JDDG Journal of the German Society of Dermatology

DOI: 10.1111/j.1610-0387.2009.07125.x

CME

Hymenoptera venom allergy

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JDDG; 2010 · 8:114–129 | Submitted: 19. 2. 2009 | Accepted: 8. 4. 2009

Section Editor
Prof. Dr. Jan C. Simon, Leipzig

Keywords
- allergy
- anaphylaxis
- diagnosis
- emergency treatment
- hymenoptera venom
- specific immunotherapy

Summary

Allergic reactions to Hymenoptera stings usually present as large local reactions or systemic reactions with symptoms of immediate type allergy (anaphylaxis). In Central Europe they are predominantly elicited by stings of the honeybee or *Vespula spp.* Acute reactions are managed by symptomatic treatment. Long-term care includes patient education (allergen avoidance, course of action at re-sting) and prescription of an emergency kit for self-treatment. Venom immunotherapy is established as specific treatment for Hymenoptera venom allergic patients. Diagnosis of Hymenoptera venom anaphylaxis is based on history, skin tests and measurement of venom-specific serum IgE antibodies. "False negative" or "false positive" results are possible with all test methods. If standard tests are negative, additional tests using the patient's peripheral blood leucocytes can be useful. Venom immunotherapy is usually well tolerated. After reaching the maintenance dose, therapeutic efficacy should be assessed by a sting challenge test. If the patient again develops a systemic reaction, an increase of the maintenance dose (usually 200 µg are sufficient) nearly always induces protection. In most patients venom immunotherapy can be stopped after (3 to) 5 years. However, if there is an increased risk of sting anaphylaxis due to intense allergen exposure (e. g. in beekeepers) or if there are individual risk factors for particularly severe reactions (especially mastocytosis and/or elevated baseline serum tryptase concentration, severe cardiovascular disease), modifications of the standard venom immunotherapy are necessary.

Introduction

There are more than 100 000 species worldwide in the order Hymenoptera (class: Insecta). The venom of certain Aculeata, a division of Hymenoptera, is a main cause of allergic reactions. The most important are systemic reactions with immediate hypersensitivity (anaphylaxis). These are the focus of the present article; further background information can also be found in other publications listed under references [1–7].

Relevant Hymenoptera species

honeybees
common wasp

In Central Europe, most anaphylactic reactions are caused by honeybees (*Apis mellifera;* referred to in the following as "bees") and certain types of the common wasp (*Vespula vulgaris, V. germanica;* referred to in the following as "wasp"). Stings from other Hymenoptera such as hornets (*Vespa crabro*), *Dolichovespula* wasps, bumble bees (*Bombus spp.*) and ants (*Formicidae*) are rarely clinically relevant. Different species of Hymenoptera vary in terms of relevance for allergic reactions. This is mainly due to species population size and the insects' behavior when getting food and defending themselves, which results in more or less stings for humans. For instance,

given the use of bumblebees for pollination in greenhouses, it is not uncommon for workers to have systemic reactions to stings in response to this "peaceful" insect. A current report describes the population size and behavior of bees and common wasps that can trigger allergic reactions [8].

In other geographic areas, other Hymenoptera are important triggers of anaphylaxis. These include paper wasps (*Polistes spp.*) in Mediterranean countries and ant species such as *Solenopsis invicta* (fire ants) in the American South, and *Myrmecia pilosula* ("jack jumper") in Australia.

paper wasps

ant species

Along with Hymenoptera, other insects such as mosquitoes and gadflies (diptera) are a very common cause of local allergic reactions and occasionally even anaphylaxis.

Epidemiology

The incidence of systemic reactions in the general population to Hymenoptera stings is estimated at 0.8–5 %, and for severe local reactions 19 % [4]. Hymenoptera stings, especially wasp stings, are the most common cause of anaphylaxis in adults [9]. Skin tests and serum measurements of Hymenoptera venom-specific IgE antibodies (HV-sIgE) suggest that there is IgE-mediated sensitization in up to 25 % of the population. The German Federal Office of Statistics reported 335 deaths between 1990 and 2006 after stings from bees, wasps, or hornets [10]. However, the actual incidence of fatal sting reactions is presumably much higher, as anaphylaxis is often not recognized. Although there is no significant relationship between Hymenoptera venom anaphylaxis (HV-AX) and atopy, there is an association between sensitization to Hymenoptera venom and a predisposition to atopy.

IgE-mediated sensitization in up to 25 %

Anaphylaxis is often not recognized.

Hymenoptera venom

Hymenoptera venom is a conglomerate of many substances. The various venom types contain low-molecular weight substances, peptides and proteins that often have enzyme properties. Cytotoxic and neurotoxic effects are mainly attributable to peptides and phospholipases, while hyaluronidase acts together with biogenic amines as a "spreading factor." Less is known about the substances that make up vespid venom than those in bee venom. The composition of Hymenoptera venom can vary depending on the development of the insect and its living conditions.

The major allergens in bee venom are phospholipase A2, hyaluronidase, which has 50 % sequence homology with wasp venom hyaluronidase, and presumably phosphatase and a serine protease; additional allergens are allergen C and melittin. The major allergens in Vespula venom are phospholipase A1, hyaluronidase, and antigen 5. Other allergens can also be relevant. Most of the major allergens have been characterized molecularly and several recombinant forms have been produced.

The major allergens in bee venom are phospholipase A2, hyaluronidase and presumably acid phosphatase and serine protease.

The major allergens in Vespula venom are phospholipase A1, hyaluronidase, and antigen 5.

Although there are several fundamental differences between the allergens in bee and wasp venom, 50 % or more of patients with HV-AX show reactivity to both bee and wasp venom on serology. In these "double-positive" patients, there can be independent sensitization to both venom types, a cross-reaction to hyaluronidase in bee and wasp venom, or a reaction to cross-reactive carbohydrate determinants (CCD) [11]. Hyaluronidase is present in both types of venom and is the main allergen containing CCD. CCD epitopes are widespread in the plant and animal kingdoms ("panallergens"), and there is cross-reactivity between pollen and food allergies. Bumblebee venom is related to bee venom, but it also contains proteins that are not found in bee venom. There is considerable cross-reactivity with venom from *Vespula, Dolichovespula*, and Vespa; cross-reactivity is lower with venom from Polistes species.

double-positive

cross-reactive carbohydrate determinants

Hymenoptera stings

The Hymenoptera stinger, which delivers the venom, developed from the ovipositor – in other words, only females can sting. Between 50 µg and 140 µg venom are delivered by a bee sting and up to about 3 µg in a wasp sting. When a bee stings a human being, it usually loses its stinger and attached sac with the venom, which continues to be delivered for about one minute. Wasps can retract the stinger and sting repeatedly because, unlike a bee's stinger, a wasp's stinger has no barbs. There are exceptions, however, and while the presence of a stinger can provide a clue as to whether the patient was stung by a bee or wasp, it is not a certain indication.

Between 50 µg and 140 µg venom are delivered by a bee sting and up to about 3 µg in a wasp sting.

Clinical presentation

Local reactions

The toxic effect of the venom delivered in a Hymenoptera sting leads to painful or itching redness and swelling at the site of the sting. The affected site is usually less than 10 cm in diameter and resolves within about a day. An "extensive local reaction" is defined as one with a diameter exceeding 10 cm with redness and swelling generally persisting for more than 24 hours. Such reactions are presumably allergic, but not necessarily IgE-mediated. In very rare situations, a local toxic reaction or allergic swelling after a sting involving the airways can cause life-threatening obstruction. Respiratory symptoms following aerogenic transmission of allergens from the body of the bee have also been reported.

An "extensive local reaction" has a diameter of more than 10 cm with redness and swelling and usually persists for more than 24 hours.

Systemic reactions

Systemic reactions (generalized reactions) are characterized by symptoms that go beyond a local reaction at the site of the sting.

Anaphylaxis

Anaphylaxis is the most critical type of hypersensitivity reaction to a Hymenoptera sting.

Anaphylaxis is the most critical type of hypersensitivity to a Hymenoptera sting. It is triggered by IgE antibodies to certain components in venom. The possibility of a rare immunological or non-immunological ("pseudo-allergic") reaction with similar symptoms, but independent of IgE antibodies, has been postulated but not yet proven.

HV-AX is usually triggered by a single sting. Most reactions begin within 30 minutes, but some may take longer– in vary rare situations even several days. Symptoms range from skin involvement only (flush, generalized urticaria, angioedema) to mild respiratory, cardiovascular or gastrointestinal symptoms or even serious bronchial obstruction or anaphylactic shock, often with loss of consciousness and cardiac or respiratory arrest. The severity of the individual clinical reaction should be classified based on symptoms. Ring and Meßmer have proposed a classification of symptoms (Table 1). Another frequently used classification was developed by H.L. Mueller.

The severity of the individual reaction should be classified based on symptoms.

permanent morbidity

Most patients recover without further complications, but permanent morbidity, especially from myocardial or brain infarction, or arterial or venous thrombosis are possible. The main causes of death related to anaphylaxis are bronchial obstruction and cardiovascular failure as well as disseminated intravascular clotting and adrenaline overdose [12]. Anaphylactic events in pregnant women may cause death or permanent damage to the fetus, especially involving the central nervous system.

The primary causes of death related to anaphylaxis are bronchial obstruction and cardiovascular failure.

Intoxication

If there are many stings, the effects of the toxin can cause serious symptoms or even death. Rhabdomyolysis, hemolysis, cerebral disorders, and liver or renal parenchymal damage can result. Such reactions are uncommon.

If there are many stings, the toxin's effects can lead to serious symptoms or even death.

Unusual sting reactions

Sting reactions with "unusual" clinical presentations are very rare. The pathogenesis of such reactions remains uncertain. Neurological, renal, cardiovascular disease, serum sickness, vasculitis, thrombocytopenic purpura and dermatitis have been reported.

In very rare instances "unusual" sting reactions occur.

Diagnosis

Specific immunotherapy (SIT) is highly effective to protect patients with bee or wasp venom anaphylaxis. SIT is based on the results of diagnostics, which confirm an IgE-mediated allergy. The goal of diagnosis is:

- to classify the type of reactions,
- to identify the responsible insect, and
- to explain the pathomechanism.

Additional diagnostic measures - beyond taking a patient history - are necessary when HV-AX is presumed. Given that the rate of sensitization in the general population is 25 %, "positive" test results are common and can be unsettling for the patient (and doctor) if there is no history HV-AX and there is thus no indication for SIT. Further diagnostic testing is only wise if it appears that the results could help to classify a reaction and be useful for treatment recommendations.

Table 1: Severity grading of anaphylactic reactions (after Ring and Meßmer) [16]*.

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

*Classification is based on most severe symptoms (none of the symptoms are mandatory).

Past recommendations for performing sensitization tests not before two weeks after the sting (but then as promptly as possible) due to a possible refractory period are no longer considered current: skin tests done in the first week after a sting and again 4 to 6 weeks later and measurement of HV-sIgE are more reliable than a single test [13]. If it is not possible to conduct two tests, the procedure should be as previously. If the skin test reaction and/or HV-sIgE measurements do not produce the expected result given in the patient's history, and if a critical decision such as whether or not to perform SIT depends on this, the tests should be repeated .
If the sting was not from a bee or wasp, the possibilities for diagnosis are limited since the allergens of other species are unavailable or are not available for all necessary tests.

Patient history

The patient is asked about symptoms and course of the sting reaction, number of sting reactions, clues to the type of insect responsible, and individual risk factors for anaphylaxis.

visible skin symptoms

Important for retrospective diagnosis of anaphylaxis are visible skin symptoms such as generalized urticaria or angioedema. These are not necessarily present, and if the reaction is severe, patients sometimes only recall loss of consciousness. If there are no objective symptoms, subjective symptoms such as fear, paresthesia, heart palpitations, faintness/dizziness, or sweating are suggestive of a psycho-vegetative response, but do not rule out an anaphylactic reaction. In patients with unclear reactions, the treating physician's report and any records of the reaction and related treatment should be requested and reviewed. The differential diagnosis of anaphylaxis should be taken into consideration [14]. Other differentials, especially with stings involving the face, are local reactions involving the skin or mucous membranes. Other triggers of anaphylaxis such as medication or food should also be considered.

subjective symptoms

The differential diagnosis of anaphylaxis should be taken into consideration.

The patient can usually report that he or she was stung by a bee or wasp, but distinguishing between a bee and a wasp is often a problem. Details surrounding the sting event provide the main clues to the culprit insect (Table 2).

distinguishing between a bee and a wasp

Table 2: Clues to the culprit insect.

Bee	Wasp
Rather more "peaceful" (except near beehives)	Rather more "aggressive"
Spring to late summer (also on warm winter days)	Summer to late autumn
Stinger remains in the skin after stinging	Usually retract stinger after stinging
Mainly near beehive or flowers	Usually around food or waste

Table 3: Risk factors for patients with Hymenoptera venom anaphylaxis.

Intense exposure • Beekeepers, family members and neighbors of beekeepers • Occupations such as fruit sellers, bakers, lumberjacks, firemen, farmers • Leisure activities such gardening, swimming, golf • Bicycling, motorcycle riding
Increased risk of anaphylaxis • History of previous severe sting reactions (grade III or IV, significant bronchial obstruction) • Older age (40 years or older) • Cardiovascular disease • Asthma • Certain medications such as beta blockers (including eye drops), ACE inhibitors, possibly non-steroidal antirheumatic drugs • Physical or psychological stresses • Basal serum tryptase concentration > 10 µg/l (then sometimes mastocytosis) • Mastocytosis (often systemic manifestation)

Individual patient risk is higher in people with a history of many stings due to higher exposure as well as in patients with risk factors for severe reactions.

Individual patient risk is higher in people with a history of many stings due to higher exposure as well as in patients with risk factors for severe reactions (Table 3). For instance, about 80 % of patients with HV-AX and mastocytosis, anaphylactic reactions have level III or IV severity, while such severe reactions occur in only about 20 % of patients without signs of mastocytosis. Other accompanying reactions, as well as any contraindication to SIT, should be included in the patient history.

In patients with HV-AX, an inspection of the skin is indicated in order to detect cutaneous mastocytosis.

Skin inspection

At least in adults, any form of mastocytosis is a risk factor for especially severe anaphylaxis. In patients with HV-AX, an inspection of the skin is indicated to detect cutaneous mastocytosis; it does not have to be associated with an elevated basal serum tryptase concentration (bSTC). Attention should be paid to very discrete skin symptoms of mastocytosis ("occult" cutaneous mastocytosis; Figure 1).

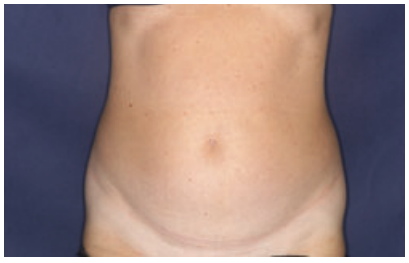

Figure 1: Inconspicuous lesions of cutaneous mastocytosis in a patient with Hymenoptera venom anaphylaxis.

Skin tests

Skin testing is performed with bee venom and venom from *Vespula spp.* – as well as other insect allergens if necessary. The usual positive and negative controls are done. To reduce the risk of systemic side effects, testing is done with incremental concentrations. If there is a risk of a life-threatening response even to the skin test, the patient is admitted to the hospital for testing and follow-up observation. Otherwise the tests are performed on an outpatient basis.

The following procedure may be used: a skin-prick test begins with a venom concentration of 1 µg/ml, which is increased until a positive reaction is elicited. Readings are conducted every 15 minutes and the concentration is increased to 10, and

skin-prick test

100 µg/ml. If there is no reaction, an intradermal test is performed with 1.0 µg/ml. If the skin-prick test is negative, an intradermal test is mandatory. An alternative is to perform strictly intradermal testing (0.001/0.01/0.1/1.0 µg/ml), although this is less comfortable for the patient.

intradermal test

A skin-prick test with aeroallergens (cat, house dust mites, grass pollens) is useful for detecting atopic diathesis.

In vitro tests

serum IgE antibodies

Specific IgE antibodies to bee and wasp venom (and other insects if necessary) can be measured in the serum. Various types of tests are available, and one should select the most exact method possible.

boostering

The concentration of HV-sIgE to the causal venom increases sharply a few days or weeks after the sting as a result of boostering in response to antigen exposure and then often decreases again, sometimes within already a few weeks. This pattern can help identify the culprit insect.

additional studies

If HV-sIgE is not detectable, even after testing twice, and if the patient history and skin test results fail to yield a therapy-relevant diagnosis, additional tests may be performed. These include a basophil activation test, cellular antigen stimulation test (CAST), or histamine release test with peripheral blood cells. Serum concentrations of Hymenoptera venom-specific IgG antibodies can provide information on allergen contacts. IgG antibodies may be pathophysiologically significant in serum sickness-like or other unusual reactions.

If HV-sIgE is found to bee or wasp venom, and if only one of these seems to be the responsible trigger, inhibition tests can be used to try to detect cross-reacting antibodies which often target CCD. These widespread pan-allergens are found, for example, on bromelain or horseradish peroxidase, which thus – as with MUXF (CCD component in bromelain) – can be used in screening for such antibodies. Antibodies to CCD are not necessary clinically irrelevant [15]. If they are detected – as with other cross-reacting HV-sIgE – their presence must be carefully weighed together with all findings.

Basal serum tryptase concentrations should be determined in patients with HV-AX.

BSTC should be determined in patients with HV-AX. At elevated concentrations (> 10 µg/ml) there is an increased risk of extremely serious sting reactions [5]. Often such patients also have mastocytosis, usually with skin symptoms. In mast cell disease (mastocytosis and/or elevated bSTC) additional diagnostic tests may be necessary with regard to mastocytosis.

Evaluating the results of diagnostic tests

The results of diagnostic testing depend on different variables and should be carefully interpreted. The following main points should be considered:

- The patient's own account of whether HV-AX was caused by a bee or wasp is usually unreliable.
- There is no positive correlation between degree of sensitization and the severity of previous or future reactions.
- "False negative" and "false positive" results can occur with any test.
- In wasp venom allergy, unlike in bee venom allergy, there are no or only low concentrations of specific serum IgE to the triggering insect.
- The increase in HV-sIgE immediately after the sting is followed by a later – and sometimes rapid – decrease to undetectable levels. Skin test reactivity fluctuates less over time.
- Lower reaction thresholds in skin tests with Hymenoptera venom and higher concentrations of HV-sIgE are more common in patients with atopic diathesis.

non IgE-mediated reaction or other elicitors

In less than 2 % of our patients with HV-AX, skin tests and measurements of HV-sIgE fail to detect Hymenoptera venom sensitization; in about half of these patients, sensitization is detected by a basophil activation test or a histamine release test. Failure to detect sensitization to Hymenoptera venom using all of these methods may be attributable to test failure, a non IgE-mediated reaction (e.g., immune complex anaphylaxis), or other elicitors of anaphylaxis.

Sting challenge tests

Challenge testing is the gold standard for diagnosis of food or drug allergy-induced anaphylaxis. A sting challenge with a live insect should not be used in patients with

HV-AX who are not desensitized, given that the allergen dose cannot be incrementally increased and a difficult-to-control or even life-threatening reaction can occur. Moreover, such sting challenge tests in patients with a history of prior HV-AX are not helpful, as the absence of systemic symptoms does not exclude the possibility of a systemic reaction to a later sting.

Principles of therapy

Management of an acute reaction

Treatment of local reactions includes topical therapy consisting of a high potency topical corticosteroid (cream or gel) combined with a moist dressing every few hours 2–3-times per day. This should be started as soon as possible after the sting. An oral H1-blocking antihistamine is also recommended. For severe local reactions, oral corticosteroids may be given for a few days (initially 0.5–1 mg prednisone equivalent/kg body weight), after ensuring that there are no contraindications.

Emergency care for HV-AX is given according to current guidelines [16].

In unusual sting reactions, systemic corticosteroids are generally the basic therapy.

Long-term treatment

The major components of therapy are

- Avoidance of the allergen,
- Self-administration of therapy by the patient after the next sting, and
- SIT in patients with HV-AX.

allergen avoidance

Patients should be instructed in person and also by written information [7] on allergen avoidance.

self-administration of treatment

emergency kit

For self-administration of treatment in the event of a future sting, the patient should be provided with an "emergency kit" and be instructed to carry it at all times. The procedure in the event of a sting should be explained (removal of the stinger if it is still in the skin, use of emergency medication, and notification of other persons or a doctor as well as positioning; details are given in [7]).

Severe local and unusual sting reactions

Patients with more pronounced local reactions to Hymenoptera venom should be given an emergency kit with an H1-blocking antihistamine and a highly effective topical corticosteroid in a cream or gel for immediate use in the event of a sting. If a sting occurs, the patient should seek medical attention as soon as possible to determine whether short-term systemic corticosteroid therapy is needed. In stings on the face or neck, follow-up observation may be needed to ensure prompt management of any respiratory tract obstruction.

In unusual reactions as well, the use of systemic corticosteroids should be determined as quickly as possible.

Anaphylaxis

Patients with HV-AX are given an emergency kit with the following:

antihistamine

corticosteroid

epinephrine

β2-sympathomimetic for patients with asthma

- A rapid-acting H1-blocking antihistamine for oral use,
- A corticosteroid (100 mg prednisone equivalent for adults) for oral use (or as a suppository in young children) and
- Epinephrine for intramuscular autoinjection (in adults 0.3 mg; in children weighing 15 to 30 kg 0.5 mg per kg).
- Patients with asthma or clear asthmatic reaction in HV-AX also receive a rapid-acting β2-sympathomimetic for inhalation.

In pediatric patients, the choice of emergency medication depends on age; detailed information has been recently published [17]. In patients at risk for side effects to epinephrine (e.g., patients with severe cardiovascular disease, hyperthyroidism), self-administration of epinephrine should be reviewed by a cardiologist.

Patients who have not yet been desensitized, and those who are desensitized but in whom the effectiveness of therapy is uncertain, should immediately take both the antihistamine and corticosteroid if they are stung again by the culprit insect (or by an unidentified insect). Autoinjection of epinephrine is only performed if systemic symptoms develop. Desensitized patients who tolerated a sting challenge test without a generalized reaction should only use the emergency medication if there is an

unexpected systemic reaction. Any patient with a systemic reaction and - irrespective of symptoms - non-desensitized patients and those with a history of very severe reactions should seek prompt medical attention.

The working group "Anaphylaxis – Training & Education" (AGATE) has developed a training program that helps patients to cope with anaphylaxis in daily life. Patients with HV-AX should be advised to participate in this training program.

training program

Patients with anaphylaxis should not be given beta blockers or ACE inhibitors, as reactions can be particularly severe and are difficult to manage. While ACE inhibitors can almost always be replaced by other drugs, beta blockers are more difficult to replace. If there is an urgent need to use beta blockers (for example, in certain heart rhythm disorders), they should be continued (see below). Acetylsalicylic acid can be an important co-factor in food allergy-related anaphylaxis. The role of non-steroidal anti-inflammatory drugs in triggering HV-AX is not yet clear.

Patients with anaphylaxis should not be given beta blockers or ACE inhibitors.

non-steroidal anti-inflammatory drugs

Patients with HV-AX can be treated causally by SIT.

Specific immunotherapy

A standard dose of HV-SIT of 100 µg prevents a systemic reaction in 75–95 % of patients who are stung again. If treatment fails – HV-AX on sting challenge or accidental sting despite SIT – increasing the maintenance dose is almost always effective [18].

HV-SIT almost always offers protection.

Contraindications and modalities for performing SIT [3] should be taken into consideration when treating Hymenoptera venom allergy.

Indications

Allergen-specific immunotherapy with Hymenoptera venom (HV-SIT) is indicated in patients with a history of HV-AX in response to a bee or wasp sting (or bumblebee or hornet) and detection of IgE-mediated sensitization to the venom that triggered the reaction. Sensitization is detected by immediate hypersensitivity on a skin test and/or detection of HV-sIgE. If no sensitization is detected, the results of additional tests may be useful (especially CAST, histamine release test, basophil activation tests). HV-SIT is not indicated in severe local reactions or unusual sting reactions.

Allergen-specific immunotherapy with Hymenoptera venom is indicated in patients with a history of HV-AX in response to a bee or wasp sting and detection of IgE-mediated sensitization to the venom that triggered the reaction.

HV-SIT is not indicated in severe local reactions or unusual sting reactions.

We recommend HV-SIT for any adult with HV-AX, regardless of how severe (some institutions recommend it only in patients who have had a severe sting reaction). Since the occurrence and severity of anaphylaxis depend on several factors, i.e., given that a future sting can cause a more severe reaction, the pros and cons of not performing HV-SIT should be thoroughly discussed with the patient. HV-SIT is warranted in patients with respiratory or cardiovascular symptoms, with risk factors (Table 3) and impaired quality of life due to disease. Only in children aged 2 to 16 years with systemic anaphylactic reactions with only skin symptoms has it been shown that even without HV-SIT, later stings induced in less than 20 % another systemic reaction and that it was not more severe [19]. In children with such reactions, management should also take into consideration the reliability of the patient's own report and risks associated with children's behavior. It should be noted that in one study, among patients who experienced exclusively systemic skin reaction during childhood, during an average follow-up observation period of 18 years, a systemic reaction occurred to a sting event in 13 % without HV-SIT, but in none of the patients who had been treated with HV-SIT [20].

HV-SIT is warranted in patients with respiratory or cardiovascular symptoms, and those with risk factors or an impaired of quality of life due to disease.

In women of childbearing age, HV-SIT should be started before a pregnancy in order to prevent the risk of HV-AX, also for the fetus.

In women of childbearing age, HV-SIT should be started before a pregnancy.

If both bee and wasp venom allergies are present, or if there is sensitization to both venoms making it impossible to say which is the cause, the patient should be treated with both types of venom. Given the high risk of very severe HV-AX in patients with mastocytosis and/or elevated bSTC, treatment is done with both venoms if the patient is double sensitized.

HV-AX to bumblebee or hornet venom is rare. Therapy is normally done with the associated bee or wasp venom, respectively. This serves primarily to protect against reactions to a later bee or wasp sting which is much more common than a bumblebee or hornet sting. Nevertheless, in the event of HV-AX after a bumblebee or hornet sting, it is better to use the respective venom. (Bumblebee and hornet venoms are not available on the market in Germany).

HV-AX to bumblebee or hornet venom is rare.

Contraindications

In patients with HV-AX with the risk of a potentially life-threatening reaction, long-term contraindications to SIT are only relatively valid. The decision for or against HV-SIT in patients with contraindications is made on an individual basis and if necessary with the physician in charge of treating the accompanying disease. The risk-to-benefit ratio should be carefully weighed to determine whether avoiding HV-SIT, with a sometimes only hypothetical risk, is actually more risky than performing HV-SIT despite contraindications.

risk-to-benefit ratio should be carefully weighed

Certain contraindications to SIT with aeroallergens, especially severe cardiovascular disorders or diseases involving serious damage to the respiratory tract, are indeed usually an urgent indication for HV-SIT. Without HV-SIT the risk associated with a future sting is usually much greater than in correctly performed desensitization.

Common contraindications are the use of beta blockers or ACE inhibitors.

A common contraindication is the use of beta blockers (also in eye drops). It is usually possible to switch medication. If beta blockers cannot be avoided, then at least during the dose-increase phase of HV-SIT beta blockers should be discontinued or replaced. If this is not possible, the dose-increase phase of HV-SIT should be performed in a setting with emergency care including uninterrupted monitoring of ECG, blood pressure, and respiration, and then continued as usual. In patients with cardiovascular disease, generalized reactions during build-up phase and maintenance therapy of HV-SIT as well as with a later sting are equally common with or without the use of beta blockers [21]. In patients on ACE inhibitors, it is usually possible to substitute another medication. If not, then the procedure is the same as for beta-blockers.

It is usually possible to switch medication.

In patients with malignant disease, HV-SIT is performed if there is an urgent indication for doing so.

In patients with malignant disease, HV-SIT is performed if there is an urgent indication for doing so once the cancer is in remission and the highest risk of progression is past. If complications arise with regard to the cancerous disease, immunotherapy is temporarily or permanently discontinued.

In patients in whom the immune system is severely impaired, it is difficult to decide whether or not to perform HV-SIT.

It is difficult to decide whether to perform HV-SIT or not in patients in whom the immune system is severely impaired due to genetic or acquired defects, or autoimmune disease or immunosuppressant therapy. Along with the possible influence of desensitization on the immune disease or treatment, the reduced effectiveness of HV-SIT should be taken into consideration.

Well-tolerated HV-SIT may be continued during pregnancy.

HV-SIT cannot be started during pregnancy, but if it is well tolerated, it may and should be continued.

Allergen-specific immunotherapy procedures

The standard maintenance dose is 100 µg Hymenoptera venom

HV-SIT may be performed with an aqueous allergen extract or an aluminum hydroxide absorbing extract, administered by subcutaneous injection. The standard maintenance dose is 100 µg Hymenoptera venom, which is injected every 4 weeks during the first year of therapy, and then every 6 weeks. The effectiveness is dose-dependent, and it is therefore recommended that patients with bee venom allergy and risk factors (Table 3) are given an increased maintenance dose of 200 µg from the start, since HV-SIT with bee venom is less effective than that with wasp venom [22]. In therapy with wasp venom, an elevated maintenance dose from the start may occasionally be considered (for instance in patients with several risk factors).

increased maintenance dose: 200 µg

There are several treatment protocols for the build-up phase [7] with two basic sets of procedures:

rush desensitization

- Rapid desensitization (inpatient) achieving the maintenance dose within hours ("ultra-rush") or a few days ("rush");

conventional desensitization

- Conventional desensitization (outpatient) achieving the maintenance dose within weeks or months ("cluster" protocols as variants).

Protocols in which the maintenance dose is reached in several months are only suitable under certain conditions as protection is delayed and uncontrolled, additional allergen contact by accidental stings cannot be avoided with certainty. If there is an increased individual risk of severe anaphylaxis (Table 3), this should also be taken into consideration for systemic side effects of HV-SIT and therapy preferably started in the hospital with the patient under surveillance. During the build-up phase, rush desensitization is done in a hospital setting.

depot extract

If the maintenance dose is reached with an aqueous allergen extract, therapy may be continued with a depot extract. Limitations may arise from aluminum hydroxide: it

is recommended that the dose of 200 µg venom as a depot extract not be exceeded over a 4-week period if possible. If a depot extract is used, extending the injection interval to 8 weeks is possible without compromising effectiveness. In patients with significant risk factors, the usual interval between injections should be maintained to be on the safe side.

Side effects

local reactions

Most patients have pronounced local reactions at the injection site during the initial phase. These generally decrease in severity over the course of treatment. A corticosteroid cream and moist dressings can be used to treat symptoms. An additional medication with an H1-blocker (antihistamine) is also helpful.

systemic anaphylactic reactions

Systemic anaphylactic reactions are a much more important side effect. Many patients also experience symptoms such as fatigue, exhaustion, or headache, which subside over the course of treatment. In the literature, there is often no distinction between subjective symptoms and objective, systemic anaphylactic reactions as side effects and these are often lumped together as systemic side effects. In 20 selected studies [23] the frequency of systemic side effects during the initiation phase of HV-SIT is reported at 2.1 % to 50 %, and severe reactions were very rare. Systemic side effects are more common during the dose-increase phase than during maintenance therapy; in bee venom sensitization they are up to eight times more common than in wasp venom sensitization [23]. In addition, mastocytosis is a risk for side effects associated with HV-SIT: systemic anaphylactic reactions during the dose-increase phase in patients with mastocytosis occur in 18.9 % (in 9.3 % of patients without mastocytosis) [23]. In mastocytosis patients, the systemic side effects are mostly mild, but in isolated cases extremely severe reactions can occur. It is thus advisable to hospitalize the patient for the dose-increase phase and to provide for the increased risk during maintenance therapy.

mastocytosis

Local or mild systemic reactions that are limited to skin involvement can be reduced by using an accompanying medication with an H1-blocking antihistamine; severe systemic reactions cannot be prevented by doing so. Compared with aqueous extracts, depot extracts are better tolerated in terms of local as well as systemic anaphylactic reactions, but they cannot be used for rapid desensitization. The dosage increase (according to an "ultra-rush" desensitization protocol) is usually well tolerated in wasp venom allergy and according to some reports is even better tolerated than the usual rapid desensitization. Therapy of bee venom allergy with "ultra-rush" desensitization is not useful given the risk of pronounced local reactions and an increased risk of systemic side effects. Ultra-rush desensitization should only be performed in a setting with access to intensive care, especially in patients with individual risk factors.

Systemic anaphylactic reactions with HV-SIT are treated symptomatically [16], in patients with very mild symptoms an expectant approach may be adequate. If systemic side effects occur, therapy is continued after at least 12 hours, with the dose being reduced by two levels initially and then increased again according to protocol.

Systemic anaphylactic side effects are rare during the build-up phase or during maintenance therapy, and are more common in bee venom than wasp venom allergy. This may make it necessary to discontinue therapy. In patients who have had repeated systemic anaphylactic reactions, it should be assumed that HV-SIT will not prevent further systemic anaphylactic sting reactions. The recommended diagnostic and treatment measures for such situations are listed in Table 4. It is often impossible, however, to achieve long-lasting tolerance of HV-SIT.

Patients with repeated systemic anaphylactic reactions due to HV-SIT do not develop protection against renewed systemic reactions to sting events.

anti-IgE antibody omalizumab

Several recent publications have reported that the anti-IgE antibody omalizumab, given as prior therapy or as an accompanying medication, can achieve tolerability of HV-SIT that was previously not tolerated due to systemic anaphylactic side effects [24]. Until now, however, the optimal time for administering omalizumab relative to HV-SIT, the appropriate dose, and long-term effects are still unknown. Omalizumab is not approved for prevention of anaphylaxis, and it must be prescribed off-label.

Unusual side effects include serum sickness-like reactions, granulomas, and allergic vasculitis.

Unusual side effects are rarely reported. These include serum sickness-like reactions, granulomas at the injection site, or allergic vasculitis. Any symptom that arises

Table 4: Approach to manage repeated systemic reactions to venom immunotherapy.

- Identification (and possibly elimination of) co-factors in anaphylaxis
  - *Medication (especially beta blockers, ACE inhibitors, non- steroidal anti-inflammatory drugs)*
  - *Accompanying respiratory allergy or food allergy*
  - *Mastocytosis*
  - *Other accompanying disorders (e.g., focal infection, thyroid function disorder, malignancy, autoimmune disease)*
- Accompanying therapy with an H1-blocking antihistamine (possibly corticosteroid)
- Therapy for about 6 months with highest tolerated dose of insect venom (injection interval 1-2 weeks), then renewed attempt at dose increase
- As a new approach: accompanying and/or pre-treatment with anti-IgE antibodies (omalizumab)

during SIT must be investigated to determine whether it is related to therapy or not. If so, a decision must be made whether and how to proceed with therapy.

Monitoring therapy

SIT has various effects on the immune system [25]. Clinical diagnostic methods have shown, for instance, HV-SIT initially leads to an increase in skin test reactivity and HV-sIgE. Later, these reactions are less pronounced, or tests may even be completely negative. In contrast, specific IgG antibodies increase and remain elevated for a longer period of time. Initially these are IgG1 antibodies and later IgG4 antibodies. It is not yet possible to measure clinical efficacy based on laboratory parameters, but the concentration of specific IgG antibodies can be used.

sting challenge test

To check the clinical efficacy of HV-SIT a sting challenge test should be performed with a live insect in a setting with available emergency care about 6–18 months after the maintenance dose has been reached; the exact procedure has been described in detail elsewhere [26]. For patients with greater exposure (Table 3) and additional sting challenge should be done immediately after the dose-increase phase. Several larger studies (> 50 patients) have shown that among HV-SIT patients who were exposed to a sting challenge, 15-25 % did not have adequate protection [23]. HV-AX upon sting challenge indicates treatment failure. A tolerated sting challenge has a higher predictive value in terms of the results of later stings but does not prove that the patient is protected. A sting challenge test is usually performed with a single insect. Whether protected patients also tolerate several stings is unknown; however, patients rarely report that several stings were the cause of HV-AX.

HV-AX upon sting challenge indicates treatment failure.

If the sting challenge – or an accidental sting by the culprit insect - causes a HV-AX, increasing the maintenance dose can almost always achieve complete protection [18]. A maintenance dose of 200 µg is usually adequate, and rarely does a further challenge test indicate that an additional increase is necessary. A maintenance dose exceeding 300 µg should only be given after carefully weighing the risk-to-benefit ratio since there is little experience with this and toxic effects – more likely with wasp venom than bee venom – may be seen.

An increased maintenance dose can almost always achieve complete protection.

To further evaluate treatment, factors are measured that may make a dose increase or extended therapy necessary. These factors include patient history (onset or progression of accompanying disease, use of medication, tolerability of HV-SIT, reaction to accidental Hymenoptera stings) as well as skin tests with Hymenoptera venom and assessment of HV-sIgE. Tests should be performed annually and after any accidental Hymenoptera sting (immediately and again 3 to 6 weeks after the sting). Testing should also be done before performing a sting challenge test, before ending HV-SIT, or if there are major side effects related to HV-SIT. Abnormal findings (e.g., increased skin test reactivity or HV-sIgE after prolonged treatment or after stopping

evaluate treatment

therapy) must be evaluated individually and do not justify change of the treatment plan unless there are other aspects.

Duration of specific immunotherapy

After discontinuing HV-SIT the protective effect is lost in up to 15 % within a few years. Permanent protection is only achievable with lifelong therapy. Yet in the majority of patients, HV-SIT can be stopped if

Permanent protection can only be achieved with lifelong therapy.

- Treatment has lasted at least (3 to) 5 years,
- Systemic anaphylactic side effects have not occurred and
- If a sting of the culprit insect (preferably sting challenge or possibly accidental sting) has been tolerated without a systemic reaction.

If the last two conditions are not met, therapy should be continued until loss of skin reactivity and HV-sIgE to the relevant Hymenoptera venom [4, 6]. Such negative test results do not, however, preclude the possibility of a renewed HV-AX.

In patients with risk factors (Table 3), SIT cannot simply be ended after a few years. If patients have increased exposure, SIT is continued until there is no longer such intense contact; in patients with an increased risk of severe anaphylaxis, depending on individual risk profile, therapy is continued. Patients who have had cardiac arrest in HV-AX, with mastocytosis and/or elevated bSTC, or with other unusual high risks, should undergo lifelong HV-SIT. It would be more comfortable for patients on lifelong SIT if the injection intervals were extended to more than 6 weeks. Although a few studies have shown that protection is maintained even if the interval is extend to 3 or 6 months, their value is severely limited due to methodological issues. Studies with patients who have undergone SIT for bee venom allergy have shown that with semi-annual injections, there was no protection in an unacceptably high percentage of 25 % [27]. Extending the usual injection interval should not be done at this time except within the framework of studies.

The tests recommended as treatment monitoring should continue to be performed regularly, even after discontinuing HV-SIT. Sting challenge tests are not recommended for routine testing of protection studies as they may have a booster effect.

After ending HV-SIT, the patient should continue to avoid being stung and should still carry an emergency kit. If HV-AX occurs after concluding SIT, further allergy tests and treatment are required.

Conclusion

HV-AX is a common disorder that can be fatal or result in permanent damage. HV-SIT protects almost all patients from future anaphylactic reactions. Successful therapy depends on a taking a thorough patient history, determining sensitization with skin and/or in-vitro tests, evaluation of risk factors, and properly performed individual therapy. In most patients HV-SIT can be ended after (3 to) 5 years. In patients with risk factors, however, longer and sometimes lifelong treatment is needed.

individual therapy

A major problem is that at most 10 % of patients with HV-AX receive adequate care – this can have severe or even fatal consequences. Physicians and the public need to be better informed about the disease, its diagnosis, and treatment.

Abbreviations

bSTC	Basal serum tryptase concentration
CCD	Cross-reactive carbohydrate determinant
HV-AX	Hymenoptera venom anaphylaxis
HV-sIgE	Hymenoptera venom-specific IgE antibodies in serum
HV-SIT	Allergen-specific immunotherapy with Hymenoptera venom
SIT	Specific immunotherapy

Conflict of interest

None.

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Fragen zur Zertifizierung durch die DDA

1. Welche der folgenden Aussagen ist **falsch**?
a) Gesteigerte örtliche Reaktionen auf Hymenopterenstiche treten bei bis zu einem Fünftel der Bevölkerung auf.
b) Eine Sensibilisierung gegenüber Hymenopterengiften findet sich bei 5 % der Bevölkerung.
c) Hymenopterenstiche sind bei Erwachsenen die häufigsten Auslöser schwerer Anaphylaxie.
d) Systemische Reaktionen auf Hymenopterenstiche treten bei 0,8–5 % der Bevölkerung auf.
e) Die Häufigkeit tödlicher Stichreaktionen in der Bundesrepublik Deutschland ist nicht genau bekannt.

2. **Keine** häufigere Todesursache bei Anaphylaxie ist?
a) Bronchialobstruktion
b) Herzkreislaufstillstand
c) Disseminierte intravaskuläre Gerinnung
d) Leberversagen
e) Adrenalinüberdosierung

3. Welches der folgenden Enzyme ist ein Hauptallergen sowohl in Bienengift als auch in Vespula-Giften?
a) Phospholipase A1
b) Phospholipase A2
c) Saure Phosphatase
d) Hyaluronidase
e) Serinprotease

4. Wann sollten Hauttests und Bestimmung der spezifischen Serum-IgE-Antikörper in der Diagnostik der Hymenopterengiftanaphylaxie idealerweise stattfinden?
a) frühestens 2 Wochen nach Stichreaktion
b) frühestens 3 Monate nach Stichreaktion
c) in der 1. sowie in der 4. bis 6. Woche nach Stichreaktion
d) in der 1. Woche nach Stichreaktion
e) Keine der obigen Angaben ist richtig.

5. Welcher zelluläre Test ist zum Nachweis einer Sensibilisierung gegenüber Hymenopterengift in der klinischen Diagnostik bei Hymenopterengiftanaphylaxie **nicht** sinnvoll?
a) Leukotrienfreisetzungstest
b) Lymphozytentransformationstest
c) Histaminfreisetzungstest
d) Basophilen-Aktivierungstest
e) „cellular antigen stimulation test" (CAST)

6. Welche der folgenden Komponenten gehört **nicht** zum „Notfallset" des erwachsenen Patienten mit Hymenopterengiftanaphylaxie?
a) Pumpe zum Absaugen des Insektengiftes
b) schnell wirkendes H1-blockierendes Antihistaminikum
c) Glukokortikoid
d) Adrenalin-Autoinjektor
e) rasch wirksames β2-Sympathomimetikum (bei Patienten mit Asthma)

7. Bei einem 72-jährigen Hobbygärtner kam es 10 Min nach einem Insektenstich (der Patient spricht von einer „Wespe") zu Anaphylaxie mit kurzfristiger Bewusstlosigkeit. Wegen Herzrhythmusstörungen muss der Patienten mit einem β-Blocker behandelt werden. Im Prick-Schwellentest finden sich Reaktionen auf Bienen- und Wespengift in einer Konzentration von 100 µg/ml, spezifische IgE-Antikörper sind gegen Bienengift (CAP-Klasse 2) und Wespengift (CAP-Klasse 1) nachzuweisen. Die basale Serumtryptasekonzentration beträgt 16,7 µg/l, eine kutane Mastozytose besteht nicht. Welche der folgenden Aussagen ist richtig?
a) Eine spezifische Immuntherapie mit Insektengift kann nicht vorgenommen werden, da der Patient eine β-Blocker-Therapie benötigt.
b) Die höhere CAP-Klasse auf Bienengift im „RAST" belegt, dass eine Biene, und nicht – wie vom Patienten vermutet – eine Wespe Auslöser der Reaktion war.
c) Ab dem Rentenalter wird eine spezifische Immuntherapie mit Insektengift grundsätzlich nicht mehr durchgeführt.
d) Der Patient sollte mit Bienen- und Wespengift behandelt werden.
e) Bei sicherer Einhaltung einer Nachbeobachtungszeit von 30 Min kann die initiale Dosissteigerung der spezifischen Immuntherapie ambulant vorgenommen werden.

8. Bei einer 25-jährigen Bäckereiverkäuferin trat am Arbeitsplatz 6 Min nach Stich eines Insektes ein Herzkreislaufstillstand auf. Die Reanimation durch den Notarzt war erfolgreich, die Patientin erholte sich ohne bleibende Schäden. Welche der folgenden Aussagen ist richtig?
a) Die Patientin muss die Tätigkeit als Bäckereiverkäuferin aufgeben.
b) Eine spezifische Immuntherapie ist nicht möglich, da die Reaktion zu schwer war.
c) Die Patientin ist sorgfältig auf das Vorliegen einer Mastozytose zu untersuchen.
d) Die Reaktion wurde vermutlich durch einen Bienenstich ausgelöst.
e) Therapie der Wahl ist eine konventionelle Hyposensibilisierung.

9. Welche Aussage ist richtig? Ein erhöhtes Risiko für schwere Anaphylaxie besteht nicht …
a) bei höherem Lebensalter.
b) bei Mastozytose.
c) bei Asthma oder kardiovaskulärer Erkrankung.
d) im Kindesalter.
e) bei β-Blocker-Therapie.

10. Welche der folgenden Aussagen zur spezifischen Immuntherapie mit Hymenopterengift ist falsch?
a) Bei den meisten Patienten kann die spezifische Immuntherapie nach (3 bis) 5 Jahren beendet werden, wenn ein erneuter Stich und die

spezifische Immuntherapie ohne systemische Reaktion vertragen wurden.

b) Verlaufskontrollen sollten nach Beendigung der spezifischen Immuntherapie regelmäßig erfolgen.

c) Bei bestimmten Risikofaktoren wird die spezifische Immuntherapie häufig länger als 5 Jahre, manchmal lebenslang vorgenommen.

d) Wird die spezifische Immuntherapie über 5 Jahre hinaus fortgeführt, so sollten die Injektionen mit einem Abstand von 3 bis 6 Monaten erfolgen.

e) Gründe für eine lebenslange spezifische Immuntherapie sind vor allem Mastozytose und/oder erhöhte basale Serumtryptasekonzentration sowie Zustand nach Herzkreislaufstillstand bei Hymenopterengiftanaphylaxie.

Liebe Leserinnen und Leser,

Der Einsendeschluss an die DDA für diese Ausgabe ist der 19. März 2010.

Die richtige Lösung zum Thema „Die Rolle der epidermalen Barriere beim atopischen Ekzem“ in Heft 10 (Oktober 2009) ist: 1e, 2a, 3c, 4d, 5b, 6c, 7a, 8d, 9d, 10a.

Die richtige Lösung zum CME-Spezial ebenfalls in Heft 10 (Oktober 2009) lautet: 1b, 2c, 3b, 4b, 5d, 6c, 7b, 8d, 9e, 10a, 11d, 12c, 13a, 14c, 15d, 16d, 17c, 18d, 19b, 20d, 21a, 22e, 23e, 24a, 25d, 26b, 27c, 28c, 29e, 30e.

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