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Ewa Cichocka-Jarosz

HYMENOPTERA VENOM ALLERGY IN HUMANS

Abstract: Hymenoptera *venom allergy in humans*
Reactions to *Hymenoptera* stings may appear as local or systemic responses. According to European data, the incidence of systemic reactions to *Hymenoptera* stings in the general population is 0.3–7.5%, with the value being 0.3-0.8% in children and 14–43% in beekeepers. The most common systemic allergic (anaphylactic) reactions are caused by honeybees (*Apis mellifera*), and certain species of wasps in the family *Vespidae*. Severe generalized immediate-type allergic (anaphylactic) reactions to insect stings are of the highest clinical importance. They affect skin, gastrointestinal tract, respiratory and cardiovascular system. The classification of severity of anaphylactic reaction following insect stings is based on the 4-grade Mueller scale.

Crucial in patomechanism of anaphylaxis are specific IgE antibodies directed against the components of the venom, which mediate the activation of mast cells, the main effector cells of anaphylaxis. Therapeutic management in insect venom allergy should be considered in the context of prophylaxis, intervention in case symptoms develop, prevention in the form of venom specific immunotherapy (VIT). There are two steps of VIT 1. Initial dose venom immunotherapy (given according to four protocols which differ the time to reach the maintenance dose) 2. Maintenance dose VIT, usually equal 100 μg. Standard treatment time should span 3–5 years. The main mechanisms of immune tolerance that are initiated by VIT are associated with: 1. a decreased reactivity of effector cells, 2. expansion of T regulatory lymphocytes with IL-10 expression. Therapeutic effectiveness amounts to 90–100% in wasp venom allergy and approximately 80% in bee venom allergy.

Key words: allergy to *Hymenoptera* venom, venom allergy diagnosis, venom immunotherapy

EPIDEMIOLOGY AND NATURAL HISTORY OF VENOM ALLERGY

Methodology of epidemiological studies is based on:

a) cross-sectional investigational research,

b) evaluation of *in vivo* and *in vitro* tests confirming IgE-mediated venom allergy,

c) retrospective analysis of medical records, including emergency department visits, taking into consideration ICD diagnosis codes,

d) combination of the above methods.

In questionnaire-based epidemiological studies, 56.6–94.5% of adult responders (depending on climatic conditions) report at least one *Hymenoptera* sting. The incidence of insect venom allergy determined based on positive skin test results

and/or positive serum IgE determinations in adult population of individuals who do not manifest symptomatic reactions to stings is 9.3–28.7%, while in individuals with intense exposure to stings (beekeepers) it amounts to 30–60% [1]. In clinical assessment, reactions to stings may appear as local and systemic responses. According to European data, the incidence of systemic reactions in the general population is 0.3–7.5%, with the value being 0.3–0.8% in children and 14–43% in beekeepers [2]. In children, the majority of systemic reactions limited to skin only tend to disappear with age. Deaths due to systemic anaphylaxis following insect stings are rare (0.03–0.48 deaths per 1 million inhabitants per year) [3, 4]. To use an example, in the years 1990–2006, in Germany, 335 deaths were noted (an equivalent of 20 deaths per year), where the direct cause was an insect (a wasp, bee or hornet) sting. The world literature on the subject does not report a single death of a child following *Hymenoptera* stings. According to studies [5, 6] based on a retrospective analysis of medical records, including ICD diagnosis codes, and focusing on causes of anaphylaxis in children in Europe, insect stings occupy the second place after foods (with peanuts being the predominant causative factor), while in adult patients in Australia, *Hymenoptera* stings are the third most common cause of anaphylaxis after foods and medications [7, 8].

In Poland, two published epidemiological studies of insect venom allergy were carried out in the Lower Silesia region, each of them being a two-stage investigation. The first stage consisted of a questionnaire that was completed by a patient alone, while the second aimed at data objectivization through completing the same questionnaire while assisted by a physician and included a randomly selected group of patients who had previously responded positively to questions addressing allergic reactions to insect venom. The results of both studies were similar — in I part of study prevalence of sting reactions equals 20.7%, including large local reaction in 16%, while systemic reactions in 12.9% (according to Mueller grade as follows: 8.7% — grade I, 2.5% — grade II, 1.5% — grade III, 0.2% — grade IV). Authors reported a high degree of conformity between the prevalence of severe systemic reactions to stings as assessed by the patients and verified by the physicians, while the indices of prevalence of large local reactions and mild systemic reactions as assessed by the patients were overestimated [9, 10].

SOURCE OF ALLERGENS

The most common anaphylactic reactions are caused by honeybees (*Apis mellifera*), and certain species of wasps (US — yellow jacket) in the family *Vespidae* (particularly *Vespula vulgaris* and *V. germanica*). Anaphylaxis is only occasionally caused by other species of *Vespidae*, such as *Dolichovespula spp.*, hornets (US — yellow hornet, Latin — *Vespa crabro*) and bumblebees (*Bombus spp.*). The highest prevalence of bee venom allergy is noted in people with high exposure to stings — beekeepers, their family members, and those living nearby beehives [3].

The European and American nomenclature of particular insect species is divergent [2]. There are basic differences in the morphology of *Hymenoptera*, characteristic properties of their stings and composition of venom. The venomous stinger in *Hymenoptera* evolved from the egg-depositing apparatus. Up to 140 μg of venom is released per a single bee sting (usually 50 μg), and about 3 μg per a wasp sting. In bee stings, the stinger and venom apparatus remain in the skin and continue to release the venom afterward, while wasps can usually retract their stingers after stinging. The knowledge on venom composition and the structure of its allergens is the basis of appropriate diagnostic management and treatment of *Hymenoptera* venom allergy. In case of bees, venom is collected from the venom sac by electrical stimulation developed by Benton [11]. The method of obtaining wasp venom from natural sources is more difficult and consists in collecting venom sacs from individual insects after anesthetizing the entire nest followed by its freezing. After thawing, the stingers are removed from particular wasps to isolate venom sacs and extract venom [12]. The technique is employed due to safety reasons. Separation of venom components into particular specific gravity-dependent fractions is performed using classic chromatography [13]. Thanks to such methods, the structure and amino acid sequence of *Hymenoptera* venom components have been understood. Molecular biology methods allow for producing recombinant venom analogs (Protein Database, www.allergen.org). The systematic nomenclature of purified allergens constituting venom components is based on the Linnaean taxonomy abbreviations, while the Arabic numerals denote the chronology of their discovery. The procedure is in accordance with the recommendations of the Allergen Sub-Committee of the World Health Organization and International Union of Immunological Societies [14]. In view of their biological role, allergens are divides into major and minor, with the criterion of discrimination being the percentage of >50% of allergic individuals who test positive for specific IgE antibodies for a given venom component [15]. The most important major allergens of honey bee venom are phospholipase A_2 (*Api m1*), a cytotoxic enzyme, and hyaluronidase (*Api m2*), whose amino acid sequence is in 50% identical with wasp venom hyaluronidase. Another component, melittin (*Api m4*), which constitutes 50% of bee venom dry mass, is a minor allergen, but it manifests a potent cytotoxic activity. The principal components and major allergens of wasp venom include phospholipase A_1 (*Ves v1*), hyaluronidase (*Ves v2*) and antigen 5 (*Ves v5*). Additionally, the venom of both *Hymenoptera* species contain low molecular compounds (histamine, catecholamines) and peptides (bee venom — apamin, MCD peptide, tertiapin, cardiac peptide, wasp venom — mastoparan, kinins) with a locally high cytotoxic potential that may be extended in case of multiple stings. The known allergens constituting the components of bee and wasp venom are characterized in Table 1 [16].

Table 1

Overview of the identified *Apis melifera* and *Vespula vulgaris* venom allergens [16], modified. MW — molecular weight, CRP — carbohydrate-rich protein, DPP IV — dipeptidylpeptidase IV, DW — dry weight, MRJP — Major Royal Jelly Protein

Allergen	Common name/function	MW (kDa)	Potential N-glycolisation	% DW
Api m 1	Phospholipase A2	17	1	10–12%
Api m 2	Hyaluronidase	45	2	1–3%
Api m 3	Acid phosphatase	49	2–3	1%
Api m 4	Mellitin	3	0	50
Api m 5	Allergen C/DPP IV	100	5–7	1%
Api m 6	Cysteine-rich trypsin inhibitor	8	0	1–2
Api m 7	CUB serine protease	39	2–4	?
Api m 8	Carboxyl-esterase	70	4	?
Api m 9	Serine carboxy-peptidase			
Api m 10	Ikarapin-CRP	55	3	?
Api m 11.0.101	MRJP 8	65	6	?
Api m 11.01.201	MRJP 9	60	3	?
Api m 12	Vitellogenin	200	1	?
Ves V 1	Phospholipase A1	35	0	6–14
Ves v 2a	Hyaluronidase	42	2–4	1–3
Ves v 2b	Hyaluronidase	42	2	
Ves v 3	DPP IV	100	3	1
Ves v 4	CUB protease	42	2–4	?
Ves v 5	Antigen 5	25	0	5–10
Ves v 6	Vitellogenin	200	4	?

SYMPTOMATOLOGY OF INSECT STINGS REACTIONS

Exposure to *Hymenoptera* insects venom may cause both local and generalized reactions, including severe, life-threatening systemic hypersensitivity reactions. The phenomenon seems to be associated with several factors:

1. subcutaneous penetration of the allergen, resulting in its higher concentration *in situ*,
2. the number, allergic poly-sensitization and physical properties of venom allergens, the majority which are low molecular proteins that easily diffuse into the circulatory system,
3. chemical properties of venom components, the majority of which demonstrate enzymatic activity against cell membrane phospholipids, thus facilitating local toxic activity,
4. availability of mast cells, which are much more widely represented in the skin as compared to other tissues.

In practice, the highest clinical importance is characteristic of severe generalized allergic (anaphylactic) reactions. Their symptoms affect the skin, gastrointestinal tract, respiratory and cardiovascular system. The classification of anaphylactic reactions following insect stings is based on the 4-grade Mueller scale (Table 2) [2].

Table 2

Classification of systemic reaction to insect stings by Mueller [2]

Grade I	Generalized urticaria, itching, malaise, and anxiety
Grade II	Any of the above plus two or more of the following: angioedema, chest constriction, nausea, vomiting, diarrhea, abdominal pain, dizziness
Grade III	Any of the above plus two or more of the following: dyspnea, wheezing, stridor, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster
Grade IV	Any of the above plus two or more of the following: fall in blood pressure, collapse, loss of consciousness, incontinence, cyanosis

While assessing neurological symptoms understood as altered levels of consciousness, the Glasgow scale is employed. Various authors emphasize the possibility of the patient developing Kounis syndrome or in other words acute coronary syndrome as the effect of mediators (histamine, leukotriene C4, prostaglandin D_2) released from the coronary arteries mast cells in adults and children [17, 18]. Of lesser importance are symptoms other than anaphylactic, the symptomatology of which is presented in Table 3 [19].

Table 3

Symptomatology of other than anaphylaxis reactions to insect stings [19]

Type of reaction	Symptomatology
Local toxic reaction (normal)	Area of pain, redness and swelling <10 cm in diameter, lasting <24 hours and resolving spontaneously.
Large local reaction	Swelling >10 cm in diameter which persists for >24 hours. Even in case of very LLR's, they are treated as mild allergic reactions. May induce non-infectious lymphangitis. Only very rarely LLR's situated near the airways do cause clinically significant airway obstruction.
Unusual reaction	Occurs within few hours to few days after the sting. Usually: 1. neurological symptoms of unknown origin: Guillain-Barré syndrome, neuritis, epilepsy, psychosis. 2. others: nephrotic syndrome, Schönlein-Henoch purpura, serum sickness. May accompany local or systemic allergic reactions.
Systemic toxic reaction	Occurs after multiple stings. May be fatal. In children, a fatal dose is equal to 500 bee stings [2]. A high dose of venom toxins causes multiple organ failure. Typical symptoms: weakness, vomitus, diarrhea, wheezing, pulmonary edema. Psychosis, visual impairment, hemolysis, rhabdomyolysis, thrombocytopenia and hemoglobinuria with renal failure may be present.

PATHOMECHANISM OF HYMENOPTERA VENOM ANAPHYLAXIS

With respect to its pathogenesis, *Hymenoptera*-allergens anaphylaxis is a typical immediate-type allergic reaction. Specific IgE antibodies directed against the components of the venom mediate the activation of mast cells and basophils, effector cells of anaphylaxis, leading to the release of mediators that cause the acute manifestation of the disease. In the greatest majority of cases, a single sting is causative for the reaction. The acute reaction usually develops 10–30 minutes after the sting, although the latency might be shorter or longer. Dual reactions within a few hours may also occur.

Mast cells, the principal effector cells of anaphylaxis, differentiate from pluripotential CD34+ stem cells and their precursors demonstrate the ability to circulate with blood and home to all tissues except the brain tissue. The richest representation of mast cells is found in the skin and mucosa and submucosa of the respiratory and gastrointestinal systems. Based on different staining of intracellular granules, one can distinguish the population of MC_T mast cells that contain tryptase only and MC_{TC}, which contain — in addition to

tryptase — also another neutral serine protease — chymase, carboxypeptidase (a zinc-dependent metalloprotease) and G cathepsin. The division is concurrent with the functional differentiation of the homed stem cells into two groups: T lymphocyte-dependent mast cells (only tryptase is present in the cytoplasmic granules and among metabolites of arachidonic acid derivatives, C_4 leukotriene predominates over D_2 prostaglandin) and non-lymphocyte T-dependent mast cells (all proteases typical for mastocytes are represented in the granules and among metabolites of eicosanoids, D_2 prostaglandin predominates over C_4 leukotriene) [20, 21]. As a result of the IgE-dependent reaction, mediators are released from the granules (where they are stored in an active form) or synthesized *de novo (*from cell membrane phospholipids*),* similarly as cytokines, chemokines and growth factors. Preformed and synthesized *de novo* mediators play a crucial role in anaphylaxis and determine clinical symptoms of the early (usually occurring within 5–30 minutes) phase of the allergic reaction, such as swelling, increased vascular permeability and bronchial spasm. Cytokines, chemokines and growth factors determine the clinical presentation of the late phase (generally developing within 2–6 h) that is associated with chronic inflammation; they are of a lesser importance in anaphylaxis. Clinical symptoms evoked by the activity of mastocyte mediators mostly affect the organs where the pool of the homing mast cells is large. In diseases occurring with excessive proliferation of mast cells and an increase of their pool in the body (the so-called clonal mast cell disorders, such as mastocytosis), due to a large load of the released mediators, the anaphylactic reaction may be particularly violent and life-threatening.

Since 1987, tryptase has been recognized as a biomarker of the anaphylactic reaction to insect venom and mastocytosis, as mast cells constitute its practically only important source [22] — the tryptase content in mastocytes is 100–1000 times higher as compared to basophils, while the mediator is absent in the remaining cells. Human tryptase occurs in two forms — as non-active pro-α- and pro-β-tryptase and active, mature β-tryptase. The available methods of determining tryptase concentrations allow for detecting both the pro-form and the mature form. The majority of tryptase determined in body fluids of healthy individuals represents the constitutive, ever-present pro-α-tryptase and pro-β-tryptase, which are a marker of the entire mastocyte pool in the body that is useful in assessing clonal mastocyte disorders. On the other hand, concentrations levels of mature β-tryptase stored in mast cell granules increase in the course of anaphylaxis in consequence of mast cell degranulation, constituting a marker of their activation also *post mortem* [23]. Genes encoding both forms of tryptase and their location in humans are known: α tryptase — *TPSA1* gene (16p13.3), β tryptase — *TPSAB1* gene (16p13.3) [24]. Attempts have been also made to use PAF and PGD2 metabolites in studies on anaphylaxis as the main prostanoid that is released from mast cells in the course of IgE-dependent activation [25–28].

DIAGNOSIS OF *HYMENOPTERA* VENOM ALLERGY

Diagnostic management of *Hymenoptera* venom allergy is employed solely in patients with a history of the generalized anaphylactic reaction. Its objectives are to:

1. verify the reaction grade and objectivize the symptoms,
2. identify the species of the insect that triggered the symptoms,
3. determine the pathomechanism of the reaction,
4. define additional risk factors.

The first objective is achieved based on taking the medical history of the patient and analyzing medical records pertaining to the post-sting reaction. Identification of the insect and determination of the pathomechanism are implemented through studies *in vivo* and/or *in vitro*, which aim at demonstrating specific IgE to bee and wasp venom by skin testing and serum-specific IgE. Optimally, the diagnostic management should be performed twice: within several days following the sting and after 3–6 weeks after the systemic reaction [29, 30]. In practice, testing is more commonly done once and then the recommended timing is within 3–6 weeks following the sting. Testing is performed using skin pricks with the concentration range of 0.01–100 μg/ml. If the results of the above tests are negative, intradermal tests must absolutely be performed (0.02 ml volume of venom allergen solution with increasing concentration values from 0.001 to 1.0 μg/ml) [2, 31]. In view of their higher sensitivity, in some centers only intradermal tests are done, as they are believed to be decisive (the gold standard) in allergy to insect venom. Determinations of serum specific IgE should be performed employing the most sensitive methods, such as UniCAP or Immulite 2000, which are characterized by zero concentration detectability and their results, are expressed on a 6-grade scale [32]. In some patients who test positive both for wasp and bee venom, it is necessary to determine whether double positivity is caused by true sensitization to allergens characteristic of both *Hymenoptera* species. In the majority of patients, positivity for components of both venoms result from a cross-reaction to common carbohydrate determinants (CCD), which belong to plant and food panallergens. A considerable progress in diagnostic management of double sensitization has been achieved owing to recombinant allergens of major *rApi m1*, *rVes V1* and *rVes V5* [16, 33, 34]. The method for determining recombinant major allergens (ImmunoCAP, Phadia) is also available in Poland.

Non-standard diagnostic management of insect venom allergy that is offered only by a few centers is the basophil activation test (BAT) with flow-cytometric determination of the expression of the activation markers (CD63 and CD203) [35–37]. Reports have been published on a potential effectiveness of the test in the diagnostic management of reactions with negative results of venom specific IgE [38], as well as in monitoring insect venom immunotherapy [39–41] and in patients with mastocytosis [42, 43]. If the medical history of the patient

indicates severe life-threatening anaphylaxis following the insect sting, concomitant risk factors should be determined. To achieve this goal, the baseline tryptase (bsT) concentration should be determined as the marker of mastocyte pool in the body. Concentration values <10 μg/l are regarded normal. Concentration levels >11.4 μg/l indicate clonal mast cell disorders and considerably increase the risk of the patient developing life-threatening symptoms following the sting [44]. Concentration levels >20 μg/l are included among the diagnostic criteria of systemic mastocytosis [45]. In view of possible mastocytosis without concomitant skin lesions, in patients after life-threatening post-sting reactions, there is all the more reason for bsT determination [46]. Despite the fact that clonal mast cell disorders are a particularly rare disease entity in children, clinical assessment of the skin should always take into consideration *urticaria pigmentosa* [47]. Elevated bsT in children with severe urticaria pigmentosa-type lesions is a predictor of anaphylaxis severity after insect stings [48]. Risk factors for anaphylaxis due to *Hymenoptera* venom are presented in Table 4 [19]. The increasing role of bsT assessment in insect venom allergy is supported by studies of large cohorts of patients that indicate its usefulness both in diagnostic management and immunotherapy monitoring in these patients [28, 49–53].

Table 4

Risk factors for anaphylaxis due to Hymenoptera venom [19]

Risk of frequent exposure	— Beekeepers, their families and neighbors — Other professions, including: fruit and baked foods sellers foresters, gardeners, firefighters, farmers, construction workers, truck drivers — Intense outdoor activity
Elevated risk of severe anaphylaxis	— Prior epidode(s) of severe sting anaphylaxis (grade III and IV) — Age >40 — Cardiovascular disease — Asthma — Physical and mental stress — Certain drugs: β-blockers (including eye drops), ACE inhibitors — bsT conc. >11.4 μg/l (mastocytosis is not rare in such cases) — Cutaneous (urticaria pigmentosa) or systemic mastocytosis

Another issue is securing blood for tryptase determinations in the course of an acute anaphylaxis episode. In such circumstances, blood should be collected within 15 minutes to 3 hours following the onset of symptoms. The procedure of material preparation is not difficult; optimally, the <5 ml volume (in children — 0.5 ml) of blood collected to a clot tube should be centrifuged and stored at –20°C. Tryptase is stable; 50% of tryptase is determinable even after 4-day storing at room temperature [54]. Determinations of tryptase concentration are performed using ImmunoCAP Tryptase (Phadia).

FUNDAMENTALS OF THERAPEUTIC MANAGEMENT OF *HYMENOPTERA* VENOM ALLERGY

Therapeutic management should be considered in the context of the following:

1. prophylaxis through avoiding contact with the triggering factor,
2. intervention in case symptoms develop,
3. prevention in the form of venom specific immunotherapy [55].

Regardless different health service organization in European countries, following the guidelines both in diagnostic and treatment procedures is crucial with reference to patient's safety, and doctor's law's consequences [56].

In the interventional management of the patient manifesting anaphylaxis symptoms, promptness of intervention is of fundamental importance. In case of fully symptomatic anaphylaxis, adrenaline is a life-saving agent. Here, when given in standard doses, advantage is taken of its effect on adrenergic receptors: α_1 (decreased vascular leakage, increased peripheral resistance, decreased mucosal edema), α_2 (inhibition of insulin and noradrenalin release), β_1 (positive chronotropic and inotropic effects) and β_2 (bronchodilation, intensification of glycogenolysis, inhibition of release of inflammatory mediators) [57]. There are no absolute contraindications for adrenaline administration. In the course of initial intervention during anaphylaxis, oxygen is to be promptly administered, vigorous fluid resuscitation should be commenced, help should be called for and the principle of laying the patient flat with elevated lower extremities needs to be observed, what protects the affected individual from death in the mechanism of superior vena cava syndrome and empty ventricle syndrome. It should be remembered that medications other than adrenaline (antihistamines and systemic glucocorticosteroids; in patients with asthma and bronchial obturation — additionally rapid acting inhaled β_2-mimetics) are only adjuvant treatment in anaphylaxis. Lack of well-documented case-control studies on treatment of patients undergoing anaphylactic reactions is emphasized, with the exception of reports addressing insect venom immunotherapy [58, 59]. More advanced intervention management in the course of anaphylaxis is a subject of separate reports [60–63]. In view of the importance of the problem, consensuses on management principles in anaphylaxis are constantly updated [64] and their implementation in everyday practice improves the quality of interventions employed [65].

The history of subcutaneous insect venom immunotherapy spans approximately 50 years. In the initial phase, insect whole body extract therapy was employed. With time, the method was proven to be of low effectiveness and the allergen dose of low reproducibility and this is why at present, while providing therapeutic management with initial and maintenance doses, water solutions of venom extract are employed, while in maintenance therapy there is an additional possibility of using *depot* preparations. Investigations on common availability of recombinant allergen preparations are increasingly more advanced; such preparations are

individually selected to match the sensitization profile of the patient (*component resolved diagnosis* — CRD) [66, 67].

Specific venom immunotherapy (*venom immunotherapy* — VIT) is the treatment of choice in patients (both adult and pediatric above 5 years of age, in keeping with the current recommendations though in severe cases lower age limit is flexible) in cases when both the below given criteria are met [2]:

1. severe generalized reaction in past medical history with respiratory symptoms (grade III according to H.L. Mueller) and/or circulatory symptoms (grade IV according to H.L. Mueller),
2. IgE-dependent allergy to a given *Hymenoptera* species.

In case of generalized systemic non-life threatening reactions (systemic reactions grade I and II according to H.L. Mueller), the decision to employ venom immunotherapy may be affected by other factors, such as high exposure (occupational, family members of beekeepers, individuals dwelling close to apiaries), concomitant cardiovascular diseases, mastocytosis, mental factors (e.g. profoundly deteriorated quality of life due to fear of insect stings that renders normal daily functioning impossible). In patients with confirmed double sensitization VIT with extracts of both wasp and bee venom is indicated. Its therapeutic effectiveness is high, amounting — depending on the type of allergy — to 90–100% in wasp venom allergy and approximately 80% in case of allergy to bee venom [2]. In comparative studies performed in cohorts of desensitized vs. non-desensitized patients, a significant decrease of risk of severe systemic reactions has been observed in desensitized individuals [68, 69]. The recently emphasized new advantage of VIT is the improvement of quality of life of the patients, both in adults and children [70–73]. The criteria of qualifying patients for VIT according to EAACI are presented in Table 5 [1].

Table 5

Indication for venom immunotherapy according to EAACI guidelines [79]

Type reaction adults/children	Diagnostic tests (skin tests and/or IgE)	Decision regarding venom immunotherapy
Respiratory and/or cardiovascular symptoms — III°/IV° in Mueller's grade	Positive Negative	Yes No
Urticaria/oedema — I°/II° if risk factors or QoL impairment present	Positive Negative	Yes No
Large local	Positive or negative	No
Unusual reaction	Positive or negative	No

VIT is also not taken into consideration in individuals, in whom IgE specific to wasp or bee venom has been detected accidentally and their medical history

is negative for sting-following reactions. Similarly, VIT is not recommended in patients with toxic reactions, atypical or extensive local reactions, although in the United States, there have been published pilot studies on selected cases of desensitization of patients with extensive local reactions [74]. Sublingual administration of venom specific immunotherapy in patients with extensive local reactions, although presented in case reports, is not recommended [75, 76].

The protocols of initial immunotherapy that allows for achieving the maintenance dose may be characterized as follows:

1. accelerated (several hours up to several days); the in-hospital treatment is provided using the *ultra-rush* or *rush* method,

2. conventional or cluster, when the treatment is provided over a prolonged period (from several to ten-odd weeks).

Reports based on randomization of patients to three desensitization protocols employing the initial dose indicate a significantly lower prevalence of adverse symptoms, both local and systemic, in patients treated according to the ultra-rush protocol as compared to the rush or conventional protocol [77].

With the standard maintenance dose of 100 μg/ml, what corresponds to approximately two bee stings and as many as several score wasp stings, the maintenance phase of the therapy should span 3–5 years. In justified cases, e.g. in patients with clonal mastocyte disorders or in individuals undergoing desensitization who continue to manifest systemic reactions after field stings, what indicates lack of appropriate immune protection, the maintenance dose of the venom extract may be gradually increased up to 200 μg, with the treatment protocol starting anew. In the first year of therapy, the interval between administrations of subsequent maintenance doses is four weeks, in case of 2–5-year therapy — six weeks, and in cases of depot extract given as a maintenance dose, the planned interval between the doses is increased to eight weeks. In view of the minimized, but still apparent risk of the patient developing a systemic reaction, each individual with the past history of anaphylactic shock, in spite of the immunotherapy, should be equipped with an anaphylactic kit and always have it on his person. In Polish centers of internal medicine, the most commonly employed protocol of management with the initial dose is the rush protocol, and in pediatric centers — *ex aequo* the conventional and ultra-rush protocols [78]. It is estimated that at present, approximately 200 children and several hundred adults are undergoing treatment.

Contraindications to venom specific immunotherapy in patients allergic to *Hymenoptera* venom do not differ from the generally accepted contraindications pertaining to immunotherapy for other allergens. They include lack of the patient's cooperation, age below 5 years of life (in case of life-threatening reactions, the criterion is not restrictive in character), active neoplastic or autoimmune diseases, severe decompensated generalized diseases, chronic organ failure, pregnancy (preliminary immunotherapy) and other situations where the benefit/risk ratio

is not advantageous for the patient. Administration of β-receptor blockers and angiotensin converting enzyme (ACE) inhibitors is recognized as an additional risk factor of the patient developing systemic adverse effects, especially during the phase of employing increasing immunotherapy doses [2, 79].

The fundamental objective of venom specific immunotherapy is to produce induced tolerance in peripheral T lymphocytes to sensitizing allergens. Once the immune tolerance is achieved, T regulatory lymphocytes (TREG) start to produce great amounts of anti-inflammatory cytokines. The hitherto understood mechanisms of immune tolerance that are initiated by specific immunotherapy are associated with [80–90]:

1. a decreased reactivity of antigen-presenting cells (dendritic cells) and peripheral effector cells (mastocytes, basophils, eosinophils) following allergen stimulation (the effect appears after several days of treatment),

2. expansion of T regulatory lymphocytes (TREG, $CD4^+$ $CD25^+$ $Foxp3^+$) and expression of their cytokine pattern (IL-10); the full effect is observed after several months of treatment,

3. suppression of Th1 and Th2 cells,

4. a regulatory effect on B lymphocyte-dependent synthesis, with limitation of specific IgE production and at the same time intensified production of IgG4 and/or IgA blocking antibodies (the effect is observed after several years of treatment).

Early changes have been recently described, appearing within the few initial hours after the sting and associated with an accelerated tryptophan degradation in blood polynucleated cells and monocytes, increased IL-10 synthesis and increased expression of ILT (*immunoglobulin-like transcript*) family members [91, 92]. Nevertheless, not a single laboratory test allows for confirming effective immunotherapy. Hence, in immunoprotection monitoring and for possible determination of the moment when termination of treatment is warranted, the gold standard is sting challenge of the patient by a live insect [93]. It allows for identifying these patients, in whom treatment can be safely terminated (in no less than 6–18 months following the achievement of maintenance dose). In practice, the procedure is employed only in infrequent centers. Sting challenge is not recommended as a diagnostic tool in patients not undergoing desensitization as it is potentially dangerous. The most recent reports indicate that determining the gene expression profile may be a valuable tool in individual patients in estimating risk factors of severe insect venom anaphylaxis, also in individuals with latent forms of mastocytosis [94–96].

CONFLICT OF INTEREST STATEMENT

None declared.

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Ewa Cichocka-Jarosz, M.D., Ph.D.
Department of Pediatrics
Jagiellonian University Medical College
Chair: Prof. Jacek J. Pietrzyk
ul. Wielicka 265, 30-663 Kraków
Phone +48 12 658 02 56; Fax +48 12 658 44 46
E-mail: mijarosz@cyf-kr.edu.pl