleitende Hautsymptome können bei Patienten mit klonaler Mastzellerkrankung auftreten.
   b. Bei Kindern mit einer Grad-II-Stichanaphylaxie besteht keine Indikation für eine Hymenopterengiftimmuntherapie, da Kinder hinsichtlich des Outcomes eine bessere Prognose haben als Erwachsene.
   c. Bei einer Grad-I-Stichanaphylaxie eines erwachsenen Patienten spielt der QoL keine Rolle für die Therapieentscheidung.
   d. MAO-Hemmer können in Kombination mit Adrenalin zu Hypotension und Bradykardie führen.
   e. Man spricht bei der Hymenopterengiftallergie von einer gesteigerten Lokalreaktion, wenn es sich um eine örtliche Stichreaktion von >5 cm Durchmesser handelt, die mindestens 18 Stunden persistiert
10. Welche Aussagen hinsichtlich der Indikationen/Kontraindikationen der Hymenopterengiftimmuntherapie treffen zu?
   a. Wenn während einer gut vertragenen Hymenopterengiftimmuntherapie eine Schwangerschaft eintritt, muss die Therapie unmittelbar beendet werden.
   b. Die Einnahme von Betablockern und ACE-Hemmern stellen nach der neuen europäischen Leitlinie eine absolute Kontraindikation dar.
   c. Kindern < 5 Jahre kann grundsätzlich keine Hymenopterengiftimmuntherapie empfohlen werden.
   d. Eine organspezifische, stabile Autoimmunerkrankung stellt keine Kontraindikation für die Einleitung einer Hymenopterengiftimmuntherapie dar, wenn sie indiziert ist.
   e. Patienten mit erhöhter bST und/oder klonaler Mastzellerkrankung bedürfen keiner über die normale Therapiedauer von maximal fünf Jahren hinausgehender Therapie.

Liebe Leserinnen und Leser, der Einsendeschluss an die DDA für diese Ausgabe ist der 31. Oktober 2018. Die richtige Lösung zum Thema „Tumoren der Kopfhaut“ in Heft 6 (Juni 2018) ist: (1d, 2b, 3b, 4c, 5c, 6a, 7e, 8a, 9a, 10d).

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