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Modern Aspects of Hypersensitivity to Stinging Insects

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Abstract—The prevalence of insect allergy and specific features of hypersensitivity to stinging insects are considered. The importance of pathogenetic treatment for this type of allergies is shown, as well as its solution via the creation of a new domestic drug, a bee venom allergoid, and its adoption into practical allergology.

Keywords: insect allergy, hypersensitivity to stings, allergen-specific immunotherapy, anaphylactic shock
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INTRODUCTION

Allergies are currently a disease with an ever-increasing prevalence (Il'ina, 1996; Luss, 2009; Fedoskova, 2008, 2013). The World Health Organization (WHO) predicts that the 21st century will be the epoch of allergy. The prevalence of allergic diseases increases two- to three times every decade, having currently reached the scale of an epidemic. Allergic pathology is among the six most prevalent human diseases. In fact, every sixth American, every fourth German, and every fifth citizen of earth suffers from allergy. The data published by the Federal Medical and Biological Agency of Russia in 2008 show that the prevalence of allergic diseases in different regions of Russia is 19–40% among the adult population and over 27% among children and teenagers (Bogova et al., 2008). Allergic diseases are widespread and present a serious social, economic, and medical problem (Khaitov, 2002).

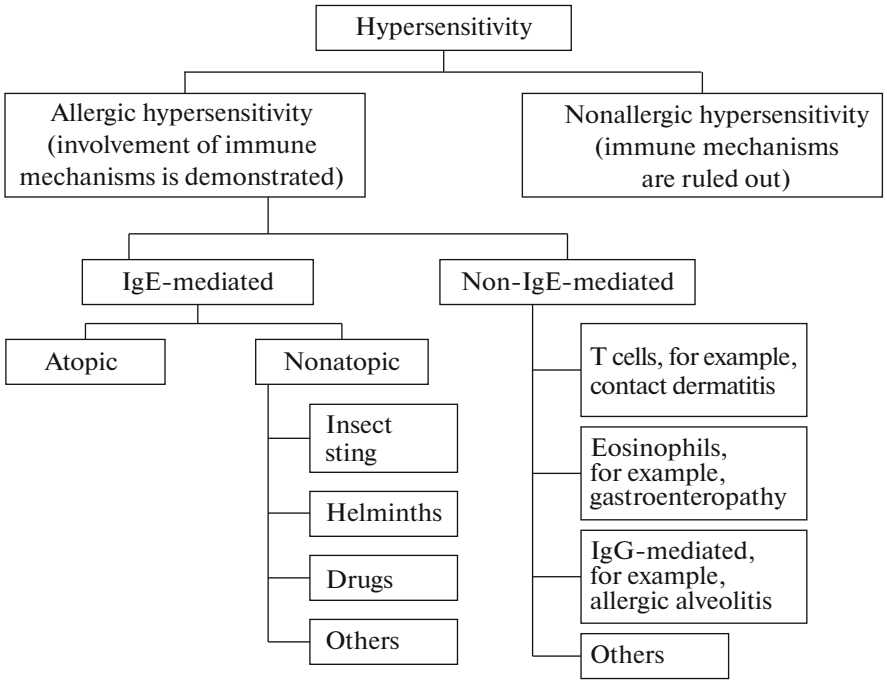
The current classification and nomenclature for allergic diseases was elaborated by a research team by the initiative of the European Academy of Allergy and Clinical Immunology (Johansson et al., 2001) and later revised with participation of the World Allergy Organization, WAO (Johansson et al., 2004). The experts believe that an important criterion of allergic states is hypersensitivity, i.e., the objectively reproduced manifestations and symptoms developing in response to the impact of certain environmental factors at doses that fail to induce these manifestations in normal individuals. The concept of hypersensitivity unites all types of hyperresponsiveness manifestations, including the variant mediated via synthesis of IgE antibodies. As Birnbaum et al. (1994) demonstrated, the prevalence of atopy among the patients IgE-sensitized to stinging insect venoms is the same as in the normal population. Thus, the true allergy to insect stings is a nonatopic IgE-mediated allergic hypersensitivity (figure).

Unlike a true allergic response, a direct impact of high doses of chemical factors on the mast cell membrane can induce hyperresponsiveness of the body to the acting factor, followed by liberation of histamine and other mast cell mediators, entailing manifestation of all signs characteristic of the pathophysiological stage in the body's response to mast cell mediators. In the literature, such states are described as pseudoallergic responses (Fedoseeva and Rakhmanin, 2012). In particular, a human stung by a bee is affected by several micrograms of allergen, which is comparable to an annual dose of inhaled pollen allergens (Müller, 1990). Thus, the responses to bee venom are reflected in the current classification for hypersensitivity (Johansson et al., 2001, 2004; figure).

Currently, the mechanisms underlying the effects of allergens of several stringing insects (bees, wasps, hornets, etc.) are the least studied area in the diagnosis and therapy of insect allergy. In particular, the presence of toxins in the venoms of stinging insects necessitates a focused study of the mechanisms underlying their action.

The insects forming the insect fauna of our planet have existed for over 300 million years and comprise over one million species (Fedoskova, 2007). Insecta is a component of the Arthropoda subphylum, the richest on Earth in its species diversity (Stanek, 1972; Roslavtseva, 1990; Drynov, 2003).

Arthropoda are divided into five classes, namely, Arachnida (scorpions, spiders, mites, etc.) comprising 30000 species; Crustacea (crabs, lobsters, etc.), comprising 25000 species; Insecta (insects), 700000 species; Diplopoda (millipedes), 7000 species; and Chilopoda (centipedes), 2000 species (Perez-Santos, 1995).



Nomenclature and classification for hypersensitivity according to Johansson et al. (2001).

The evidence that insects and most of the arthropods are sources of allergens sensitizing humans are numerous (Feinberg and Benaim-Pinto, 1956; Reisman et al., 1983; Golden, 1998; Fedoskova, 2008). Allergologists have been long interested in insect allergens, especially the allergens of the species belonging to the order Hymenoptera. The term Hymenoptera (from Ancient Greek "hymen" for membrane and "pteron" for wing) unites the insect species able to sting (Mamaev, 1976; Pytskii et al., 1984) and comprises over 100000 species.

The hypersensitivity responses to contact with insects were known long before Pirquet introduced the term allergy to scientific use. Earlier, these responses were regarded as toxic and later were classified as allergic. Perhaps, one of the first references to an insect allergy is the inscription on the tomb of Menes, an Ancient Egyptian pharaoh (28th century BC), stating his death by insect sting (Drynov, 2003). However, the nature of the response to Hymenoptera stings until the 20th century was regarded as a toxic shock (Bousquet et al., 1982). Only in the 1930s did Benson demonstrate in his focused studies an allergic genesis of the response to Hymenoptera stings (Pytskii et al., 1984).

The epidemiological data on insect allergy in the Russian and European literature are rather sparse. Bilo and Bonifazi (2009) published consolidated data that demonstrate that 56.6–94.5% of adult individuals, depending on the climate and region, have been stung at least once by a stinging insect.

According to Russian researchers (Bogova et al., 2008), 0.4–8% of the Russian population are allergic to the venom of stinging insects (wasps, hornets, and bees). Internationally used approaches to the classification of allergic responses to Hymenoptera venom are somewhat different. According to the classification by Mueller (1966), 2.4–26.4% of individuals develop large local reactions (LLRs), reaching 38% in the cohort of beekeepers, versus systemic reactions (SRs), which developed in 0.5–3.3% of the population in America and 0.3–7.5% of the population in Europe (Incorvaia et al., 1997; Fernandez et al., 1999; Antonicelli et al., 2002; Moffitt et al., 2004; David and Golgen, 2007; Bilo and Bonifazi, 2008; Münstedt et al., 2008; *White Book*..., 2014). The studies of insect allergy in this country give similar data. The hypersensitivity responses among certain social cohorts, for example, beekeepers, are observable at a rate of 40% (Gushchin et al., 1987). According to the data for Europe (Bousquet et al., 1982), the rate of toxic responses reaches 7%. It has been also noticed that the rate of severe systemic responses (anaphylactic shock) varies in the range of 0.3–42.8% of all systemic responses (Bilo and Bonifazi, 2008; Table 1).

A specific feature of the studies on insect allergy is that several factors should be taken into account when assessing epidemiological characteristics. First and foremost, there are some methodological problems. Gushchin and Chitaeva (2003) emphasize that the mode of performing the medical history, its quality, and the focus on detection of allergic responses to bee stings play a significant role when collecting the corresponding information. The absence of unified approaches to collecting information gives incomplete

Table 1. Percentage rates of general and insect anaphylaxis cases (data from European studies)

Country	Period, years	Cohort	Anaphylaxis		Lethal cases
			general, number of cases	rate of insect variant, % of total	
Italy	11	Ch	107	29	0
Australia	1	A	142	17.5	1 (bee sting)
Italy	2	A	140	1.5	0
France	1	A	12	25	0
Australia	9	A and Ch	1149	30	–
Hong Kong	6	A and Ch	282	7.1	0
Australia	3	Ch	57	5.3	0
Thailand	5	A and Ch	101	11	1
United States (Texas)	1	A and Ch	464	34.1	4
Australia	5	Ch	123	3	1

A, adults and Ch, children.

Table 2. Rates of fatal anaphylaxis cases over the studied period, including those caused by insect stings

Country	Period, years	Total number	Insect stings (rate of fatal cases, %)	Insect species		
				wasp	bee	others
United Kingdom	1992–2001	202	47 (23)	29	4	14
New Zealand	1985–2005	18	4 (22)			
United States (Florida)	1996–2005	89	9 (20)	2	2	5
Australia	1997–2005	112	20 (18)	13		7

medical histories that frequently omit the severity of allergic responses. The way out used in Europe to solve this problem is the extrapolation of available data on the systemic responses to Hymenoptera venom allergy on the general characteristics of anaphylaxis (Bilo and Bonifazi, 2009).

There are extremely few epidemiological studies into insect allergy in Russia. Note the works by Fassakhov et al. (2014) on the rate of anaphylactic shock (ASh) in allergy patients after insect stings. The authors have analyzed 493 cases of ASh manifestation and diagnosis in hospitalized patients and demonstrated that 133 patients developed true allergic responses to insect stings. These results are similar to the data by European researchers. Analysis of the results by Fassakhov et al. (2014) shows a high rate of ASh caused by insect stings (27%) among hospitalized ASh patients. In most cases, ASh resulted from the stings of wasps (59%), bees (16.7%), hornets, and bumblebees (5.2%) with 18.6% of unidentified insects. Men are at a higher risk of stings (58%). In the ASh clinical manifestations, the syndrome of heart failure occurs most frequently (79.7%). Emergency teams use adrenalin for arresting ASh only in 30% of the cases (Fassakhov et al., 2014).

The annual mortality rate caused by hymenopteran stings is 0.03–0.48 per 1000000 population (Bilo and Bonifazi, 2008, 2009; *White Book*..., 2014). The available data considerably vary depending on the region and the methods used for assessing allergic responses in patients. The WAO reports the highest annual mortality rate caused by insect stings in France (0.48 per 1000000 population), followed by Switzerland (0.45), Denmark (0.25), Germany (0.18), United States (0.16), Australia (0.10), and United Kingdom (0.09) with the lowest rate observed in Italy (0.03). According to Bilo and Bonifazi (2009), fatal insect stings account for approximately 20% of the anaphylactic responses (Table 2).

Most frequently, the shock led to death in 10–15 min. Angioneurotic edema of the upper respiratory tract with subsequent asphyxia developed in 25% of the patients. The fatal responses were mainly observed in individuals over 40 years old.

Thus, the problem of allergy to hymenopteran stings is undoubtedly topical despite the relatively low rate of detected cases, because of the frequent severe anaphylactic responses with a high frequency of fatal cases. This is clearly demonstrated by the results presented by the European Academy of Allergy and Clinical Immunology in Munich (April 2013) at the

Table 3. Classification of systemic allergic responses according to Mueller (1966)

Degree of response	Symptoms
I	Generalized urticaria, skin itching, distress, and anxiety; time of development, <30 min
II	Symptoms of group I and ≥two of the following manifestations: vascular edema, compressing pain, nausea, vomiting, diarrhea, abdominal pain, and vertigo
III	Any symptom of group II and ≥two of the following manifestations: labored breathing, stridor, and panting
IV (anaphylactic shock)	Any symptom of group III and ≥two of the following manifestations: arterial blood pressure fall, collapse, fainting fit, involuntary urination, defecation, cyanosis, and uterine contraction (miscarriage)

Table 4. Classification of systemic allergic responses according to Ring and Messmer (1977)

Class	Manifestations			
	skin	gastrointestinal	respiratory	cardiovascular
1	Itching, exudation, urticaria, and subcutaneous fat edema	None	None	None
2	Ditto	Nausea and intestinal strictures (colic)	Rhinorrea, hoarseness, and labored breathing	Tachycardia, hypotonia, and arrhythmia
3	"	Vomiting, involuntary defecation, and diarrhea	Laryngeal edema, bronchial spasm, and cyanosis	Shock
4	"	Ditto	Respiratory arrest	Cardiac arrest

Hymenoptera Venom Allergy School. One of the main topics there was the diagnosis and therapy of the bee venom allergy with published recommendations for diagnosing and treating anaphylaxis in allergies to Hymenoptera venom elaborated by the WAO. At the end of 2013, the Russian Association of Allergologists and Clinical Immunologists published a draft of federal recommendations on the main issues in clinical allergology. These recommendations pay significant attention to the acute states developed in the case of Hymenoptera venom hypersensitivity and propose schemes for allergen-specific immunotherapy (ASIT), as well as indications and contraindications for the specific therapy.

Note that the difficulties in diagnosis, prevention, and treatment of insect allergy, especially bee venom allergy, is determined by the current absence of the therapeutic and diagnostic allergens of Hymenoptera venoms approved for clinical use by the Russian Ministry of Public Health in the Russian market. Thus, the importance of the problem of insect allergy is evident.

CLINICAL PICTURE

A normal skin response to stinging is a pain syndrome, local blister with a diameter to 5 mm, and small edema with a diameter of several centimeters. As a rule, the symptoms caused by a sting in a healthy individual disappear in several hours. Pain and hyperemia are induced by a direct irritating effect of histamine and serotonin, as well as a cytotoxic effect of melittin on cells. Pain, edema, and hyperemia at the site of sting are caused by several mediators.

Clinical manifestations of the hypersensitivity to Hymenoptera stings appear at local and systemic levels. The LLRs are distinguished according to characteristic edema and erythema with a diameter of >10 cm at the site of sting and skin itching. These symptoms remain for >24 h and up to 12 days in individual cases (Mueller, 1966) and can be accompanied by lymph node edema and lymphangitis with fever. An increase in swelling after a sting in the oral cavity is likely to suggest the development of a systemic response. The systemic responses (SRs) are classified in a more complex manner. The most usable classification of systemic responses is that proposed by Mueller in 1966 (Table 3) and modified by Ring and Messmer in 1977 (Table 4).

The European Academy of Allergy reports that the systemic allergic response (SAR) in the case of repeated stings is developed by <5% of patients with the initial local response, by 15–30% of individuals with initial mild SAR, and by >50% of individuals after initial severe SAR (Gushchin and Chitaeva, 2003; Shvets, 2004).

Recent studies have clarified certain risk factors that can make the SARs to Hymenoptera venom more severe. These factors also potentially increase the risk for side effects of ASIT. The main risk factors are (1) an elevated level of serum tryptase and mastocytosis (as is demonstrated, most severe cardiovascular

Table 5. List of allergens in *Apis mellifera* venom from the IUIS nomenclature (2014)

Allergen	Biochemical nature	Molecular weight, kDa
Api m 1	Phospholipase A2	16
Api m 2	Hyaluronidase	39
Api m 3	Acid phosphatase	43
Api m 4	Melittin	3
Api m 5	Dipeptidyl peptidase IV (allergen C)	100
Api m 6	–	8
Api m 7	CUB-serine protease	39
Api m 8	Carboxylesterase	70
Api m 9	Serine carboxypeptidase	60
Api m 10	Icarapin-2 (a carbohydrate-rich protein)	50–55
Api m 11	Major royal jelly proteins (deglycosylated from)	50
Api m 12	Vitellogenin	200

symptoms and even fatal cases are recordable in the mastocytosis patients and more severe anaphylactic responses are observed in the individuals with an elevated serum tryptase content; Rüeff et al., 2006); (2) concomitant cardiovascular diseases (Müller, 2007); and (3) the administration of angiotensin-converting enzyme inhibitors and β-blockers. Angiotensin-converting enzyme inhibitors can increase the SAR rate, in particular, in ASIT, and β-blockers, while not increasing the SAR risk may contribute to its severity (Bilo and Bonifazi, 2009; Müller, 2007; Müller and Haeberli, 2005; *White Book*..., 2014).

The production of specific IgE and IgG antibodies is characteristic of the allergic response to Hymenoptera venom. The latter antibodies are detectable in patients for several weeks and months after stings. Most researchers associate an increase in IgG antibodies with an increase in "blocking" antibodies in the patient's body. IgE antibodies specific to bee venom have been detected in the sera of the patients with general and pronounced local responses to bee stings. High levels of IgG antibodies are more typical of beekeepers, who more frequently stung by bees (Khutueva and Fedoseeva, 2000).

As is mentioned above, the body in the case of a single sting receives several micrograms of the corresponding allergen, which is comparable to the annual dose of inhaled pollen allergens. The main groups of substances contained in the bee venom (with basic properties) are high molecular weight protein enzymes and the fraction of volatile substances.

THE ALLERGEN COMPOSITION OF BEE VENOM

The nomenclature for allergens was elaborated by the WHO/IUIS Subcommittee on Allergen Nomenclature, which was published for the first time in 1986 (Marsh et al., 1986) and then revised several times (King et al., 1994a, 1994b; 1995; Larsen and Lowenstein, 1996). An important contribution to the establishment and current state of the nomenclature for allergens was the work by Chapman (2004, 2008). The latest edition of this nomenclature took into account the recombinant and synthetic allergens and their identification by the cDNAb method.

The current nomenclature contains a wide range of Hymenopteran allergens, as well as the characterization of allergens from 30 hymenopteran species (in total, 71 allergens of these species are included).

Allergens of insects and from other sources are regarded as major if the specific IgE response to an allergen is developed by >50% of the patients with an increased sensitivity and as minor if such response is observable in <50% of the patients (Larsen and Lowenstein, 1996).

Bee (*Apis mellifera*) venom contains several substances with pharmacological and biochemical activities (such as norepinephrine, histamine, melittin, and mast cell degranulating peptide). Some of these substances display allergenic properties (Gushchin and Chitaeva, 1987).

The first edition of the nomenclature for allergens regards the allergens Api m 1, Api m 2, and Api m 4 as major honeybee venom allergens (Kuchler et al., 1989). The authors have analyzed the cDNA for phospholipase A2. Ketner later examined Api m 6 with a molecular weight of 8 kDa by peptide sequencing. So far, 12 allergens of the *A. mellifera* venom have been officially registered, studied, and described (Table 5).

The main bee venom allergens are the major allergens Api m 1 (phospholipase A2), Api m 2 (hyaluronidase), Api m 3 (acid phosphatase), Api m 4 (melittin), and Api m 7 (CUB-serine protease) and the minor allergen Api m 6, which induces 42% IgE response (Hoffman, 2006). The venom also contains other no-less significant allergens.

When diagnosing insect allergy, the clinical picture of disease and results of specific tests are the decisive factors. The following factors can confirm the allergy to insects: a correlation between clinical symptoms of allergy and an insect sting, positive skin tests to diagnostic insect allergens, and the presence of insect allergen-specific IgE antibodies in patient's blood.

Since any registered diagnostic allergens of stinging insects are absent in Russia, the main clinical method for diagnosing Hymenoptera venom hypersensitivity is a standard scheme of allergological examination, which includes the performance of medical history, objective examination, and in vitro diagnosis.

When performing a medical history, it is necessary to find out whether a patient has been earlier stung by insects; to assess the degree of patient's responses and duration of clinical manifestations; to determine, when possible, the insect species; and to estimate the efficiency of antiallergic drugs. In addition, the important information for the medical history is the development of allergic response to stings by hymenopterans (wasps, bees, and others). The medical history data are weighed according to the intensities of patient's local and systemic responses to an insect sting. In order to unify and standardize the data, a specialized questionnaire for early diagnosis of allergy to stinging insects was developed by Fedoskova and Shabanov (2013) at the Institute of Immunology (Federal Medical and Biological Agency of Russia) and is now in the process of clinical adoption.

The strategy for further diagnosis is selected based on the medical history. Pronounced clinical manifestations in response to an insect sting suggest the use of laboratory diagnostic methods. The following in vitro allergological tests are used to diagnose an insect allergy: radioallergosorbent test (RAST) for the detection of allergen-specific IgE antibodies; radioimmune test (RIT) for the detection of allergen-specific IgG antibodies; enzyme-linked immunosorbent assay (ELISA) for the detection of allergen-specific IgE and IgG antibodies; and immunoblotting.

The allergy to stinging insects is of a nonatopic IgE-mediated hypersensitivity type (Johansson et al., 2001, 2004). As has been shown, the acute systemic responses in the case of hypersensitivity of a patient with allergic diseases develop after a bee sting, not only following the pattern of a true allergy with production of IgE or IgG antibodies but also according to the pattern of pseudo-allergic responses (nonallergic hypersensitivity). Characteristic of the nonallergic hypersensitivity response is the absence of high levels of specific IgE antibodies and the involvement of target cells in the hypersensitivity response, followed by the liberation of allergy mediators (histamine, serotonin, etc.), which later act on the target organs (Ado, 1978). In this case, the state of the target (mast) cell membrane plays an important role in the pathogenesis of hypersensitivity as well as the degranulation and liberation of mast cell mediators (histamine, serotonin, etc.), which induces hypersensitivity in response to the impact of various factors without induction of the specific IgE response. In this case, stages 2 and 3 of the allergic response develop without binding of IgE antibodies to the mast cell Fc receptors, i.e., without the so-called immunological stage.

Thus, if a patient develops a hypersensitivity response to insect stings, the clinician should use differential diagnosing to distinguish between the true allergy, nonallergic hypersensitivity, and toxic responses.

Toxic responses are observable after concurrent stings/bites of several tens or hundreds of insects. Patients complain of headache, nausea, and vomiting. Stings by a hundred of insects cause hemolysis of erythrocytes and acute skeletal muscle necrosis, leading to acute renal failure and lethal outcome. The patients stung by many (over a hundred) insects need hospitalization for observation and comprehensive control of the functional state of their important organs and body systems.

If the parameters of specific IgE response are low, it is reasonable to assess the specific activity of target cells. Depending on the results of examination, it is possible to select the most efficient therapeutic tactics. Therapy with antihistamine drugs, antileukotriene agents, and stabilizers for target cell membranes in this case will be rather efficient, while these tools are merely symptomatic drugs with a positive but short-term effect in the case of an IgE-mediated response, suggesting the need for them in pathogen-specific therapy.

Several producers in Russia offer test kits for detecting histamine and other mediators of the blood basophils. The relevant literature describes combined (of anaphylactic and pseudo-allergic types) responses to the impact of bee venom on blood basophils. However, other methods (allergen-specific histamine liberation, basophil degranulation test, crossed radioimmunoelectrophoresis, cellular antigen stimulation test, and lymphocyte proliferation test) are not used in mass clinical practice, being rather laborious and expensive and requiring special training.

Thus, other clinical and laboratory methods for diagnosing hypersensitivity to bee stings are now developed and adopted by clinical practice. The elaborated scheme comprises clinical examination and the algorithm of laboratory tests for all stages in the development of hypersensitivity, namely, IgE antibodies, CD63+ expression, the level of allergy mediators upon the contact of blood basophils with bee venom, and the degree of liberation of leukotriene products.

It is commonly accepted that ASIT, which influences all components of the allergy pathogenesis, is the most effective approach. A successful ASIT course guarantees immunological tolerance to the cause-significant allergen, thereby improving the life quality of patients by reducing the clinical symptoms and the

need for drugs and contributing to a complete remission for several years after the therapy is completed (Fedenko, 1999; Luss and Tsarev, 2009). At different stages of its development, ASIT had different names—desensitization, hyposensitization, preventive inoculations, antianaphylactic vaccination, active immunization, allergy shots, immunotherapy, and specific immunotherapy (Ring, 2011). ASIT is quite actively used worldwide when treating allergy to stinging insects, in particular, the allergy to bee and wasp venoms.

The basic effect of ASIT is the induction of clinical and immunological tolerance to specific allergens. This is possible at the expense of long-term desensitization with the involvement of mechanisms that modify the allergen-specific memory. It is believed that these mechanisms eventually give rise to the so-called IgG–IgG1 and IgG4 antibodies. The antibodies of these subclasses have the minimal inflammatory activity. Binding to the IgE receptors on mast cells, basophils, and other cells synthesizing IgE receptors, they block the allergen-induced IgE-dependent liberation of preformed mediators from these cells and thus inhibit the T cell-mediated response. This response in allergic diseases is directed towards production of the Th2 cytokines. The T-cell response in the case of ASIT consists in switching the synthesis of cytokines from Th2 to Th1 profile. The main produced Th1 cytokines are IL-2 and IFN-γ and the main Th2 cytokines are IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. Taking into account their effects, the former are mainly regarded as anti-inflammatory mediators, and the latter are considered proinflammatory (Nedel'skaya et al., 2012).

Many Russian researchers (Ado and Barysheva, 1986; Poroshina et al., 1995; Pytskii et al., 1999; Shvets, 2004) for a long time studied the ASIT effect on the patients with bee venom allergy. The optimal ASIT schemes in classical and accelerated variants have been developed, and the safety and efficiency of ASIT for treating this allergy have been demonstrated. However, the elaborated therapeutic schemes and the used preparations have not been approved and recommended by the Ministry of Public Health of the Russian Federation for mass clinical use. As a result, Russia lacks the registered medicinal allergens from the Hymenoptera venoms, while the work in this area continues. The Institute of Immunology designed and patented a method for producing a detoxified allergoid form of a bee venom allergen (patent no. 2279888 by V.N. Fedoseeva, I.A. Orlova, A.I. Martynov, and T.G. Fedoskova titled "An Allergoid from the Bee Venom" registered by the Russian Federation State Registry on July 20, 2006). This preparation successfully passed laboratory trials in animals and demonstrated its high efficiency on a background of decreased allergenic and toxic characteristics. A high immunogenic activity of this allergoid has been experimentally demonstrated and is 3.0–3.2 times higher than with the commonly used allergens and water–salt allergen extracts, which is an optimal indicator of ASIT efficiency.

An important aspect in solving the problem of ASIT against Hymenoptera venom involves the indications and contraindications. According to the European and Russian recommendations, the ASIT for Hymenoptera venom is used in the case of pronounced systemic responses in medical history (severe anaphylactic responses, respiratory and cardiovascular symptoms, and urticaria on the background of a pronounced risk for repeated stings and repeated systemic responses); in other cases, ASIT is not indicated (Bonifazi et al., 2005).

CONCLUSIONS

Allergy to Hymenoptera venom is a global medical challenge. Stinging can cause large local or systemic allergic responses. LLRs are defined as a reaction with a diameter >10 cm remaining for >24 h; the signs and symptoms are confined to tissues adjacent to the sting stie. The systemic responses involve generalized manifestations and symptoms and comprise the entire range of manifestations, from mild to life-threatening. Mild systemic responses may be limited to skin reactions and include edema, urticaria, and angioneurotic edema (subcutaneous fat edema). More severe systemic responses may include bronchial spasm, laryngeal edema, and hypotonia. Hymenoptera venom allergy may sometimes lead to fatal anaphylaxis.

The rate of insect allergy in medical practice is frequently underestimated, and fatal responses are not recorded in a proper manner, which underrates the scale of the problem.

The detection rate of positive specific IgE antibodies to venom is high among the population in general; however, only an insignificant part of the population develops anaphylaxis to the Hymenoptera venom. Up to 50% of the patients with fatal anaphylaxis responses have no documented history of the previous systemic responses. The hypersensitivity to Hymenoptera venom decreases the quality of life; is the cause underlying significant socioeconomic losses; presents an occupational problem, especially for beekeepers and greenhouse workers; has negative consequences from the standpoint of employment, ability to work, rest, and sporting events; and has a considerable negative financial effect in public health service. However, hypersensitivity to Hymenoptera venom can be efficiently treated with ASIT and the corresponding medicinal allergens.

The *WAO White Book on Allergy* (2013) gives the most comprehensive description of the problems in the diagnosis and treatment of hypersensitivity to Hymenoptera stings (*White Book*..., 2014). The statements listed there are also true for our country; however, the absence of unified approaches to patient management and, what is most important, the

absence of approved preparations for the diagnosis and treatment of the allergy to stinging insects are more topical problems of te Russian allergology in view of controlling Hymenoptera venom hypersensitivity.

Thus, the wide abundance and considerable diversity of stinging insects in the environment, the inability to predict their stings and contact with them, and the severity and polymorphism of clinical symptoms of insect allergy (Müller, 1990, 2007; Birnbaum et al., 1994; Golden et al., 1998; Bonifazi et al., 2005; Bilo and Bonifazi, 2009) determine the need in development of tools for the specific diagnosis, treatment, and prevention of insect allergy.

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