REVIEW ARTICLE

Insect sting allergy in adults: key messages for clinicians

Marita Nittner-Marszalska[1], Ewa Cichocka-Jarosz[2]

1 Department of Internal Disease, Geriatrics and Allergology Medical University of Wroclaw, Wroclaw, Poland
2 Department of Pediatrics, Jagiellonian University Medical College, Kraków, Poland

KEY WORDS

insect venom allergy, tryptase, venom--allergen immunotherapy

ABSTRACT

During their lifetime, 94.5% of people are stung by wasps, honeybees, hornets, or bumble-bees (order Hymenoptera). After a sting, most people show typical local symptoms, 5% to 15% develop local allergic reactions, and 3% to 8.9%—systemic allergic reactions (SARs), which may be potentially life-threatening in about 10% of them. In mild forms of Hymenoptera-venom allergy (HVA), the leading symptoms are urticaria and edema (grades I and II, respectively, according to the Mueller classification). Severe SARs are classified as grade III (respiratory symptoms) and IV (cardiovascular symptoms). Rare manifestations of HVA are Kounis syndrome and takotsubo cardiomyopathy. All patients after an SAR require standard (skin test, IgE, tryptase) or comprehensive (component diagnosis, basophil activation test) allergy testing. All patients with severe systemic symptoms (hypertension, disturbances in consciousness) should be tested for mastocytosis. Additionally, a relationship was found between the severity of HVA symptoms and intake of angiotensin-converting enzyme inhibitors (ACEIs). There is a similar concern, although less well-documented, about the use of β-blockers. Patients with HVA who have experienced a SAR are potential candidates for venom immunotherapy (VIT), which is effective in 80% to 100% of individuals treated for 3 to 5 years. An increased risk of a VIT failure has been reported in patients with systemic mastocytosis and those treated with ACEIs. In certain groups (beekeepers, patients who develop a SAR to stings during a VIT with a standard dose, as well as those with a SAR to maintenance doses of VIT), a twice higher maintenance dose is recommended. Indications, contraindications, treatment protocols, and vaccine doses are regulated by the international guidelines of allergy societies.

Correspondence to:
Ewa Cichocka-Jarosz, MD, PhD, Klinika Chorób Dzieci, Katedra Pediatrii, Uniwersytet Jagielloński, Collegium Medicum, ul. Wielicka 265, 30-663 Kraków, Poland, phone: +48 12 658 20 11, fax: +48 12 658 44 46, e-mail: mijarosz@cyf-kr.edu.pl
Received: August 4, 2015.
Revision accepted: August 31, 2015.
Published online: September 3, 2015.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2015; 125 (12): 929-937

The occurrence of Hymenoptera-venom allergy Allergic reactions to insect bites result most frequently from stings of flying insects of the Hymenoptera order. From among over 100 000 species of Hymenoptera, the ones mainly responsible for sting reactions are usually honeybee (*Apis mellifera*) as well as wasps and hornets (eg, *Vespula germanica, V. vulgaris, V. rufa, Vespae sp.*). However, potential perpetrators of Hymenoptera allergy are diverse and vary with geography. In southern Europe, there are paper wasps (*Polistinae subfamilies*); in the United States, there are fire ants (*Solenopsis invicta*); and in Australia, there are Jack jumper ants (*Myrmecia pilosula*) that seem to cause more problems. A large number of Hymenoptera species, their ways of feeding, and their aggressive defense behavior result in as many as 56.6% to 94.5% of people experiencing at least 1 sting in their lives.[1]

In most affected persons, a Hymenoptera sting results in local itching and mild induration. There are some individuals, however, who additionally respond to a sting by developing sensitization manifested by the presence of venom-specific immunoglobulin E (IgE) antibodies (vsIgE) to various components of insect venoms (in honeybee venom, 12 allergens have been identified so far: Api m1 – Api m 12; in wasp venom, 5 allergens have been identified: Vesp v 1, V v 2, Vesp v 3, Vesp v5, and Ves v 6).[2] Venom sensitization is the key factor for but is not synonymous with venom allergy. Sensitization to Hymenoptera venoms may be asymptomatic (hypersensitivity not clinically relevant) or symptomatic defined as Hymenoptera--venom allergy (HVA). The asymptomatic sensitization is common and found in 9.3% to 40.7% of the general population and in 30% to 60% of beekeepers (which reflects the effect of exposition to

TABLE 1 Classification of allergic reactions to insect stings[35,48]

Large local reaction	Swelling >10 cm in diameter, which persists for >24 hours	
systemic allergic reaction to insect stings by the Mueller classification	grade I	generalized urticaria, itching, malaise, and anxiety
	grade II	any of the above plus ≥2 of the following: angioedema, chest constriction, nausea, vomiting, diarrhea, abdominal pain, dizziness
	grade III	any of the above plus ≥2 of the following: dyspnea, wheezing, stridor, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster
	grade IV	any of the above plus ≥2 of the following: fall in blood pressure[a], collapse, loss of consciousness[b], incontinence, cyanosis
systemic allergic reaction to insect stings by the Ring and Messmer classification	grade I	skin lesions and/or slight increase of body temperature
	grade II	detectable, but not life-threatening, cardiovascular reactions (tachycardia, hypotension)
	grade III	shock, life-threatening, smooth muscle spasm (uterus, bronchi, etc)
	grade IV	cardiac arrest

a defined as: <90 mmHg in subjects >17 years of age
b While assessing neurological symptoms understood as altered levels of consciousness, the Glasgow scale is employed.

sting on sensitization to insect venoms).[3-5] Only a part of venom-sensitive people develop clinical symptoms of allergic reactions, which can be large local (LLR) or systemic (SAR). LLRs are the most frequent manifestation of HVA. Most studies in adult populations report the frequency of LLRs between 5% and 15%, but some studies—even up to 26%.[1,6,7] Among beekeepers, the frequency of LLR ranges between 12% and 38%.[4] SARs in the course of HVA occur in 3% to 8.9% of adults.[1,6] The prevalence of systemic symptoms of HVA is significantly higher in 2 groups of patients: beekeepers (14%–43%) and adult patients with mastocytosis.[1,4,8,9] Not all HVA adult patients suffering from mastocytosis present with an equally high percentage of systemic symptoms: the highest occurs in patients with indolent systemic mastocytosis without skin lesions (ISMs[–]: 73%) and in patients with the baseline serum tryptase (bsT) level in the range from 20.4 to 29.9 μg/l.[9,10] The lowest percentage of systemic symptoms of HVA occurs in patients with systemic mastocytosis (SM) and bsT levels below 6.1 and above 191 mcg/l or in aggressive subtypes of SM (10%).[10,11] The rarest mastocytosis variant associated with HVA is cutaneous mastocytosis (CM: 0%–7%).[11]

Though HVA-SAR are potentially life-threatening, the reported mortality rates are low, ranging from 0.03 to 0.48 deaths per 1 000 000 persons per year. However, the mortality data may be underestimated because many deaths from stings go unrecognized or are misinterpreted.[1] Deaths are reported mainly in male adults.[1]

Clinical manifestations of Hymenoptera venom allergy and possible reactions to a subsequent sting Insect stings normally cause painful, sometimes itching and burning, local indurations not exceeding 2 to 3 centimeters in diameter. They usually disappear after a few hours but, at times, they persist for several days. Some individuals develop large swellings (not only from the insect stings, but also from a variety of insect bites), which may indicate a nonallergic irritability of the skin.

Allergic reactions to stings can be local or systemic. An LLR is defined as a swelling at the sting site exceeding 10 centimeters, developing from a few minutes to several hours after the event. LLRs located on the arms or legs can be very extensive and can last for days or even weeks, limiting daily activities and physical functioning. Sometimes LLRs are accompanied by lymph node enlargement, lymphangitis, and fever. The latter symptoms have to be differentiated from serum sickness or from infections that rarely occur in patients with an LLR because the bacteriostatic qualities of Hymenoptera venoms are believed to prevent the formation of abscesses and the occurrence of infectious lymphangitis as complications following an insect sting. LLRs resulting from a sting on the head, especially in the periorbital area, can be manifested by the swelling of the eyelids, which may be confused with angioedema, which is one of the manifestations of SAR.[12,13] Largely, LLRs are mild and not dangerous, the important exception being LLRs in the oral region that may involve tongue or throat swelling and consequent upper airway obturation. The pathomechanism of an LLR involves IgE-dependent early and late-phase allergic reactions. In patients with an LLR, the risk of a SAR to a subsequent sting is low (5%–10%), being similar to the risk of a SAR in the general population.[7]

The spectrum of SARs, which are mostly IgE-mediated, is categorized by 2 classifications, each including 4 grades (TABLE 1). The classification by Mueller grades the major symptoms from mild to life-threatening events: I – urticaria, II – angioedema, III – respiratory disorders, and IV – anaphylactic shock. The other one, proposed by Ring and Messmer, characterizes the leading symptoms from the mildest (skin lesions), through not life-threatening cardiovascular reactions, followed by

TABLE 2 Global classification of mast-cell disorders and pathological mast-cell reactions[30]

Proposed term	Primary definition
mast-cell hyperplasia[a]	increased numbers of monoclonal MCs, an underlying disease usually found and no signs of MCA detectable, also seen in lymphoproliferative disorders and after administration of stem-cell factor
mastocytosis (± MCAS)	increased number of (mono)clonal MCs
systemic mastocytosis	SM criteria (3 minor or 1 major + 1 minor) met (SM variants, including MCL
cutaneous mastocytosis	MIS criteria fulfilled but SM criteria not met (CM variant)
mastocytoma	localized, benign, presumably (mono)clonal
mast-cell sarcoma	localized, aggressive (mono)clonal MCs
mast-cell activation syndrome	MCA by the criteria of diagnosis[30]
primary MCAS	CM, SM or "(mono)clonal MCAS"
secondary MCAS	atopy or other disorder associated with MCA
idiopathic MCAS	no reason for MCA found
myelomastocytic conditions	MC lineage involvement in myeloid neoplasms
tryptase AML	criteria for SM or MML not met, tryptase + blasts
myelomastocytic leukemia[b] (± MCAS)	MC lineage involvement in MDS/AML with at least 10% of cells being clonal MCs in bone marrow and/or peripheral blood smears and no evidence/criteria for SM

a MC hyperplasia is not an intrinsic MC disorder but is a reactive state that can be seen in a wide variety of conditions, and in many instances, the clinical significance and mechanisms of MC expansion remain unclear.
b MML has not yet been included in the official World Health Organization classification, although the condition is clearly defined by criteria, can clearly be discriminated from MCL, and is of clinical significance because of a poor prognosis of these patients (similar to MCL but worse than other AML and MDS because of drug resistance).

Abbreviations: AML, acute myeloid leukemia; CM, cutaneous mastocytosis; MCA, mast-cell activation; MCAS, mast-cell activation syndrome; MCL, mast-cell leukemia; MC, mast cell; MDS, myelodysplastic syndrome; MIS, mastocytosis in the skin; MML, myelomastocytic leukemia; SM, systemic mastocytosis

anaphylactic shock, up to cardiac arrest. Most systemic reactions begin within 30 minutes after a sting. Usually, the sooner such a reaction occurs, the more severe it is. Typically, SAR symptoms subside within a few hours, but in the case of 2-phase anaphylaxis, a relapse of symptoms is possible after 6 to 11 hours in 5% of the affected individuals.[14] Hypotension accompanying a SAR is a predictive factor for 2-phase anaphylaxis.

The most severe and life-threatening scenario of HVA involves cardiovascular symptoms, for which a number of pathogenic factors can be responsible, including hypotension due to the hypovolemic shock, hypoxia, and the cardiotoxicity of mast-cell mediators released in the course of IgE-mediated reactions. Cardiovascular HVA symptoms include acute atrial flutter, atrial and ventricular fibrillation, and acute coronary syndrome in the form of myocardial infarction. Another cardiac condition that results from the concurrence of acute coronary syndromes with mastocyte activation induced by IgE (but also by non-IgE) hypersensitivity agents is Kounis syndrome.[15-17] Patients manifesting type I of Kounis syndrome have normal coronary arteries without predisposing factors for coronary artery disease. In such patients, an acute allergic challenge induces a coronary artery spasm with normal cardiac enzyme or troponin levels or a coronary spasm progressing to acute myocardial infarction with elevated cardiac enzyme and troponin levels. Patients manifesting type II of Kounis syndrome have coexisting atheromatous coronary disease. In such individuals, an acute allergic episode can induce plaque erosion or rupture manifesting as an acute myocardial infarction. Type III of Kounis syndrome occurs in patients with coronary disease after coronary stent implantation. Finally, the classic cardiac complication due to an insect sting is takotsubo cardiomyopathy, a nonischemic, transient, reversible left ventricular dysfunction, also known as broken heart syndrome or stress cardiomyopathy.[18]

Apart from the general dangers associated with an insect sting, there is a specific one concerning pregnant women. An insect sting can cause uterine contraction, which may result in a spontaneous abortion.

The symptomatology of nonallergic reactions to insect stings, both unusual and toxic symptoms, is presented in TABLE 2. The majority of reported unusual reactions are of neurological origin and include polyradiculomyelitis with tetraparesis (as in Guillain–Barré syndrome), epileptic cramps, extrapyramidal symptoms, and ischemic episodes with permanent central nervous damage.[12,19]

Patients with Hymenoptera-venom allergy at high risk of a severe allergic reaction It is of great clinical importance to identify the risk factors that may predispose HVA individuals to develop SARs to a subsequent field sting. The following factors have been proposed as descriptive of this group: a history of a previous SAR (grade III or IV), concomitant cardiovascular diseases, treatment with

TABLE 3 Symptomatology of other than anaphylaxis reactions to insect stings[13,19]

Type of reaction	Symptomatology
unusual reaction may accompany local or systemic allergic reactions occur within few hours to few days after the sting	cardiac symptoms: acute coronary syndromes, cardiomyopathy, cardiac rythm disorders neurological symptoms of unknown origin: stroke, Guillain–Barré syndrome, neuritis, demyelination syndromes, myasthenia gravis, myelo- and polyradiculopathy, epilepsy, psychosis others: nephrotic syndrome, Schönlein–Henoch purpura, serum sickness, soft tissue necrosis
systemic toxic reaction occur after multiple stings	Potentially fatal: in adults, a fatal dose is equal to 800 bee stings; a high dose of venom toxins may cause multiple organ failure or other symptoms such as: weakness, vomitus, diarrhea, wheezing, pulmonary edema, psychosis, visual impairment, hemolysis, rhabdomyolysis, hemoglobinuria with renal failure.
eye ball insect sting	Symptoms range from mild conjunctivitis, anterior uveitis, corneal disorders, to sudden loss of vision; local damage caused by the stinger retained in the cornea can be clinically associated with severe conjunctival injection, chemosis, marked corneal edema, and hyphema. Subsequently, partially dislocated lens, lens abscess, partial iris atrophy, cataract formation, and optic neuropathy have been noted. In the case of eyeball penetration, the allergic local allergic reaction may appear. The anterior chamber-associated immune deviation may prevent anaphylaxis and late immunological answer reaction.

β-blockers and angiotensin-converting enzyme inhibitors (ACEIs), elevated bsT levels, mastocyte activation syndrome (including mastocytosis), and older age.

The major predictive factor determining the possibility of a subsequent SAR to a sting is the severity of the previous reactions: the more severe the previous reaction, the greater the risk of a subsequent reaction being of similar or higher severity. This correlation is illustrated by data from observational studies: the risk of a recurrence of severe systemic symptoms after a field sting in persons with SAR I and II ranges from 20% to 40%, while in patients with SAR III and IV, it is as high as 60% for up to 20 years of follow-up.[20]

Cardiovascular diseases are also recognized as an important factor increasing the risk of severe anaphylaxis after a sting. The causative role for this mechanism is attributed to mastocyte, which is the key effector cell in anaphylaxis. Considering an increase in the density of mastocytes in the intima and adventitia of the arterial wall in patients with ischemic heart disease (IHD), a high concentration of mastocyte mediators in such a strategic place heightens the risk of a severe reaction to an allergen.[21,22] Increased numbers of mastocytes that pose a risk of potentially severe reactions to allergens concern not only patients with IHD, but also those with other cardiac diseases, such as aortic valve stenosis (in the calcified areas of human stenotic aortic valves).[23] A negative effect of cardiovascular diseases on the course of anaphylaxis is proved by the postmortem analyses of patients with HVA who died from anaphylaxis. A study analyzing 29 patients who died following an insect sting found that most of the patients had preexisting cardiovascular or lung diseases; among 12 individuals subjected to autopsy, IHD was found in 10 and cardiomyopathies in 7 (some patients had comorbidities).[24]

The course of HVA-induced anaphylaxis may become more severe with the use of β-blockers and ACEIs, which are common in the treatment of hypertension, IHD, and heart failure. β-blockers are perceived as drugs that may aggravate cardiovascular manifestation and inhibit the efficiency of adrenaline used in the standard management of anaphylaxis.[25] In turn, ACEIs may deepen hypotonia occurring in anaphylaxis through increasing the concentration of bradykinin (by inhibiting its degradation by ACEIs) as well as through hindering the compensatory vasoconstriction response induced by the renin–angiotensin system. The negative effect of ACEIs on the severity of anaphylactic reactions (potentialized by the concurrent use of β-blockers) has been confirmed by clinical and experimental studies.[26-29] A multicenter study conducted in a group of 962 HVA patients suggested that the use of ACEIs constitutes a risk of a severe reaction to an insect sting.[28]

Patients with elevated bsT level (>11.4 ng/ml) have more severe (mostly cardiovascular) symptoms and a higher risk of the occurrence of HVA symptoms after subsequent stings than those with normal bsT levels.[8-10,28] This group includes mostly patients with ISM with and without skin lesions, patients with other forms of SM (the World Health Organization classification defines 7 variants of SM; **TABLE 3**), and those with monoclonal mastocyte activation syndrome (MMAS).[30] MMAS, also known as the primary MC activation syndrome (MCAS) or clonal MC activation disorder, is diagnosed in patients with unexplained or recurrent anaphylaxis without skin lesions who do not fulfill the criteria for SM, have documented *KIT*-mutated clonal mastocytes, and usually express CD25 on bone-marrow mastocytes.[10] A remarkable association between elevated bsT levels and the occurrence of cardiovascular symptoms in HVA patients does not only suggest a higher risk of an anaphylactic reaction to a subsequent sting

in HVA patients with mastocytosis but also, in consequence, constitutes an obligatory indication for tryptase tests and diagnostic workup for primary mast-cell disorders in all HVA patients who present with cardiovascular symptoms and hypotonia after a sting. However, it must be stressed that in light of the recent reports, mastocyte disorders may also be suspected in patients presenting with a SAR with hypotension and showing no skin symptoms (urticaria, angioedema) irrespective of tryptase levels.[31,32] In contrast, in patients with extremely high tryptase levels (above 191 ng/ml) and patients with an aggressive form of SM, severe systemic HVA symptoms are rare.

Elevated serum tryptase levels could be a risk factor for more severe systemic reactions and a higher mortality rate due to HVA in elderly people.[33] A correlation between a significant increase in bsT levels and aging has been documented. The reason for this phenomenon is yet unknown. Beside mastocytosis, the possible causes of higher bsT levels also include other disease states associated with older age such as acute myelocytic leukemia, myelodysplastic syndromes, hypereosinophilic syndrome associated with the *FLP1L1-PDGFRA* mutation, or renal insufficiency.[34]

Standard diagnostic procedures in patients with a suspicion of Hymenoptera-venom allergy Diagnostic tests for HVA are limited to patients with a history of a systemic reaction to the Hymenoptera sting. There is no other indication for the diagnostic workup for HVA. Its objectives are to: 1) verify the reaction grade and make an objective assessment of symptoms (medical history, tryptase levels); 2) identify the species that caused the symptoms; 3) determine the IgE-mediated pathomechanism of the reaction; and 4) define additional risk factors.

A carefully taken medical history is most important for the correct diagnosis of HVA. It is recommended to verify the anaphylactic origin of the sting reaction by the measurement of serum tryptase levels. To do that, blood volume of about 2 ml should be collected within 15 minutes to 3 hours following the onset of symptoms. After clotting, the sample must be centrifuged and stored at –20°C. Another blood sample should be taken again for the measurement of bsT levels after at least a few hours following the resolution of symptoms. Higher tryptase levels measured immediately after the sting as compared with bsT levels confirm anaphylaxis. High bsT levels are a risk factor for an SAR to an insect sting in the future. As mentioned above, in these patients, diagnostic procedures for mastocytosis should be performed in reference centers (bone marrow study, *KIT*-mutation analysis).

The aim of diagnostic procedures is to either demonstrate or exclude the presence of specific IgE to bee or vespid venoms by skin testing and serum-specific IgE tests, optimally after 3 to 6 weeks following the occurrence of an SAR. Testing is performed by skin prick tests with the allergen concentration at a range from 100 to 300 µg/ml. In the case of negative results, intradermal tests are performed (venom allergen solution [0.02 ml] with increasing concentrations from 0.001 to 1.0 µg/ml).[35] Venom skin tests are the most sensitive for the diagnosis of HVA. Serum-specific IgE tests should be performed using the most sensitive methods. Depending on a country, the diagnosis of HVA is an outpatient or inpatient procedure.

IgE-negative patients (both negative vsIgE and skin test results) constitute less than 2% of individuals reporting a history of allergic symptoms following a Hymenoptera sting. In such cases, the in vitro basophil activation test (BAT) is recommended, which is a flow cytometry-based functional assay that assesses the degree of cell activation after exposure to a certain concentration of venom. Basophils are identified by specific markers ($CCR3^+/CD3^-$, $CD123^+/HLA\text{-}DR^-$ and $IgE^+/CD203c^+$), and their activation is measured by means of monoclonal antibodies coupled to specific fluorochromes. In HVA, both specific surface activation markers CD203c and CD63 were found to have similar kinetics with the maximum expression detected after 20 minutes of allergen stimulation.[36] The first BATs performed with recombinant allergens represent an additional step forward in developing highly sensitive in vitro tests for a specific diagnosis of HVA.[37] BAT is performed only in specialized medical centers.

A common problem with an in vitro diagnosis of HVA is encountered in patients with double positive test results for bee (HBV) and wasp venom (VV), who constitute approximately 40% to 50% of all HVA cases.[38] Sometimes, this double positivity reflects true double sensitization to both HBV and VV. More often, however, it is accounted for by "false double sensitization", which is clinically irrelevant and can be based on the presence of homologous allergens both in HBV and VV (hialuronidase, dipeptylpeptydase, vitellogenin). Another cause of "false double sensitization" may be the presence of IgE antibodies directed against cross-reactive carbohydrate determinants, which are glycol-epitopes of the allergens. In this case, IgE antibodies are directed against an α-1,3-linked fucose residue of the N-glycan core found in insects and plants.[39] New diagnostic methods based on the evaluation of IgE antibodies against individual allergenic molecules of venom (component-resolved diagnosis) have led to a significant advance in distinguishing true double sensitization from irrelevant cross-reactivity. The currently available venom allergenic components, Api m1, Ves v 1, and Ves v 5, allow for a positive diagnosis of HV-allergic patients with the accuracy of 95% for VV allergy and 63% for BV allergy. Api m 3 and Api m 10 allergenic components are expected on the market soon, which should raise the sensitivity of BV diagnosis to 87.5%.[40,41]

TABLE 4 Indications for venom immunotherapy according to the European and American guidelines[35,48]

Type of reaction in adults	Diagnostic tests (skin tests and/or IgE)	Decision regarding venom immunotherapy
respiratory and/or cardiovascular symptoms – III /IV grade according to the Mueller classification	positive	yes
	negative	no
urticaria/edema – I/II if risk factors or reduced quality of life is present	positive	yes (European); yes >16 year olds (United States)
	negative	no
large local	positive or negative	usually no[a]
unusual reaction	positive or negative	no

a patients with frequent and unavoidable stings resulting in repeated large local reactions may benefit from venom immunotherapy (United States)

TABLE 5 Relative and absolute contraindications to venom immunotherapy[50]

relative contraindications	asthma partially controlled
	autoimmune disorders in remission
	malignant neoplasia(s)
	angiotensin-converting enzyme inhibitors
	children 2–5 years of age
	human immunodeficiency virus infection (stages A, B) – $CD4^+$ >200/µl
	psychiatric and/or mental disorders
	chronic infections
	immunodeficiencies
	use of immunosuppressive drugs
absolute contraindications	asthma uncontrolled
	autoimmune disorders in active forms (nonresponding to treatment)
	pregnancy: initiation of venom immunotherapy is prohibited, while maintenance course is allowed
	children <2 years of age
	acquired immune deficiency syndrome

How to treat allergic reactions to field stings? Medical management of allergic symptoms after a sting depends on their severity. In the case of LLRs, topical therapy with a corticosteroid ointment combined with a moist dressing (applied 2–3 times daily) is recommended. For a prominent LLR, an H_1-antyhistamine and oral corticosteroids may be necessary. In rare cases of an LLR in the oral cavity that involve local swelling, aggressive treatment (as in systemic reactions) is required. In severe SARs, it is crucial to start an intervention as soon as possible. In the case of anaphylaxis, adrenaline is a life-saving treatment. When administered intramuscularly into the anterolateral part of the quadriceps muscle, it reaches the highest blood concentration after 8 minutes. Hence, this site is recommended for adrenaline application in all age groups.[42] There are no absolute contraindications for adrenaline administration during anaphylaxis. As additional measures, the patient should be laid flat with legs raised as a protection from death due to empty superior vena cava/empty ventricle syndrome, oxygen should be given (flow, 6–10 l/min) and intravenous fluids (10 ml/kg within 10 minutes) should be administered. Other medications (antihistamines, systemic corticosteroids, short-acting β_2-agonists) are the second-line treatment in anaphylaxis.[42,43]

All individuals with a past history of an anaphylactic reaction should be instructed in the use of and equipped with an anaphylactic kit (including adrenaline autoinjector), which they should always keep handy. They should also be referred to an allergy specialist.

Who requires venom immunotherapy? The only causative treatment of HVA is venom immunotherapy (VIT). This treatment is very effective as it reduces the risk of a recurrent SAR to about 5% in patients allergic to wasp venom and to 10% to 20% in those allergic to bee venom.[44] VIT also significantly improves the quality of life in venom-treated individuals.[45,46] VIT is the treatment of choice in patients fulfilling both clinical and immunological criteria: a severe generalized reaction to sting in the past medical history with respiratory or circulatory symptoms or both (grade III–IV according to Mueller) and the presence of vsIgE-antibodies to the venom of the responsible Hymenoptera species (any positive result of skin prick tests or intradermal tests or vsIgE, or

a combination thereof). According to the European Academy of Allergy and Clinical Immunology (EACCI) and the American Academy of Allergy Asthma and Immunology guidelines, VIT can be also considered in adult individuals with moderate allergic symptoms (grade I–II according to Mueller) with risk factors or impaired quality of life due to HVA (TABLE 4).[47,48]

VIT is not recommended in patients with unusual, toxic, and atypical reactions.[47,48] Moreover, it is not recommended in patients with extensive local reactions either, although in the United States, a pilot study on selected cases of desensitization of patients with this type of a reaction was published.[49] Other current contraindications to VIT according to the 2015 EAACI guidelines are more flexible nowadays than in the past (TABLE 5).[50]

There are 2 steps of the VIT procedure: the initial (up-dosing) phase of immunotherapy with aqueous venom extracts and the maintenance phase with aqueous or depot venom extract. The initial phase of VIT may be performed according to 4 protocols which differ with respect to the time over which the maintenance dose is reached: slow (16–20 weeks); modified rush (6–8 weeks); rush (2–3 days), and ultra-rush (3.5 hours). The standard maintenance dose is equal to 100 μg administered at scheduled intervals of 4 to 12 weeks. The maintenance dose of venom extract should be increased to 200 μg in bee keepers, in patients who did not tolerate the insect sting at a dose of 100 μg, and in subjects with systemic side effects during the maintenance phase of VIT.

In patients with confirmed double sensitization, VIT with extracts of both wasp and bee venom is recommended. VIT should be continued for 3 to 5 years. After minimum 3 years of VIT, preferably after 5 years of VIT, a decision to stop VIT should be considered. Long-term protection after termination of VIT is established in patients treated longer than 3 years. Lifelong VIT is recommended in patients with mastocytosis.[48]

Although VIT is very effective, in a few percent of HVA patients, there is a possibility of the treatment's failure, the consequence of which may be recurrence of severe systemic reactions to a subsequent sting. The identified factors believed to be responsible for VIT failure include older age, coexistence of cardiovascular or pulmonary diseases, elevated bsT levels, mastocytosis, MC-related diseases, and allergic systemic reaction to venom injections. Currently, there are no laboratory tests that could confirm the efficacy of VIT. Good tolerance of filed sting or sting challenge with an insect may confirm protection achieved in the course of VIT. Sting challenges should be performed only in specialized centers according to the existing guidelines of allergy societies.[51,52] The new possibility to assess VIT efficacy in the future may be provided by gene expression analyses.[53,54]

VIT protects almost all HVA patients from future allergic symptoms. A major problem is the underdiagnosis and undertreatment of HVA patients who miss allergy specialist consultation. Medical doctors of all specialties must be informed about HVA and the possibility of its causal treatment. A Polish study on the current practice in HVA treatment by allergologists shows a high congruence with the EAACI guidelines.[55]

REFERENCES

1 Bilo MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. Clin Exp Allergy. 2009; 39: 1467-1476.

2 Spillner E, Blank S, Jakob T. Hymenoptera allergens: from venom to "venome". Frontiers in Immunol. 2014; 5: 1-7.

3 Sturm GJ, Kranzelbinder B, Schuster Ch, et al. Sensitization to Hymenoptera venoms is common, but systemic sting reactions are rare. J Allergy Clin Immunol. 2014; 133: 1635-1643.

4 Annila IT, Annila PA, Mörsky P. Risk assessment in determining systemic reactivity to honeybee stings in beekeepers. Ann Allergy Asthma Immunol. 1997; 78: 473-477.

5 Richter AG, Nightingale P, Huissoon AP, et al. Risk factors for systemic reactions to bee venom in British beekeepers. Ann Allergy Asthma Immunol. 2011; 106: 159 -116.

6 Nittner-Marszalska M, Liebhart J, Liebhart E, et al. Prevalence of Hymenoptera venom allergy and its immunological markers current in adults in Poland. Med Sci Monit. 2004; 10: 324-329.

7 Severino M, Bonadonna P, Passalacqua G. Large local reactions from stinging insects: from epidemiology to management. Curr Opin Allergy Clin Immunol. 2009; 9: 334-337.

8 Górska A, Niedoszytko M, Lange M, et al. Risk factors for anaphylaxis in patients with mastocytosis. Pol Arch Med Wewn. 2015; 125: 46-53.

9 Bonadonna P, Perbellini O, Passalacqua G, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. J Allergy Clin Immunol. 2009; 123; 680-681.

10 Bonadonna P, Bonifacio M, Lombardo C, Zanotti R. Hymenoptera Anaphylaxis and C-kit Mutations: An Unexpected Association. Curr Allergy Asthma Rep. 2015; 15: 550-557.

11 Van Anrooij, van der Veer E, de Monchy JG, et al. Higher mast cell load decreases the risk of Hymenoptera venom-induced anaphylaxis in patients with mastocytosis. J Allergy Clin Immunol. 2013; 132: 125-130.

12 Mueller UR. Insect sting allergy. Clinical picture, diagnosis and treatment. Gustav Fischer Stuttgart New York. 1990; 35-46.

13 Cichocka-Jarosz E, Weglarz M, Romanowska-Dixon B. Hymenoptera stings in eyeball-clinical symptoms, patomechanism and treatment. Klin Oczna. 2009; 111: 80-83.

14 Lee S, Bellolio MF, Hess EP, et al. Onset and Predictors of Biphasic Anaphylactic Reactions: A Systematic Review and Meta-analysis. J Allergy Clin Immunol Pract. 2015; 3: 408-416.

15 Kounis NG. Hymenoptera stings, anaphylactic shock and the Kounis syndrome. N Am J Med Sci. 2013; 5: 159-160.

16 Nittner-Marszalska M, Kopeć A, Biegus M, et al. Non-ST segment elevation myocardial infarction after multiple bee stings. A case of "delayed" Kounis II syndrome? Int J Cardiol. 2013; 166: e62-e65.

17 Ridolo E, Olivieri E, Montagni M, et al. Type I variant of Kounis syndrome secondary to wasp sting. Ann Allergy Asthma Immunol. 2012; 109: 79-81.

18 Mert GÖ, Biteker FS, Mert KU, et al. Takotsubo cardiomyopathy or Kounis syndrome or both? Int J Cardiol. 2015; 179: 16.

19 Mingomataj EC, Bakiri AH, Ibranji AA, Sturm G. Unusual reactions to Hymenoptera stings: what should we keep in mind? Clinic Rev Allerg Immunol. 2014; 47: 91-99.

20 Bilo MB. Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment. Allergy. 2011; 66; 35-37.

21 Kaartinen M, Penttila A, Kovanen PT. Mast cell of two types differing in neutral protease composition in the human aortic intima. Demonstration of tryptase- and tryptase/chymase containing cells in normal intimas, fatty streaks and the shoulder region of atheromas. Arterioscler Thromb. 1995; 14: 966-972.

22 Atkinson JB, Harlan CW, Virmani R. The association of mast cells and atherosclerosis: a morphologic study of early atherosclerotic lesions in young people. Hum Pathol. 1994; 25: 154-159.

23 Wypasek E, Natorska J, Grudzień G, et al. Mast Cells in human stenotic aortic valves are associated with the severity of stenosis. Inflammation. 2012; 36: 449-456.

24 Saswary T, Muller U. fatalities from insect stings on Switzerland 1978 to 1987. Schweiz Med Wochenschr. 1994; 124: 1887-1894.

25 Muller UR, Haeberli G. Use of beta-blockers during immunotherapy for Hymenoptera venom allergy. J Allergy Clin Immunol. 2005; 115: 606-610.

26 Ober AI, MacLean JA, Hannaway PJ. Life-threatening anaphylaxis to venom immunotherapy in a patient taking an angiotensin-converting enzyme inhibitor. J Allergy Clin Immunol. 2003; 112: 1008-1009.

27 Stumpf JL, Shehab N, Patel AC. Safety of Angiotensin-converting enzyme inhibitors in patients with insect venom allergies. Ann Pharmacother. 2006; 4: 699-703.

28 Ruëff F, Przybilla B, Biló MB, et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase-a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. J Allergy Clin Immunol. 2009; 124: 1047-1054.

29 Nassiri M, Babina M, Dolle S, et al. Ramipril and metoprolol intake aggravate human and murine anaphylaxis: evidence for direct mast cell priming. J Allergy Clin Immunol. 2015; 135: 491-499.

30 Valent P, Akin C, Arock M. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol. 2012; 157: 215-225.

31 Alvarez-Twose I, González-de-Olano D, Sánchez-Muñoz L. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. Int Arch Allergy Immunol. 2012; 157: 275-280.

32 Zanotti R, Lombardo C, Passalacqua G, et al. Clonal mast cell disorders in patients with severe Hymenoptera venom allergy and normal serum tryptase levels. J Allergy Clin Immunol. 2015; 136: 135-139.

33 Guenova E, Volz T, Eichner M, et al. Basal serum tryptase as risk assessment for severe Hymenoptera sting reactions in elderly. Allergy. 2010; 65: 919-923.

34 Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009; 114: 937-951.

35 Bonifazi F, Jutel M, Biló BM, et al. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. Allergy. 2005; 60: 1459-1470.

36 Hoffmann HJ, Santos AF, Mayorga C, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. Allergy. 2015. [E-pub ahead of print].

37 Balzer L, Pennino D, Blank S, et al. Basophil activation test using recombinant allergens: highly specific diagnostic method complementing routine tests in wasp venom allergy. PLoS One. 2014; 9: e108619.

38 Spillner E. Blank S, Jakob T. Perspectives, pitttfalls and current status of molecular diagnosis in insect venom allergy. Allergy J. 2012; 21: 249-256.

39 Jappe U, Raulf-Heimsoth M, Hoffmann M, at al. Hymenoptera venom allergy diagnosis improved by screening for cross-reactive carbohydrate determinants and reciprocal inhibition. Allergy. 2006; 61: 1220-1229.

40 Eberlein B, Krischan L, Darsow U, et al. Double positivity to bee and wasp venom: improved diagnostic procedure by recombinant allergen-based IgE testing and basophil activation test including data about cross-reactive carbohydrate determinants. J Allergy Clin Immunol. 2012; 130: 155-161.

41 Ebo DG, Van Vaerenbergh M, de Graaf DC, et al. In vitro diagnosis of Hymenoptera venom allergy and further development of component resolved diagnostics. Expert Rev Clin Immunol. 2014; 10: 375-378.

42 Simons FE, Ardusso LR, Bilo MB, et al. World Allergy Organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J. 2011; 4: 13-37.

43 Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014; 69: 1026-1045.

44 Boyle RJ, Elremeli M, Hockenhull J, et al. Venom immunotherapy for preventing allergic reactions to insect stings. Cochrane Database Syst Rev. 2012; 17; 10:CD008838.

45 Oude Elberink JN, De Monchy JG, Van Der Heide S, et al. Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. J Allergy Clin Immunol. 2002; 110: 174-182.

46 Cichocka-Jarosz E, Brzyski P, Tobiasz-Adamczyk B, et al. Development of children's hymenoptera venom allergy quality of life scale (CHVAQoLS). Clin Transl Allergy. 2013; 3: 25.

47 Bonifazi F, Jutel M, Biló BM, et al. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. Allergy. 2005; 60: 1459-1470.

48 Golden DB, Moffitt J, Nicklas R, et al. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma & Immunology (AAAAI); American College of Allergy, Asthma & Immunology (ACAAI); Joint Council of Allergy, Asthma and Immunology. Stinging insect hypersensitivity: a practice parameter update 2011. J Allergy Clin Immunol. 2011; 127: 852-854.e1-23.

49 Golden DB, Kelly D, Hamilton RG, Craig TJ. Venom immunotherapy reduces large localreactions to insect stings. J Allergy Clin Immunol. 2009; 123: 1371-1375.

50 Pitsios C, Demoly P, Bilò MB, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy. 2015; 70: 897-909.

51 Ruëff F, Przybilla B, Müller U, Mosbech H. The sting challenge test in Hymenoptera venom allergy. Position paper of the Subcommittee on Insect Venom Allergy of the European Academy of Allergology and Clinical Immunology. Allergy. 1996; 51: 216-225.

52 Nittner-Marszalska M, Bant A, Bodzenta-Lukaszyk A, et al. [Insect-sting challenge in patients with hymenoptera venom allergy Polish Allergy Society Expert Group Position Paper]. Alergia Astma Immunologia. 2010; 15: 134-138. Polish.

53 Niedoszytko M, Bruinenberg M, de Monchy J, et al. Changes in gene expression caused by insect venom immunotherapy responsible for the long-term protection of insect venom-allergic patients. Ann Allergy Asthma Immunol. 2011; 106: 502-510.

54 Niedoszytko M, Gruchała-Niedoszytko M, Jassem E. Gene expression analysis in allergology: the prediction of Hymenoptera venom allergy severity and treatment efficacy. Clin Transl Allergy. 2013; 3; 35.

55 Cichocka-Jarosz E, Diwakar L, Brzyski P, et al. Congruence of the current practices in Hymenoptera venom allergic patients in Poland with EAACI guidelines. Arch Med Sci. 2011; 7: 832-839.

ARTYKUŁ POGLĄDOWY

Alergia na jad owadów – kluczowe informacje dla klinicystów

Marita Nittner-Marszalska[1], Ewa Cichocka-Jarosz[2]

1 Klinika Chorób Wewnętrznych, Geriatrii i Alergologii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu, Wrocław
2 Klinika Chorób Dzieci, Katedra Pediatrii, Uniwersytet Jagielloński, Collegium Medicum, Kraków

SŁOWA KLUCZOWE

alergia na jad owadów, immunoterapia alergenowa na jad owadów, tryptaza

STRESZCZENIE

W ciągu życia 94,5% ludzi doznaje użądlenia przez osy, pszczoły, szerszenie lub trzmiele (rząd: błonkoskrzydłe). W jego wyniku u większości ludzi występuje typowy odczyn miejscowy, u 5–15% pojawia się alergiczna reakcja miejscowa, u 3–8,9% alergiczna reakcja systemowa (*systemic allergic reaction* – SAR), która u ~10% z nich stanowi potencjalnie zagrożenie życia. Głównymi objawami w łagodnych postaciach alergii na jad owadów (Hymenoptera-*venom allergy* – HVA) są pokrzywka i obrzęk naczynioruchowy (odpowiednio I° i II° wg klasyfikacji Muellera). Ciężkie odczyny alergiczne kwalifikowane są do III° (objawy ze strony układu oddechowego) i IV° (objawy sercowo-naczyniowe). Rzadkimi manifestacjami HVA są zespół Kounisa i kardiomiopatia *takotsubo*. Wszyscy pacjenci po przebytej SAR wymagają diagnostyki alergologicznej standardowej (testy skórne, IgE, poziom tryptazy) lub poszerzonej (diagnostyka komponentowa, test aktywacji bazofilów). Wszystkie osoby z ciężkimi objawami systemowymi (spadek ciśnienia, zaburzenia świadomości) wymagają diagnostyki w kierunku mastocytozy. Dodatkowo wykazano związek pomiędzy ciężkością objawów HVA a stosowaniem inhibitorów konwertazy angiotensyny (*angiotensin-converting enzyme inhibitors* – ACEI). Podobne, choć mniej udokumentowane są zastrzeżenia dotyczące stosowania β-blokerów. Chorzy z HVA po przebytej SAR są potencjalnymi kandydatami do immunoterapii alergenowej (*venom immunotherapy* – VIT), która jest skuteczna u 80–100% leczonych przez 3–5 lat. Zwiększone ryzyko niepowodzenia tej terapii wykazano u chorych z systemową mastocytozą oraz u pacjentów leczonych ACEI. W wybranych grupach chorych (pszczelarze, osoby reagujące systemowo na użądlenia w trakcie VIT dawką standardową oraz osoby z reakcją systemową na kolejne dawki podtrzymujące VIT) zalecana jest dwukrotnie wyższa niż standardowo dawka podtrzymująca. Wskazania, przeciwwskazania, wybór schematu leczenia oraz wysokość dawek szczepionki są regulowane przez wytyczne międzynarodowych towarzystw alergologicznych.

Adres do korespondencji:
dr hab. med. Ewa Cichocka-Jarosz, Klinika Chorób Dzieci, Katedra Pediatrii, Uniwersytet Jagielloński, Collegium Medicum, ul. Wielicka 265, 30-663 Kraków, tel.: 12 658 20 11, fax: 12 658 44 46, e-mail: mijarosz@cyf-kr.edu.pl
Praca wpłynęła: 04.08.2015.
Przyjęta do druku: 31.08.2015.
Publikacja *online*: 03.09.2015.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2015; 125 (12): 929-937