EAACI Guidelines on Allergen Immunotherapy: hymenoptera venom allergy

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Short title: EAACI Venom Immunotherapy Guidelines

Key words: allergen immunotherapy, bee venom, systemic sting reaction, venom immunotherapy, vespid venom,

Abbreviations:
AAI, adrenaline autoinjector; AIT, allergen immunotherapy; ACEI, Angiotensin-converting enzyme inhibitors; AGREE II, Appraisal of Guidelines for Research & Evaluation; BAT, basophil activation test; CBA, controlled before and after studies; CCT non-randomized controlled clinical trial; EAACI, European Academy of Allergy and Clinical Immunology; ELIFAB, Enzyme-linked immunosorbent facilitated antigen binding; LLR, large local reaction; MAOI, Monoamine oxidase inhibitors; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SR, systematic review; SSR, systemic sting reaction; VIT, venom immunotherapy.
Abstract

Hymenoptera venom allergy is a potentially life-threatening allergic reaction following a bee, vespid or ant sting. In Europe, systemic sting reactions (SSR) have been reported in up to 7.5% of adults but less than 0.8% of children. SSR can be mild with generalized skin reactions only or moderate to severe with a risk of life-threatening anaphylaxis. Patients are advised to carry an emergency kit comprising of adrenaline, H1-antihistamines, and corticosteroids depending on the severity of their previous sting reaction(s). The only treatment that can potentially prevent further SSR is venom immunotherapy (VIT). These Guidelines have been prepared by the European Academy of Allergy and Clinical Immunology’s (EAACI) Taskforce on Venom Immunotherapy (VIT) and are part of the EAACI AIT Guidelines. They aim to provide evidence-based recommendations for the use of VIT. The guidelines have been informed by a formal systematic review and meta-analysis and have been produced using the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach. The process included representation of the full range of stakeholders. VIT is indicated in venom allergic adults and children to reduce subsequent moderate to severe SSR. It is also recommended in adult patients with generalized skin reactions only and impaired QoL due to its significant improvement compared to an adrenaline auto-injector (AAI). These guidelines aim to give practical advice on performing VIT and key sections cover general considerations before initiating VIT, evidence-based, clinical recommendations for VIT, risk factors for side-effects and for relapse of SSR and a summary of gaps in the evidence.
Section A: Introduction

Insects stings by Hymenoptera species are very common; 56.6–94.5% population has been stung at least once in their lifetime. The most frequent clinical presentations of Hymenoptera venom allergy are large local reactions (LLR) and systemic sting reactions (SSR). A large local reaction has been defined as a swelling exceeding a diameter of 10 cm lasting longer than 24 hours. In systemic sting reactions, mild symptoms usually manifest as generalized skin symptoms including flushing, urticaria and angioedema. Typically, dizziness, dyspnea and nausea are examples of moderate reactions, while shock and loss of consciousness, or even cardiac or respiratory arrest all define a severe sting reaction. The rate of self-reported SSR in European epidemiological studies ranges from 0.3 to 7.5% in adults and 0.2 to 0.8% in children. LLRs occur in 2.4% to 26% of the general population. Severe reactions are life-threatening and may potentially cause death.

Although only 0.03 to 0.48% fatalities/1 000 000 inhabitants/year are reported, Hymenoptera sting mortality may have been underestimated, due to deaths by unrecognized stings.

Patients with Hymenoptera venom allergy are advised to carry an emergency kit comprising of H1-antihistamines, corticosteroids, and adrenaline depending on the severity of their previous sting reaction(s). The only treatment that can potentially prevent further systemic sting reactions is subcutaneous venom immunotherapy (VIT), which is reported to be effective in 77–84% of patients treated with bee venom and in 91–96% of patients receiving vespid venom.

These Guidelines have been prepared by the European Academy of Allergy and Clinical Immunology’s (EAACI) Taskforce on Venom Immunotherapy (VIT) and are part of the EAACI Guidelines for Allergen Immunotherapy (AIT). The Guidelines aim to provide evidence-based recommendations for the use of VIT in adults and children. The primary audience are clinical allergists although they are also likely to be of relevance to all other healthcare professionals (e.g. primary care workers, other specialist doctors, nurses and pharmacists working across a range of clinical settings) dealing with insect venom allergic patients. Development of the guidelines has
been informed by a formal systematic review and meta-analysis of AIT for Hymenoptera venom allergy with systematic review principles being used to identify additional evidence where necessary.\textsuperscript{6}
Section B. Methodology

These Guidelines were produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach, a structured approach to guideline production. This is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations and steps to ensure that the risk of bias is minimized at each step of the process.

The process started in April 2015 beginning with detailed face-to-face discussions agreeing the process and the key clinical areas to address, followed by face-to-face meetings and regular web-conferences in which professional and lay representatives participated. The present guidelines are based on the systematic review and they follow the methods and criteria applied.

Clarifying the scope and purpose of the guidelines

The scope of these EAACI Guidelines is multifaceted, providing statements that assist clinicians in the optimal use of AIT in the management of patients with AR and identifying gaps for further research.

Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on VIT represented a range of 16 countries and disciplinary and clinical backgrounds, including allergists, pediatricians, primary care doctors, ophthalmology, ENT, pharmacists, immunologists, nurses and patient representatives. Representatives of immunotherapy product manufactures were given the opportunity to review and comment on the draft guidelines as part of the peer review and public comment process. These comments were considered by the Taskforce and, where appropriate, revisions were made.

Systematic reviews of the evidence

The initial full range of clinical questions that were considered important were rationalized through several rounds of iteration to agree on one key question: what is the effectiveness, cost-effectiveness
and safety of VIT in patients. This was then pursued through a formal systematic review of the evidence.

Formulating recommendations

We graded the strength and consistency of key findings from these systematic reviews to formulate evidence-based recommendations for clinical care [Oxford Centre for Evidence-based Medicine] (Box 2). This involved formulating clear recommendations with the strength of evidence underpinning each recommendation. Where the systematic review did not cover the clinical area, we took a hierarchical approach reviewing other evidence until we could formulate a recommendation, i.e.: (i) other systematic reviews on the subject to see if these provided any clarity on the topic; (ii) randomized controlled trials (RCTs) within these systematic reviews; (iii) other RCTs known to Taskforce members; and (iv) a consensus-based approach. Recommendations apply to all ages unless otherwise indicated in the tables. Experts identified the resource implications of implementing the recommendations, barriers, and facilitators to the implementation of each recommendation, advice on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation.

Peer review and public comment

A draft of these guidelines was externally peer-reviewed by invited experts from a range of organizations, countries, and professional backgrounds. Additionally, the draft guidelines were made available on the EAACI Website for a 3-week period in May 2017 to allow a broader array of stakeholders to comment. All feedback was considered by the Taskforce and, where appropriate, final revisions were made in the light of the feedback received. We will be pleased to continue to receive feedback on these Guidelines, which should be addressed to the corresponding author.

Identification of evidence gaps

The process of developing these Guidelines has identified a number of evidence gaps which are prioritized.
1 Editorial independence and managing conflict of interests

2 The production of these Guidelines was funded and supported by EAACI. The funder did not have
3 any influence on the guideline production process, on its contents or on the decision to publish.
4 Taskforce members’ conflict of interests were declared at the start of the process and taken into
5 account by the Taskforce Chairs as recommendations were formulated. Final decisions about
6 strength of evidence for recommendations were checked by the methodologists who had no conflict
7 of interests in this area.

8 Updating the guidelines

9 EAACI plans to update these guidelines in 2022 unless there are important advances before then.
Section C. General considerations before initiating venom immunotherapy

General indications

VIT is indicated in children and adults following a systemic reaction exceeding generalized skin symptoms with a documented sensitization to the venom of the culprit insect with either skin tests and/or specific serum IgE tests/or the basophil activation test. VIT should also be considered for adults with skin symptoms only but high risk of re-exposure and/or impairment in quality of life. VIT is not indicated if no sensitization to insect venom can be verified. VIT is also not indicated in patients with unusual reactions that cannot be attributed to type I immediate reactions such as thrombocytopenic purpura and vasculitis, rhabdomyolysis or renal failure after multiple stings. The risk for future systemic reactions is low in patients with LLR, in whom only 2-7% developed SSR in the future. As patients with repeated LLRs have been reported to have a minimal risk for SSR, VIT is generally not recommended in these patients. However, subcutaneous VIT has been shown to reduce the size and duration of LLR. Therefore, VIT could be considered a treatment option in patients with recurrent, troublesome LLRs (Table 1).

Absolute and relative contraindications and VIT in patients with special conditions

A European position paper on clinical contraindications has been recently published tackling all relevant contraindications in detail. Below contraindications are briefly described, and recommendations are given in Table 2.

Cardiovascular disease

Fatality studies have shown that particularly elderly patients with Hymenoptera venom allergy and pre-existing cardiovascular disease have an increased risk of dying from a sting. Therefore, in contrast to respiratory allergies, VIT is commonly performed in elderly patients. Based on the risk / benefit profile, cardiovascular diseases per se is not a contraindication for VIT.
Beta-blockers

There is good evidence that anaphylaxis does not occur more frequently in patients receiving beta-blockers, as recently summarized in an EAACI position paper\textsuperscript{14}. However, these patients may be at increased risk of more severe systemic reactions, and emergency treatment with adrenaline may be less effective. Elderly patients with Hymenoptera venom allergy and cardiovascular disease treated with beta-blockers are considered to be particularly at high risk of death in the case of an insect sting. Based on the risk/benefit profile, there is no contraindication for VIT in patients treated with beta-blockers\textsuperscript{14}.

Angiotensin-converting enzyme inhibitors (ACEI)

Large studies conclude patients taking ACEI does not affect the safety of VIT\textsuperscript{16, 17}. One study reported a higher risk for more severe SSR\textsuperscript{18}, however there is a growing evidence base that ACEI intake does not increase the risk for severe SSR in untreated patients\textsuperscript{19-21}. Additionally, in univariate analysis, results are often biased by patient’s age which has been shown to be a strong risk factor\textsuperscript{19, 21, 22}. One multicenter study reported that all patients on ACEI tolerated a sting challenge or field sting during VIT\textsuperscript{23}, whereas in another study patients taking ACEI had a higher risk for relapse\textsuperscript{24}. However, the risk of ACEI might have been overestimated due to the very small patient group and highly selected patients with suggested cardiovascular comorbidity\textsuperscript{25}.

Malignant neoplasia

AIT was safely administered in patients suffering concomitantly from venom allergy and lower stage cancer in a small case series of four patients\textsuperscript{26}. However, controlled studies about the risk or effectiveness of AIT are available in malignant neoplasias\textsuperscript{27}. Therefore, malignant neoplasias are considered an absolute contraindication, even if there is no evidence of unfavourable effects\textsuperscript{14}. There is no evidence on any effect of VIT on the efficacy of chemotherapy, however VIT should be stopped upon starting or changing a treatment for neoplasia. The benefits of VIT should be weighed against the possible burdens of the treatment and the activity of the tumour disease.
Autoimmune disorders

Caution should be exercised when prescribing VIT to patients with multi-organ autoimmune disorders. Due to a lack of available data, there is a relative contraindication in autoimmune disorders in remission and an absolute contraindication in active forms. Organ-specific autoimmune disorders, such as e.g. diabetes mellitus, Hashimoto’s thyroiditis, Crohn’s disease, colitis ulcerosa, and rheumatoid arthritis are not considered a contraindication when the disease is stabilized before initiation of VIT. Immune-suppressive medication could though negatively influence effectiveness of VIT.

Monoamine oxidase inhibitors (MAOI)

The prescribing of MAOIs is now extremely limited, due to the wide range of dangerous interactions. The major concern with their use in the context of AIT is that they prevent the breakdown of sympathomimetic drugs; therefore, in the case of side-effects emergency treatment with adrenaline could result in severe hypertension or tachycardia.

Children below 5 years of age

Severe sting reactions are rare in infants and children of preschool age (<5 years) and so far only non fatal reactions have been described in literature. In the rare event of a SSR, decisions should be made on an individual basis considering the risk of future severe reactions. There are no specific concerns regarding children older than 5 years and the same recommendations in case of different presentations, co-morbidities and co-medication apply.

Pregnancy

The incidence of prematurity, toxemia, abortion, neonatal death and congenital malformation appears to be similar in patients on AIT during pregnancy compared to the general population. During VIT only two mild side-effects were observed in 43 pregnancies. Although data are scarce, VIT appears to be safe in pregnant women. Due to the high risk of relapse after early termination of VIT and
the low risk of side-effects\textsuperscript{16, 33}, a well-tolerated ongoing VIT regime during pregnancy can be
continued, using the last well-accepted VIT dose administered before pregnancy.

3 Mastocytosis

Mastocytosis is a risk factor for both the occurrence of Hymenoptera allergy and for more severe
reactions\textsuperscript{34}. VIT is usually well tolerated by the majority of patients with underlying systemic
mastocytosis\textsuperscript{35}, although side-effects can occur more frequently\textsuperscript{36}. In a recent large study on patients
with confirmed systemic mastocytosis and severe initial sting reactions (63% suffered from loss of
consciousness) it could be shown that VIT was safe and effective\textsuperscript{37}. Whether elevated serum tryptase
levels increase the risk for side-effects is still a debated issue and robust data are scarce. One study
showed a slightly elevated risk for side-effects\textsuperscript{16}, whereas others did not identify a higher risk\textsuperscript{17}
which may be related to a very low overall rate in objective side effects. Generally, there is no
evidence from the literature that VIT should be performed indefinitely in patients with
mastocytosis\textsuperscript{38}.

4 Quality of life

For many patients, any allergic reaction (regardless of severity) is a frightening experience. Given
the effort required to avoid accidental exposures and the inherent uncertainty of success, living with
an insect allergy negatively influences quality of life. This is particularly due to emotional distress
and the necessity of being alert during activities of daily living\textsuperscript{39}. VIT effectively improves quality
of life in vespid venom allergic patients even when they do not experience a re-sting\textsuperscript{40}. In a study
where patients were offered a sting challenge after VIT, 80% of patients reported a significantly
increased quality of life after tolerating a sting challenge\textsuperscript{41}. Therapy with the adrenaline autoinjector
alone was shown to negatively impact on health related quality of life\textsuperscript{40, 42}, a significantly increased
burden for patients\textsuperscript{43} and a higher level of anxiety and depression\textsuperscript{44}. In contrast, more than 90% of
patients perceived VIT as (extremely) positive\textsuperscript{43}, with health and allergy-related quality of life
improved significantly during treatment\textsuperscript{40, 42, 45}, dysfunctional beliefs decreased\textsuperscript{45} and anxiety and
depression levels were the lowest among VIT treated subjects. In a randomized study evaluating dermal reactors, quality of life was also impaired in these systemic reactors and venom immunotherapy was also able to improve their quality of life in contrast to the adrenaline-auto-injectors.


Section D. Venom immunotherapy: evidence based, clinical recommendations

Available venoms

Venom of *Apis mellifera* and *Vespula* spp is generally available in Europe, whereas venom of *Polistes* spp is accessible in those countries where allergy to *Polistes* species is most often occurring. Bumble bee venom is needed if the systemic sting reaction and sensitization is actually caused by bumble bee stings, for example in bumble bee keepers and green house gardeners. Unfortunately, bumble bee venom for VIT is currently only available in single countries.

Preparation of venom

Throughout Europe, non-purified aqueous, purified aqueous extracts and purified aluminium hydroxide adsorbed preparations (so-called “depot” extracts) are used to perform subcutaneous VIT. The efficacy is supported by studies using both sting challenge and ‘in-field’ stings. The aqueous extracts can be used for ultra-rush, rush, clustered and maintenance phases. Purified aluminium hydroxide adsorbed preparations are only administered for the conventional build-up and maintenance schedule. Treatment can be switched from aqueous to depot preparations following the up-dosing phase. Depot extracts seem to be associated with fewer local side effects than aqueous preparations. Results though may have been biased by the slower build-up phase with depot extracts and purified aqueous extracts extracts result in fewer large local reactions compared with non-purified aqueous extracts. A systematic literature review has documented a similar rate of systemic reactions when depot and aqueous venom allergen extracts were used. However, the use of purified / non-purified aqueous extract was not taken into account. A comparative study in bee venom allergic patients indicates the superiority of the purified aqueous extract over the corresponding non-purified aqueous preparation under the same rush protocol in terms of systemic reactions during the buildup phase (Table 3).

Treatment with more than one venom

Selection of the correct venom extract(s) is important to ensure optimal efficacy of VIT.
Sensitization to venom from more than one Hymenoptera species is common in insect venom allergic patients and it can be difficult to determine if this reflects sensitization due to cross-reactivity of shared allergenic determinants in the different venoms or genuine sensitization to more than one species. However, in most of these cases treatment with only one venom appears to be sufficient. A major diagnostic problem is that currently available tests, including component-resolved diagnosis, are not able to distinguish between asymptomatic sensitization and clinically relevant allergy with LLR and SSR. However, if the initial sting reaction was severe and all allergy tests are more or less equally double positive to vespid and to bee venom, VIT with both venoms should be considered. As there is only limited cross-reactivity between bee and vespid venom and vespid and Polistes venom, simultaneous injections with both venoms should be safe. This approach is common in the US and partly in Europe, however, no studies have examined this (Table 3).

Preventive pre-treatment

In numerous double-blind, placebo-controlled trials, it has been shown that pretreatment with H₁ antihistamines improves the tolerability of VIT. More recent studies showed that levocetirizine decreased the rate of SSR and fexofenadine LLR and cutaneous SSR. Importantly, effectiveness of VIT was not negatively influenced. Antihistamines were usually administered 1-2 hours before the injections or sometimes twice daily (Table 3).

Treatment protocols

VIT is performed by subcutaneous injections. VIT consists of an up-dosing (dose increase) phase and a maintenance phase is necessary to ensure a sustained effect of VIT. Conventional protocols, where the maintenance dose is reached in several weeks to months, can be administered in out-patient clinics. In an effort to reach the maintenance dose faster, rush and ultra-rush protocols with several injections on consecutive days are performed in hospitals. Maintenance dose is either reached within a few days or a few hours respectively. Cluster protocols, with several injections per day usually 1-2 weeks apart, are also a quick alternative to conventional protocols.
Importantly, the risk of side-effects is not associated with the severity of initial reactions, high venom-specific IgE levels, and skin test reactivity at low test concentrations. Conventional regimes appear to be best tolerated while rush and ultra-rush protocols are associated with more side-effects.

Up-dosing

The recommended starting dose in up-dosing protocols lies between 0.001 and 0.1 μg. However, it has been shown that a starting dose of 1 μg is usually safe and not associated with a higher rate of side effects in adults or in children. A maximum dose of 100 μg venom allergen dose usually offers adequate protection against systemic allergic sting reactions in the majority of venom allergic subjects.

Maintenance

A maintenance dose of 100 μg venom is significantly more effective than 50 μg. This dose is equivalent to the dry weight of approximately two honeybee stings or 5 wasp stings and has been adhered to as the recommended maintenance dose since the first controlled trial. A higher dose seems to give a better protection when needed. A dose of 200 μg is recommended in patients who develop systemic allergic reactions following a field sting or sting challenge while on 100 μg maintenance VIT. An increased maintenance dose should also be considered in allergic populations at high risk of multiple stings, such as beekeepers and in a few special cases with accumulated risk factors for treatment failure.

The interval for maintenance VIT with 100 μg venom recommended by the manufacturers has been 4 weeks for aqueous preparations and 6 weeks for purified aluminium hydroxide adsorbed preparations (depot extracts). According to expert consensus, injections are usually given every 4 weeks in the first year of treatment, every 6 weeks in the second year, and in case of a 5 year treatment every 8 weeks from year 3. Extending the maintenance interval to 3 to 4 months did not reduce effectiveness or increase side-effects, which could be relevant in terms of convenience and
1 economic savings if life-long treatment is necessary. A dose interval of 6 months did not provide
2 suitable protection in bee venom allergic patients (Table 3).
3
4 **Duration of VIT**
5 Termination after approximately one or two years leads to a relapse rate of 22-27% . Some
6 studies concluded that VIT for 3 years may be sufficient, particularly in patients with only mild to
7 moderate initial sting reactions. Nevertheless, most of the studies have come to the conclusion that
8 an at least 5-year treatment is superior in long-term effectiveness (Table 3).
9
10 **Effectiveness**
11 The effectiveness of bee and vespid VIT is different. The effectiveness of VIT for preventing future
12 SSR ranges from 77 to 84% for bee venom compared to 91 to 96% for vespid venom. The
13 underlying reasons are still unclear. It has been speculated that the amount of venom delivered by a
14 honey bee sting is much larger and more consistent. This may also explain the difference in the
15 reaction rate to sting challenges, which has also been observed in untreated patients. It also
16 appears that the broad sensitization pattern in bee venom allergic patients may play a role in the
17 lower effectiveness of bee VIT. For example, some patients are predominantly sensitized to Api m
18 10, which is underrepresented in certain available bee venom extracts. The specific preparation
19 does not seem to have an impact on the effectiveness. The effectiveness of aqueous and purified
20 aluminium hydroxide adsorbed preparations has been shown to be similar.
21
22 **Effectiveness of VIT after up-dosing phase**
23 Only one recent study has looked at how rapidly protection occurs. In bee VIT 89% tolerated the
24 sting challenge one week after reaching the maintenance dose in a 3-5 day rush protocol or a 3-4
25 month conventional protocol. Those who were not protected tolerated the sting challenge
26 immediately after increasing the dose to 200µg.
27
28 **Effectiveness during/after maintenance VIT**
29 Most effectiveness data are obtained during VIT. Re-sting reaction rates of 0-10% .
after discontinuation of vespid VIT have been reported. Relapses after bee VIT are more frequent: 17\% relapsed one year after stopping VIT\textsuperscript{95}. There is only very few reports on the outcome following VIT withdrawal for more than 5 years, and there is no data for more than 10 years after discontinuing VIT. In two studies 7\%-7.5\% of patients treated with vespid venom relapsed after 7 to 10 years\textsuperscript{83, 84}, while 15.8\% after bee VIT had re-sting reactions\textsuperscript{84}. Another study compared relapse rates after 4 and approximately 10 years and reported relapse rates of 10.2 and 16.2\%, respectively\textsuperscript{96}. In children, the long term outcome is superior compared to adults: only 5\% with moderate-to-severe reactions relapsed after up to 20 years after stopping VIT\textsuperscript{10}.

9 Carriage of adrenaline auto-injectors during and after VIT

It is still a debated issue whether adrenaline auto-injectors (AAI) should be carried during and after VIT, and it has also been difficult to reach a consensus on that topic. According to the EAACI position paper “Self-medication of anaphylactic reactions due to Hymenoptera stings”, 13\% of experts/authors would still prescribe patients who initially only had generalized skin symptoms an AAI after VIT; and 100\% considered recommending carrying an AAI in patients who initially suffered from moderate to severe reactions after terminating VIT if risk factors for treatment failure were present\textsuperscript{97}. However, most patients are protected after reaching the maintenance dose\textsuperscript{74}. Therefore, patients usually do not need to carry AAIs at this point, particularly if their sting reaction had been mild or they had tolerated a sting challenge or field sting during VIT. It should also be considered that carrying an adrenaline autoinjector negatively impacts on health-related quality of life\textsuperscript{40, 42} (Table 3).
Section E. Risk factors for systemic side-effects and relapse of systemic sting reactions

Risk factors for systemic side-effects

The frequency of systemic side effects in large multi-center studies ranges from 8.4 to 20%33, 69, 98. Several risk factors for the occurrence of systemic side-effects have been described. Most of the studies include only small numbers of patients and data are conflicting. The most important risk factor is treatment with honey bee venom. It has been consistently reported that there is a 3.1 to 6.0-fold higher risk for systemic side-effects due to treatment with bee venom71, 98, 62. Rapid dose increase during the build-up phase is a weaker but also established risk factor33, 98. A controversial risk factor for side-effects during VIT is elevated serum tryptase/mastocytosis. An EAACI multicenter study found a slightly elevated risk when tryptase was elevated in vespid venom allergic patients (OR 1.56 (CI 1.15-2.10)98, whereas another study performed in honeybee venom allergic patients did not70. A study only in patients with mastocytosis came to the conclusion that VIT is safe and efficacious37. Although still a debated issue, ACE inhibitors and beta-blockers are not independent risk factors for side-effects17, 98, 99. Importantly, severe initial sting reactions17, 69, 98, high skin test reactivity and high sIgE levels17, 69, 70 are not a risk factor for side-effects (Table 4).

Management of side-effects during VIT

Side-effects are generally mild and do not require medical treatment17, 33. In the case of side-effects, a common procedure is reducing the allergen dose (going two steps back) and continue with the second last well tolerated dose of VIT. If not yet considered, premedication with H1 antihistamines should be established. When side-effects prevent reaching the maintenance dose, premedication with Omalizumab can be given. Currently only case reports have documented the usefulness of Omalizumab100-102 but there is also one negative report103 (Table 4).

Risk factors of relapse of SSR (Table 4)
Age and type of venom allergen

Children generally have a more favorable prognosis than adults\textsuperscript{10, 83, 96}. One study reported relapses in only 3% of bee venom allergic children\textsuperscript{104}, while 17% of relapses were found in the adult population\textsuperscript{95}. The rate of relapse also depends on the severity of the primary reaction (0% vs 5% in children with mild vs. moderate-to-severe reactions, respectively)\textsuperscript{10}. Direct comparison in the same population showed a relapse rate of 8.3% in children as compared to 13.1% in adults who were restung up to 7 years after stopping VIT\textsuperscript{84}. Analysis of studies in which sting provocation tests after stopping VIT were performed\textsuperscript{84, 85, 87, 94, 95, 104-106} as well as a recent systematic analysis on the relapse risk indicate a higher risk of relapse in bee venom allergic patients (0-9% for wasp venom and about 20% for bee-venom treated patients)\textsuperscript{107}. A very recent large study supports these data (rate of relapse for wasp venom 3.9% and for honey bee 15.8% respectively)\textsuperscript{24}. The reason for this difference is not entirely clear but might be attributed to the fact that some extracts used for bee VIT do not contain all relevant allergenic components\textsuperscript{92}.

Severity of reaction prior to VIT

Two studies have concluded that the grade of the SSR prior to VIT was not relevant to the probability of a relapse\textsuperscript{95, 106}, whereas another small study has reported a higher relapse rate in patients who have had a severe SSR before VIT\textsuperscript{85}. In a larger study, relapses were observed in 4% with mild but 14% with severe pretreatment reactions\textsuperscript{83}. In fact, relapses seem to be similar in pattern and severity (or even more serious) to pre-VIT reactions in the same patient\textsuperscript{96}.

Systemic side-effects during VIT

Patients who developed systemic allergic side-effects during VIT showed a relapse risk of 38%, while those who did not only had a 7% risk\textsuperscript{95}. Two more studies reported similar results (46% vs. 8% and 16.4 vs. 5.4% respectively\textsuperscript{24, 87}).

Mastocytosis /elevated serum tryptase levels

A large multicenter study could not detect a higher rates for therapy failure\textsuperscript{23}, and 86% of
mastocytosis patients were protected after initiation of VIT\textsuperscript{37}. However, one study indicated that patients with tryptase >20 and/or mastocytosis in the skin had a 2.7-fold higher risk for therapy failure\textsuperscript{24}. Available data are scarce and heterogeneous but it appears that mastocytosis is not a major risk factor for relapse.
1 \textbf{Section F. Procedures to monitor VIT}

2 Many attempts have been made to find parameters to monitor immunotherapy. Although
3 immunological differences between treated and untreated patients have been reported, available
4 parameters are still inappropriate to estimate the individual risk for relapse of SSR and the sting
5 challenge remains the gold standard in identifying unprotected patients (Table 5).

6 \textbf{Sting challenges / field stings}

7 Performing sting challenges is still the most reliable method and still gold standard to monitor
8 effectiveness of VIT. VIT is effective immediately after reaching the maintenance dose and
9 interval\textsuperscript{74}. Therefore, if feasible, sting challenges should be performed as early as possible to identify
10 those who are not protected with the standard dose. If sting challenges cannot be performed,
11 information about field stings may be helpful. However, the risk of misidentification of the stinging
12 insect and the non-standardized sting procedure reduce reliability\textsuperscript{95}.

13 The reproducibility of sting challenges, at least for diagnostic purposes, is a debated issue. A study
14 on 129 patients revealed that in 95% of patients a diagnostic sting challenge provided a good
15 prediction of tolerance for subsequent field stings\textsuperscript{108}. On the other hand, it has been shown that 21%  
16 of patients not treated with VIT, who initially tolerated a sting challenge, had systemic symptoms
17 after a second challenge\textsuperscript{109}. The reliability of sting challenges to monitor effectiveness of VIT
18 appears to be high\textsuperscript{110}, although repeated sting challenges during 3 to five years after treatment
19 identified 8-10% of patients who relapsed\textsuperscript{86, 106}. Importantly, tolerated sting challenges can improve
20 health related quality of life, especially in patients reporting high impairment of health related quality
21 of life before the sting challenge\textsuperscript{41}. So, sting challenges should not only be seen in the context of
22 evaluating effectiveness but also in terms of fostering individual belief in disease-specific safety.

23 \textbf{Specific IgE and IgG4 levels}

24 It has been repeatedly shown that specific IgE levels to the respective venom decrease during VIT
25 after an initial rise during the first months of treatment\textsuperscript{48, 110}; they usually remain low even after
stopping VIT\textsuperscript{106}. VIT is associated with a significant increase in specific IgG antibodies that has initially been suggested as a marker of effectiveness\textsuperscript{111}; these immunological changes induced by VIT were also reported in bee venom allergic children\textsuperscript{112}. However, after stopping VIT, IgG starts to decrease\textsuperscript{84, 113, 114} and patients appear to be protected by a mechanism independent from venom-specific IgG\textsuperscript{111}. The sub-class of IgG antibodies is usually restricted to IgG1 and IgG4\textsuperscript{110}. However, available data do not support that sIgE, sIgG or sIgG subclasses can be used as predictors for protection during and after VIT.

\section*{Intradermal testing}

Similar to the decline of IgE levels during VIT, skin test endpoint concentrations usually decrease from before to after VIT\textsuperscript{84, 86}. No study has been able to clearly identify a relevant difference in skin test reactivity between tolerant subjects and patients with relapses\textsuperscript{84, 85, 95}. Moreover, patients with negative skin tests have been reported to have significant relapse, a few with near fatal reactions\textsuperscript{87, 96}.

\section*{Basophil activation test (BAT)}

Allergen-specific basophil response remain positive\textsuperscript{115} or even unchanged\textsuperscript{114} during VIT. However, basophil responses at submaximal allergen concentrations markedly decreased after VIT in tolerant subjects and this decline seemed to be associated with the induction of tolerance\textsuperscript{114, 116}. Also the measurement of basophil threshold sensitivity to anti-FcεRI stimulation has been proposed to monitor an early protective effect of VIT\textsuperscript{117}. BAT inhibition tests with sera of treated subjects have been successfully performed in grass pollen allergic patients\textsuperscript{118} but not yet in patients with Hymenoptera venom allergy.

\section*{Enzyme-linked immunosorbent facilitated antigen binding (ELIFAB)}

The ELIFAB is a cell-free assay which is used to demonstrate inhibition of allergen-specific IgE binding by blocking antibodies\textsuperscript{119}. One study measured the serum inhibitory activity of VIT-treated vespid-venom patients\textsuperscript{113}. During VIT, patients displayed an increased ability to inhibit Ves v 5 binding by IgE antibodies. This allergen-blocking capacity correlated with serum concentrations of
Ves v 5-specific IgG4. However, both, the inhibitory activity and IgG4 levels were reduced in patients who stopped VIT several years ago\textsuperscript{113}.

Despite of the availability of new methods such as the BAT and the ELIFAB, most of the parameters cannot exactly distinguish between patients who are protected from future SSR and those who are not at risk. Currently it is not possible to estimate the individual risk for relapse of SSR with any of the available parameters (Table 6).
Section G. Summary, gaps in the evidence and future perspectives

The EAACI Taskforce on VIT has developed these guidelines as part of the EAACI AIT Guidelines project. The guidelines have been informed by a formal systematic review and meta-analysis of VIT. The guidelines provide evidence-based recommendations for the use of VIT for patients with LLR and SSR. A summary of the guidelines is provided in Box 3 (not yet available). The recommendations should be of value to all healthcare professionals involved in the management of patients with insect venom allergy.

There are many areas in these guidelines where there is no high-quality evidence, these signify the gaps in the current evidence base. The key ones are highlighted here and in Table 6. There is a major gap in the evidence base for the clinical effectiveness of VIT in children and adolescents with recommendations at least one grade lower than for adults in most areas. Contrary to the earlier opinion, a clinically important number of children do not outgrow allergic reactions to insect stings. Therefore, VIT in venom allergic children with LLR or generalized cutaneous reactions only should be evaluated in terms of long-term efficacy. Additionally, the effect of VIT in children on health-related quality of life should be investigated. In adults, we need large observational trials with a sufficient number of patients evaluating risk factors for side-effects or therapy failure. There is also little data in the elderly particularly for patients with cardiovascular disease. Additionally, we need data from randomized cost-effectiveness and cost utility studies to use in discussions with healthcare funders. Biomarkers to predict effectiveness of VIT and to identify therapy failure are highly needed.

Despite all these gaps we have clear evidence for the clinical effectiveness of VIT for patients with SSR. There is now a need to ensure that primary care healthcare professionals know which patients might benefit from VIT, that national healthcare providers understand that VIT is cost-effective and that patients and patient support groups are aware of this approach.
References


26. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (OGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int 2014; 23:282-319.


Kontou-Fili K, Filis CI. Prolonged high-dose omalizumab is required to control reactions to venom immunotherapy in mastocytosis. Allergy 2009; 64:1384-5.


Box 1. Key terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergen immunotherapy (AIT)</td>
<td>Repeated allergen administration at regular intervals to modulate immune response in order to reduce symptoms and the need of medication for clinical allergies and to prevent the development of new allergies and asthma. This is also sometimes known as allergen specific immunotherapy, desensitization and hypo-sensitization.</td>
</tr>
<tr>
<td>Venom immunotherapy (VIT)</td>
<td>Form of allergen immunotherapy where insect venom is administered as a series of subcutaneous injections.</td>
</tr>
<tr>
<td>Aqueous venom extracts</td>
<td>Lyophilized venom which is reconstituted in albumin-containing saline diluent.</td>
</tr>
<tr>
<td>Depot venom extracts</td>
<td>Venom preparation adsorbed onto aluminium hydroxide.</td>
</tr>
<tr>
<td>Purified venom extracts</td>
<td>Venom extracts where irritant low-molecular components &lt;1000 Dalton are removed.</td>
</tr>
</tbody>
</table>
Box 2: Assigning levels of evidence and recommendations [Oxford Centre for Evidence-based Medicine]

**Level of evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Systematic reviews, meta-analysis, randomized controlled trials</td>
</tr>
<tr>
<td>Level II</td>
<td>Two groups, nonrandomized studies (e.g., cohort, case–control)</td>
</tr>
<tr>
<td>Level III</td>
<td>One group nonrandomized (e.g., before and after, pretest, and post-test)</td>
</tr>
<tr>
<td>Level IV</td>
<td>Descriptive studies that include analysis of outcomes (single-subject design, case series)</td>
</tr>
<tr>
<td>Level V</td>
<td>Case reports and expert opinion that include narrative literature, reviews, and consensus statements</td>
</tr>
</tbody>
</table>

**Grades of recommendation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>Consistent level I studies</td>
</tr>
<tr>
<td>Grade B</td>
<td>Consistent level II or III studies or extrapolations from level I studies</td>
</tr>
<tr>
<td>Grade C</td>
<td>Level IV studies or extrapolations from level II or III studies</td>
</tr>
<tr>
<td>Grade D</td>
<td>Level V evidence or troublingly inconsistent or inconclusive studies at any level</td>
</tr>
</tbody>
</table>

**Strength of recommendations**

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Evidence from studies at low risk of bias /high quality studies</td>
</tr>
<tr>
<td>Moderate</td>
<td>Evidence from studies at moderate risk of bias /moderate quality studies</td>
</tr>
<tr>
<td>Weak</td>
<td>Evidence from studies at high risk of bias /low quality studies</td>
</tr>
</tbody>
</table>

Recommendations are phrased according to the strength of recommendation: strong: “is recommended”; moderate: “can be recommended”; weak: “may be recommended in specific circumstances”; negative: “can not be recommended.”
Table1. Recommendations: indications for VIT

<table>
<thead>
<tr>
<th>Recommendations for individuals with venom allergy</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIT is recommended in adult patients with systemic sting reactions confined to generalized skin symptoms if quality of life is impaired</td>
<td>I</td>
<td>A</td>
<td>Strong to moderate based on one high quality SR (Dhami 2017) and two adult RCTs of moderate quality (Oude Elberink 2002 and 2009)</td>
<td>Carrying an adrenaline autoinjector without VIT negatively impacts on health-related quality of life.</td>
<td>Dhami 2017</td>
</tr>
<tr>
<td>VIT can be recommended in adults with recurrent, troublesome LLR to reduce the duration and size of future LLR</td>
<td>II</td>
<td>B</td>
<td>Moderate/low based on one open, controlled trial of venom allergic adults with LLR (Golden 2009)</td>
<td>Cost/benefit profile should be considered for this indication. No paediatric data.</td>
<td>Golden 2009</td>
</tr>
<tr>
<td>VIT can not recommended in patients with unusual reactions that do not represent immediate type systemic reactions</td>
<td>V</td>
<td>D</td>
<td>Weak, as no studies have focused on this. Expert consensus</td>
<td>Reactions of non-allergic nature following hymenoptera stings require neither diagnostic testing nor administration of VIT</td>
<td>Expert consensus</td>
</tr>
</tbody>
</table>
Table 2. Recommendations: VIT in patients with special conditions

<table>
<thead>
<tr>
<th>Recommendations for individuals with venom allergy</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIT can be recommended in patients with cardiovascular disease but the underlying disease should be stabilized before initiation</td>
<td>V</td>
<td>D</td>
<td>Weak based on reviews of expert opinions and one case series study</td>
<td></td>
<td>Pitsios 2015</td>
</tr>
<tr>
<td>Beta-blocker therapy may be continued during VIT, but the patient should be informed about possible risks</td>
<td>IV</td>
<td>C</td>
<td>Weak based on two case series studies and expert consensus</td>
<td>Stopping beta-blocker may even harm some patients</td>
<td>Rueff 2009 Rueff 2010</td>
</tr>
<tr>
<td>ACE inhibitor therapy may be continued during VIT, but the patient should be informed about possible risks</td>
<td>IV</td>
<td>C</td>
<td>Weak based on two case series studies and expert consensus</td>
<td></td>
<td>Stoevesandt 2014 Rueff 2010</td>
</tr>
<tr>
<td>VIT can be recommended in high risk venom allergic patients when malignant disease is stable or in remission</td>
<td>IV</td>
<td>C</td>
<td>Weak based on one case series study and expert consensus</td>
<td></td>
<td>Wöhrl 2011</td>
</tr>
<tr>
<td>VIT can be recommended in patients with organ-specific autoimmune disorders when the underlying disease is stabilised before initiation</td>
<td>V</td>
<td>D</td>
<td>Weak based on expert consensus</td>
<td>Immune-suppressive medication my negatively influence effectiveness of VIT</td>
<td>Expert consensus</td>
</tr>
<tr>
<td>VIT cannot be recommended in patients with active, multi-system autoimmune disorders</td>
<td>V</td>
<td>D</td>
<td>Weak based on expert consensus</td>
<td></td>
<td>Expert consensus</td>
</tr>
<tr>
<td>Treatment with MAOIs is not a contraindication for VIT but caution is recommended with the use of adrenaline</td>
<td>V</td>
<td>D</td>
<td>Weak based on case reports and expert consensus</td>
<td>MAOIs are nowadays rarely prescribed</td>
<td>Expert consensus</td>
</tr>
<tr>
<td>VIT in children below 5 years of age should only be considered in the case of severe sting reactions and when the child is likely to be cooperative</td>
<td>V</td>
<td>D</td>
<td>Weak based on expert consensus</td>
<td></td>
<td>Expert consensus</td>
</tr>
<tr>
<td>VIT should not be initiated during pregnancy, but a well-tolerated ongoing VIT can be continued during pregnancy</td>
<td>IV</td>
<td>C</td>
<td>Weak based on case series studies</td>
<td></td>
<td>Metzger 1978 Schwartz 1990</td>
</tr>
<tr>
<td>VIT may be recommended in patients with underlying systemic mastocytosis as it is safe and effective</td>
<td>IV</td>
<td>C</td>
<td>Weak based on two case series</td>
<td>In few patients side effects can be more frequent and severe</td>
<td>Bonadonna 2008, 2013</td>
</tr>
</tbody>
</table>
Table 3. Recommendations: preparation and venom dose, pre-treatment with antihistamines, duration of treatment, carriage of adrenaline autoinjectors during/after VIT

<table>
<thead>
<tr>
<th>Recommendations for individuals with venom allergy</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>purified aluminium hydroxide adsorbed preparations can be recommended as they have a lower frequency of local and systemic side-effects than non-purified aqueous preparations</td>
<td>I</td>
<td>B</td>
<td>Weak to moderate based on one RCT of moderate/low quality</td>
<td></td>
<td>Bilo 2012</td>
</tr>
<tr>
<td>For the majority of patients, VIT with one venom may be recommended as sufficient for protection. In patients with a history of systemic sting reactions to different insects or with severe initial reactions and clearly double positive tests, VIT with two venoms (i.e. Apis mellifera and Vespula or Vespula and Polistes) is recommended.</td>
<td>IV</td>
<td>C</td>
<td>Weak based on one case series study and expert consensus</td>
<td></td>
<td>Stoevesandt 2013</td>
</tr>
<tr>
<td>Two venoms can be administered simultaneously in the left and right arm, respectively. However, in the case of systemic side-effects, VIT should be continued with 30min intervals between injections</td>
<td>V</td>
<td>D</td>
<td>Weak based on expert consensus</td>
<td></td>
<td>Expert consensus</td>
</tr>
<tr>
<td>Pre-treatment with H₁ antihistamines is recommended as it reduces large local reactions and to some extent also systemic side-effects</td>
<td>I</td>
<td>A</td>
<td>Strong to moderate based on four RCTs, two of them were of high quality (Berchtold 1992, Reimers 2000) two of moderate quality (Brockow 1997, Müller 2008)</td>
<td></td>
<td>Müller 2008, Reimers 2000, Brockow 1997, Berchtold 1992</td>
</tr>
<tr>
<td>It is recommended to administer a maintenance dose of 100µg venom</td>
<td>II</td>
<td>B</td>
<td>Weak to moderate based on one CCT of moderate/low quality (Golden 1981)</td>
<td></td>
<td>Golden 1981</td>
</tr>
<tr>
<td>Decision</td>
<td>Grade</td>
<td>Evidence Level</td>
<td>Evidence Strength</td>
<td>Reference(s)</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------</td>
<td>----------------</td>
<td>----------------------------</td>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>If patients still react to field stings or sting challenges, a dose increase to 200µg of venom can be recommended</td>
<td>IV</td>
<td>C</td>
<td>Weak based on one case series study</td>
<td>Rueff 2001</td>
<td></td>
</tr>
<tr>
<td>It may be recommended to give injections every 4 weeks in the first year of treatment, every 6 weeks in the second year, and in case of a 5 year treatment every 8 weeks from year 3-5</td>
<td>V</td>
<td>D</td>
<td>Weak based on expert consensus</td>
<td>Bonifazi 2005</td>
<td></td>
</tr>
<tr>
<td>In the case of life-long therapy, 12 week intervals are still safe and effective</td>
<td>II</td>
<td>C</td>
<td>Moderate based one CCT (Simioni 2013) and one CBA (Goldberg 2001)</td>
<td>Simioni 2013, Goldberg 2001</td>
<td></td>
</tr>
<tr>
<td>It can be recommended to perform VIT for at least 3 years. In patients with severe initial sting reactions, a 5-year treatment is recommended</td>
<td>IV</td>
<td>C</td>
<td>Weak based on case series studies</td>
<td>Reisman 1993, Lerch 1998, Golden 1996</td>
<td></td>
</tr>
<tr>
<td>AAI can not recommended in patients with mild to moderate initial sting reactions without risk factors for relapse during and after VIT</td>
<td>V</td>
<td>D</td>
<td>Weak based on expert consensus</td>
<td>Expert consensus</td>
<td></td>
</tr>
<tr>
<td>AAI may be recommended in patients at risk of multiple stings or with risk factors for relapse during and after VIT</td>
<td>V</td>
<td>D</td>
<td>Weak based on expert consensus</td>
<td>Expert consensus</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Recommendations: risk factors and management of side effects, risk factors for relapse

<table>
<thead>
<tr>
<th>Recommendations for individuals with venom allergy</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>It may be recommended that patients treated with bee venom and those on rapid up-dosing protocols should be closely observed for side effects as they are at a higher risk of experiencing side-effects</td>
<td>IV</td>
<td>C</td>
<td>Weak based on case series studies</td>
<td>The intake of beta-blockers or ACE inhibitors are not independent risk factors for side-effects during VIT. Controversial data exist as to whether elevated serum trypatase levels/mastocytosis increase the risk for side-effects.</td>
<td>Rueff 2010 Mosbech 2000</td>
</tr>
<tr>
<td>It may be recommended that patients with severe initial sting reactions, high skin test reactivity, and high venom specific IgE levels do not require special precautions during VIT, as they are not associated with a higher risk of side-effects</td>
<td>IV</td>
<td>C</td>
<td>Weak based on case series studies</td>
<td></td>
<td>Stoevesandt 2014 Rueff 2010 Lockey 1990</td>
</tr>
<tr>
<td>In case of VIT-related side effects, a temporary reduction of the venom dose (e.g. going two steps back) may be recommended to avoid further side-effects</td>
<td>V</td>
<td>D</td>
<td>Weak based on expert consensus</td>
<td></td>
<td>Expert consensus</td>
</tr>
<tr>
<td>In case of repeated side-effects during up-dosing, pre-treatment with Omalizumab may be recommended</td>
<td>V</td>
<td>D</td>
<td>Weak based on case reports</td>
<td></td>
<td>Kontou-Fili 2008 Schulze 2007</td>
</tr>
<tr>
<td>Life-long VIT can be recommended in patients with bee venom allergy, severe initial sting reactions and systemic side-effects as they are major risk factors for relapse.</td>
<td>IV</td>
<td>C</td>
<td>Weak based on case series studies</td>
<td></td>
<td>Rueff 2013; 2014 Reismann 1993</td>
</tr>
</tbody>
</table>
Table 5. Recommendations: monitoring of VIT

<table>
<thead>
<tr>
<th>Recommendations for individuals with venom allergy</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>In adults, a sting challenge can be recommended as the most reliable method to evaluate effectiveness of VIT</td>
<td>IV</td>
<td>C</td>
<td>Weak based on case series studies</td>
<td></td>
<td>Van Halteren 1997 Golden 1996</td>
</tr>
<tr>
<td>If no sting challenge can be performed, it may be recommended to record outcomes of field stings to evaluate effectiveness of VIT</td>
<td>V</td>
<td>D</td>
<td>Weak based on expert consensus</td>
<td></td>
<td>Expert consensus</td>
</tr>
<tr>
<td>It may not be recommended to determine venom specific IgE, IgG levels, BAT response and allergen-blocking capacity to estimate the individual risk for relapse</td>
<td>IV</td>
<td>C</td>
<td>Weak based on case series studies</td>
<td></td>
<td>Lerch 1998 Müller 1991 Keating 1991</td>
</tr>
</tbody>
</table>
Table 6. Gaps in evidence

<table>
<thead>
<tr>
<th>Gaps</th>
<th>Plan to address</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value of VIT in venom allergic children with LLR or generalized cutaneous reactions only</td>
<td>RCTs</td>
<td>Medium</td>
</tr>
<tr>
<td>Value of VIT on health-related quality of life compared to adrenaline autoinjectors (AAI) in children</td>
<td>RCTs</td>
<td>Medium</td>
</tr>
<tr>
<td>Evaluation of biomarkers such as a sting challenge and basophil activation (inhibition) test in assessing the clinical efficacy of VIT in children</td>
<td>RCTs</td>
<td>High</td>
</tr>
<tr>
<td>Optimal duration of VIT in children, for example 3 versus 5 years or longer when high risk of exposure</td>
<td>RCTs</td>
<td>Medium</td>
</tr>
<tr>
<td>Identification of biomarkers for assessment of treatment success and risk for side effects and relapse</td>
<td>RCT</td>
<td>High</td>
</tr>
<tr>
<td>Evaluation of health economics of VIT</td>
<td>Cost-effectiveness analysis of RCT</td>
<td>Medium</td>
</tr>
<tr>
<td>Comparison of different VIT up-dosing schedules and maintenance doses in adults/children in terms of efficacy both short and long-term</td>
<td>RCTs</td>
<td>High</td>
</tr>
<tr>
<td>Evaluation of adherence to VIT in terms of clinical efficacy (adults/children)</td>
<td>Adherence measured in RCTs</td>
<td>Medium</td>
</tr>
<tr>
<td>Safety of VIT in adults and children with concomitant disease such as cardiovascular disease</td>
<td>Observational trials</td>
<td>Medium</td>
</tr>
<tr>
<td>Safety and efficacy of VIT in patients taking antihypertensive drugs (beta-blockers, ACEI)</td>
<td>Observational trials</td>
<td>High</td>
</tr>
<tr>
<td>Safety and efficacy of VIT in patients with elevated serum tryptase/mastocytosis</td>
<td>Observational trials</td>
<td>High</td>
</tr>
<tr>
<td>Safety of the simultaneous application of two venoms during up-dosing and maintenance phase</td>
<td>RCTs</td>
<td>High</td>
</tr>
</tbody>
</table>