

Management of occupational *Hymenoptera* allergy

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Purpose of review

Certain outdoor activities show a particularly high risk for being stung by *Hymenoptera* species. Avoidance of such stings is preferable for preventing unwanted local or systemic sting reactions. The purpose of this review is to evaluate the current knowledge on risk factors and management of *Hymenoptera* venom allergy. We will specifically focus on patients with an intense occupational exposure to *Hymenoptera* venom.

Recent findings

Repeated stings were found to increase the risk for subsequent severe anaphylactic sting reactions. The male preponderance for severe anaphylactic sting reactions probably reflects in part a sex-specific occupational exposure being higher in males. When selecting a specific venom for therapy, current knowledge of cross-reactivity between venoms of various species should be considered. If available, venom immunotherapy should be performed using the venom of the culprit insect. Recently, a pilot study also showed the efficacy of venom immunotherapy when treating large local reactions.

Summary

If an intensely exposed patient presents with a systemic anaphylactic sting reaction, efficacy of venom immunotherapy should be demonstrated by a tolerated sting challenge before allowing this patient to return to his/her occupation. Patients with bee venom allergy and an intense exposure should be treated with an increased maintenance dose of 200 µg bee venom. Patients with a history of large local reactions should be provided with an emergency kit, which should contain oral antihistamines and corticosteroids. In patients in whom local sting reactions induce symptoms of high clinical significance, an off-label use of venom immunotherapy may be discussed.

Keywords

anaphylaxis, hymenoptera venom allergy, large local reaction, occupation, risk factors, sting, systemic anaphylactic reaction, venom immunotherapy

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Introduction

Hypersensitivity reactions to *Hymenoptera* stings, which may present as large local reactions (LLRs) or systemic anaphylactic reactions (SARs), have been well documented in the general population. Recently, several reviews summarized current knowledge on important aspects of *Hymenoptera* venom allergy [1,2*,3].

Outdoor workers, however, differ in various aspects from the average patient population suffering from insect venom allergy. The general risk for *Hymenoptera* stings is increased. Consecutively, it has to be expected that the percentage of affected patients is higher among certain occupations. Furthermore, outdoor workers may be exposed to specific insects, which play only a minor role for causing sting events in the general population. Therefore, diagnostics and venom immunotherapy (VIT)

should also consider the venom of insects, which are less aggressive and only rarely involved in sting reactions in the general population. Because work-related exposure usually continues in outdoor workers, it is of major importance to prove the efficacy of VIT in this particular patient subgroup.

In the current review we will try to focus on occupational aspects of *Hymenoptera* venom allergy. We will address specific aspects of primary prevention and also of treatment in patients who have already sustained a hypersensitivity reaction to a *Hymenoptera* sting.

Epidemiology

There are a variety of insect-specific variables which influence the risk of stings and therefore also the risk of LLRs and SARs. These variables include insect type,

behaviour, habits of collecting food, size of the population, and the closeness to humans. Any professional activity that is associated with an increased risk of *Hymenoptera* stings will also increase the risk of venom sensitisation and allergy. The following are the professions or activities with an increased exposure to *Hymenoptera* species:

- (1) beekeepers and family members;
- (2) occupations such as fruit seller, fireman, lumberjack, farmer, gardener, and truck driver;
- (3) outdoor activities including gardening, picnicking, tennis, football, and cycling;
- (4) beehives or wasps nests close to living or working places.

In industrialized countries, the majority of occupations take place in indoor environments. Therefore, it is plausible that work-related venom allergy preponderates in certain occupations. A retrospective analysis [4] from Spain showed that about one-fifth of SARs occurred during working hours. Bee-keepers [5], gardeners [4], farmers, truck drivers, and masons [6] are the professions most frequently involved in occupational venom allergy. In bee-keepers and their family members, up to 32% had a history of insect sting anaphylaxis [5]. This frequency surmounts that expected for SARs to all types of *Hymenoptera* among the general population (0.34–7.5%) [7]. In addition, also the frequency of LLRs varies according to the exposure being about 12% in the general population [1] but 31% in bee-keepers [5].

Not only the frequency of sting-related hypersensitivity reactions is different between outdoor workers and the general population, but also the type of insect causing allergic reactions in outdoor workers may differ from generally relevant elicitors. Many representatives of *Vespula* species, for example *V. vulgaris* and *V. germanica*, form large populations, collect food from human-made food and react with aggressive behaviour when feeling disturbed. Therefore, *Vespula* species play a major role as elicitors of wasp sting anaphylaxis.

Because of the intense exposure, specific occupations are a risk factor for SARs to those insects, which are only rarely elicitors in the majority of insect venom allergic patients. Insects belonging to genera *Dolichovespula*, *Polistes* or *Vespa* usually do not collect food at anthropogenic sources. All these insects are generally less aggressive and usually sting only when feeling attacked [8]. Stings therefore mainly occur near the nests. In certain occupations, there is an intense exposure to the habitat of these insects, and it is there that sting reactions may occur at an increased frequency [8]. Also bumblebees are less aggressive: they react with flight behaviour when feeling attacked, and they sting usually only when being intensely provoked. In greenhouses, bumblebees are used for

the pollination of plants. Therefore, greenhouse workers may receive stings by bumblebees, which occur very rarely in the general population.

Other variables, which may contribute to the particular high sting risk among certain occupations, are derived from human-made changes of ecological balance and climate. Conventional cultivation changes the diversity of insects; the infestation levels of Formicidae were found about seven-fold higher under certain agricultural methods compared with no-tillage [9]. Invasive ants are among the world's most damaging pests [10,11]. Invasion is mostly associated with human activity, mainly transportation. Change of climate may induce a spread of species, which were previously found only in warm areas, to colder climates [8].

Prevention

For all types of unwanted sting reactions, and also in the primary prevention of hypersensitivity reactions to insect stings, reduction of exposure is recommended. Education of employees how to prevent stings should be part of the safety provisions for outdoor workers. The following are the recommendations for prevention of *Hymenoptera* stings (according to [8]):

- (1) at outdoor work: wearing of brogue and tight fitting clothes with long sleeves and trouser legs;
- (2) wearing of textile materials with light colours and smooth surface;
- (3) at picking fruits or flowers: wearing of leather gloves;
- (4) no consumption of sweet food (e.g. fruits, sweets, sugary drinks) during outdoor activity;
- (5) sting risk is increased within a distance of less than 10 m to the insects nest:
 - (a) wearing of protective clothing with nets and gloves,
 - (b) nests should not be jarred, and
 - (c) hectic movements should be avoided;
- (6) in case of a sting:
 - (a) immediate removal of the stinger, if it is still in place and
 - (b) the site of the sting should be covered, e.g. by the hand, to prevent evaporation of alarm pheromones, which could attract other insects and stimulate them to sting.

For highly exposed employees, protective clothing with nets should be routine, at least during hazardous activities, for example for bee-keepers who work in or closely to beehives, or for gardeners who work near wasp nests.

Africanized bees have a significant lower threshold of defensive response than European bees. This characteristic leads more easily to stings [12]. General preventive

measures comprise breeding of less aggressive insects, being an option at least for honey bees. In Germany, sweet temper was a main selection criterion throughout a long time when breeding honey bees. This strategy had resulted in peaceful bee colonies [8] and had reduced the aggressiveness of the insects thereby also reducing the number of stings. Therefore, thoughtful breeding is important for the primary and secondary prevention of unwanted honey bee sting reactions.

Management of large local reactions

There is no established definition of the size of a LLR. Usually, a LLR describes swelling and erythema of more than 10 cm in diameter. LLRs follow the pattern of a late-phase inflammatory response, with a delayed onset (several hours after the sting), a peak after 1–2 days, and a resolution after 3 up to 10 days. LLRs can result in massive swelling of an entire extremity, thereby causing significant morbidity and sometimes even inability to work.

It is still a matter of debate whether LLRs precede subsequent systemic reactions. Some authors recommended prescription of auto-injectable adrenaline to patients with a history of a LLR [13]. In general, we do not support this recommendation. The key problem consists in a recall bias which may occur when evaluating patients with a subsequent SAR who also report a previous LLR. There are no prospective studies that examined the size (average or large) of a preceding local reaction to a sting as a potential risk factor for a subsequent SAR. Even a correct use of auto-injectable adrenaline may cause side effects. The injection of the drug has to be regularly explained to the patient. Therefore, the prescription of this drug in patients with a history of a LLR should be restricted to high risk patients, for example those with an increased baseline serum tryptase concentration. For patients with mastocytosis, an emergency kit with auto-injectable adrenaline should be prescribed routinely even if there is no history of a LLR or SAR after an insect sting.

It is well documented that a history of a LLR is a risk factor for a subsequent LLR to an insect sting [14]. Patients should be provided with an emergency kit allowing treatment of a LLR. The patient has to be instructed to remove the stinger immediately after the sting has occurred. We recommend application of a potent topical corticosteroid to the sting site before the area is cooled with wet dressings or cool packs. The beneficial effects of antihistamines and/or systemic corticosteroids are well documented, for example for the prevention of late-phase drug reactions [15] and also of LLR during VIT [16]. Even if there are no controlled studies, it appears justified to recommend these drugs for

the self-medication of LLRs. Ideally, therapy should be initiated as soon as possible after the sting [17]. If an emergency medication had to be used, the patient should then see a physician in order to discuss the further topical and systemic medication.

According to current guidelines, venom immunotherapy is not recommended for LLRs [18,19]. Up to the recent publication of an observational study [20[•]], efficacy of VIT for treating LLRs had not yet been demonstrated. In that pilot study, patients ($n = 19$) with a history of a LLR received VIT. Efficacy of VIT was examined by repeated sting challenge tests. After the authors had applied VIT for up to 11 weeks, size and duration of LLR decreased significantly by 37 and 53%, respectively. Compared with the first year of treatment, improvement was greater after several years, and reached almost a 90% reduction in size and duration after 4 years of treatment. The authors concluded that VIT may significantly reduce the size and duration of LLRs.

However, further controlled studies will be needed to establish the safety and efficacy of VIT for treating LLRs. Furthermore, VIT is not licensed for the treatment of LLRs, and application of VIT for such reactions represents an off-label use. In patients with repeated work-related sting reactions, the statutory accident insurance might be the responsible cost object.

Management of systemic anaphylactic reactions: emergency medication

There are different recommendations of the national allergological societies regarding the composition and use of an emergency medication for personal administration. We prescribe an emergency kit containing an antihistamine and corticosteroid for oral administration and an auto-injectable adrenaline to all patients with a history of a SAR. Even if there are no symptoms the oral applicable medication shall be immediately taken after an insect sting by untreated patients; patients who are on VIT, but who still have not had a tolerated sting challenge; all patients who start to develop mild symptoms limited to the skin (e.g. pruritus, flush, urticaria; i.e. severity grade I [21]) despite a previous tolerated sting. We recommend to use auto-injectable adrenaline immediately after any systemic symptoms that are not limited to the skin (severity grade II or more [21]).

Risk factors for severe anaphylactic sting reactions

Patients who already had a SAR to an insect sting are highly likely to develop a SAR also to a future sting. For those patients, the individual risk to receive a new sting by the culprit insect is of enormous psychological

importance. According to the classification of Ring and Meßmer [21], severe reactions are defined as anaphylactic shock (grade III) or cardiopulmonary arrest (grade IV). Several risk factors are associated with the occurrence of such severe systemic anaphylactic sting reactions in patients not yet treated with VIT:

- (1) Vespidae stings are associated with more severe reactions than bee stings [22,23,24[•]].
- (2) Preceding, less severe systemic sting reactions seem to have a booster effect [22,23,24[•]] and to predispose the patient to subsequent, more severe reactions.
- (3) The male patient predominance for severe reactions [22,24[•]] probably results from a selection effect. The male preponderance might also result from a sex-specific, different degree of exposure which may vary according to the profession (e.g. outdoor occupations are more common among men than among women).
- (4) An increase in baseline tryptase concentration [24[•]].
- (5) Cutaneous and/or systemic mastocytosis [25,26].
- (6) Older age [24[•]].
- (7) Specific medication [angiotensin converting enzyme (ACE) inhibitors] [24[•]].

Because the booster effect of a preceding mild sting reaction may lead to more severe sting reactions in the future, it is essential that patients with an increased insect exposure receive VIT even if they only had mild SARs to preceding insect stings. This recommendation is of particular importance for patients presenting with additional risk factors for developing a severe SAR after a field sting.

Venom for specific immunotherapy

Licensed preparations of honey bee, *Polistes*, and *Vespula* spp. venom are available from various manufacturers in Europe and northern America. There are sufficient data that prove the safety and efficacy of VIT on the basis of these common insect venom allergens. Some venom preparations, for example bumblebee venom for immunotherapy, are only available from a few suppliers, and on the basis of an individual patient-related prescription. In addition, there is a paucity of data on related safety and efficacy of VIT with these preparations.

There is, on the one hand, a significant IgE crossreactivity between bumblebee and honeybee venom, and, on the other hand, between hornet and *Vespula* spp. venom. Therefore, it has been common practice to perform honeybee venom-based VIT in bumblebee venom allergic patients, and *Vespula* spp. venom-based VIT in patients with hornet venom allergy [27]. 'RAST'-inhibition tests and immunoblotting experiments, however, revealed biochemical differences between bumblebee and honeybee venom and also between European

(*Bombus terrestris*) and American (*Megabombus pennsylvanicus*) bumblebees [28]. There are also differences regarding the composition of European and American *Polistes* spp. [29] and *Dolichovespula* spp., respectively [30].

When applying VIT with venoms only distantly related to the venom of the culprit insect, there is a significant risk of the therapy remaining ineffective. Case reports showed ineffectiveness of VIT on the basis of a *Polistes* extract from the USA when patients had been treated in Europe [31]. Immunotherapy using honeybee venom was not effective in a bumblebee venom-allergic patient [32]. In intensely exposed patients, particularly if there are other risk factors for severe sting reactions, this risk is not acceptable. If crossreactivity to honeybee venom is not demonstrable by in-vitro test methods, VIT with bumblebee venom extract is recommended. According to case reports, treatment with a bumblebee extract was found to be safe and effective [33,34]. Therefore, one should always aim at performing VIT with the culprit venom and at using a venom source from the relevant geographic region.

Fire ants often are aggressive when disturbed and tend to live in groups. Therefore, multiple stings may occur. It was supposed that SARs are mainly elicited by multiple stings. Recently, it was shown that the majority of SARs already occurred after only one sting [35[•]]. For the treatment of ant venom allergy, only whole-body extracts are available. It is still a matter of debate whether treatment with ant venom would not be more effective than that based on whole body extracts. Whole body extracts contain significant amounts of venom. Therefore, specific immunotherapy using those extracts is the treatment of choice, as long as there are no venom-specific extracts available.

Venom immunotherapy

According to current European guidelines, VIT is recommended only for patients with a history of moderate to severe reactions [18]. In case of mild reactions, which are limited to the skin, VIT is not considered mandatory. For patients with individual risk factors or an impairment of quality of life, VIT is also recommended if there is a history of only a mild SAR.

If the patient presents with a history of a very severe reaction and if he wants to pursue his hazardous professional activity, VIT should be considered even if there are contraindications. We recently performed vespid VIT in a gardener with a history of a near fatal sting reaction [36]. He also had a history of Bechterev's (ankylosing spondylitis) and Crohn's disease; both diseases had been stable for years. Shortly after rush VIT had been started,

he had a relapse of the autoimmune disease. Symptoms were treated and VIT was temporarily stopped. After symptoms of the primary diseases had been cured, we continued VIT, which was then tolerated uneventfully, as were a subsequent sting challenge and several field stings. If VIT cannot be performed due to contraindications, we recommend that the patient gives up his hazardous professional activity.

VIT is highly effective: up to 85% of bee venom and up to 95% of the vespid venom allergic patients are protected by the standard maintenance dose of 100 µg administered every 4–6 weeks [37]. If VIT is performed, protection will start at the time when the maintenance dose was achieved: only nine of 79 patients (11.4%) who had a sting challenge immediately after the maintenance dose of 100 µg venom had been reached showed mild to moderate SARs [38]. This percentage of VIT-associated treatment failure is within the normal range when using the standard dose of 100 µg bee venom for a longer time of VIT [39,40*].

VIT with honeybee venom has been found to be less effective than VIT with vespid venom [39,40*]. Therefore, it has been recommended to treat patients who suffer from honeybee venom allergy and who are at an increased risk because of high exposure right from the beginning of VIT with an elevated maintenance dose (usually 200 µg bee venom) [18]. VIT with an increased venom dose may be also considered in patients with vespid venom allergy who present with additional risk factors (e.g. a history of a near fatal sting reaction, or mastocytosis and intense exposure).

Assessment of therapeutic efficacy by a sting challenge is strongly recommended to identify patients who would need a higher dose to achieve treatment success. For occupationally exposed patients, we recommend to perform a diagnostic sting challenge before the patient returns to a potentially hazardous professional activity. This recommendation is of particular importance

- (1) for beekeepers,
- (2) during the flying season of the relevant insects,
- (3) if the occupation itself is associated with a greater hazard after loss of consciousness (e.g. drivers, roofers), and
- (4) for patients with additional risk factors.

By increasing the venom dose used for VIT, nearly all patients can be protected who would still be reacting when treated by a lower dose. After stopping VIT, there is a relapse rate of approximately 15–20% [18]. Again, intensely exposed patients are at a particular high risk of relapse. Therefore, it is recommended to continue VIT at least for the duration of the hazardous professional activity.

Conclusion

In certain occupational settings, *Hymenoptera* stings are more likely to elicit SARs than in the average population. Patients with LLRs are provided with an emergency kit containing antihistamine and corticosteroid for oral use. Off-label use of VIT may be a treatment option in highly exposed patients with repeated severe LLRs. Even after a mild SAR, VIT is recommended for highly exposed patients, particularly if additional risk factors are present. Professionally exposed patients who suffer from bee venom allergy should be treated with an increased maintenance of 200 µg bee venom. Efficacy of VIT should be demonstrated by a tolerated sting challenge before highly exposed patients return to their hazardous professional activity. VIT should be continued as long as the individual exposure remains high. If VIT cannot be performed or if VIT is not successful, it is strongly recommended that the patient gives up his hazardous professional activity.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 150).

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