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EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy

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

This Guideline published by the European Academy of Allergy and Clinical Immunology (EAACI) has drawn on data from a systematic review of the literature, more recent published studies and multi-takeholder expert clinical opinion. This Guideline is aimed at healthcare professionals who are encouraged to take the recommendations into account in the context of delivering clinical care. This Guideline is not a substitute for professional clinical judgment, which professionals need to exercise in the context of delivering personalised healthcare.

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Abstract

Hymenoptera venom allergy is a potentially life-threatening allergic reaction following a honeybee, vespid, or ant sting. Systemic-allergic sting reactions have been reported in up to 7.5% of adults and up to 3.4% of children. They can be mild and restricted to the skin or moderate to severe with a risk of life-threatening anaphylaxis. Patients should carry an emergency kit containing an adrenaline autoinjector, H_1-antihistamines, and corticosteroids depending on the severity of their previous sting reaction(s). The only treatment to prevent further systemic sting reactions is venom immunotherapy. This guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Venom Immunotherapy as part of the EAACI Guidelines on Allergen Immunotherapy initiative. The guideline aims to provide evidence-based recommendations for the use of venom immunotherapy, has been informed by a formal systematic review and meta-analysis and produced using the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach. The process included representation from a range of stakeholders. Venom immunotherapy is indicated in venom-allergic children and adults to prevent further moderate-to-severe systemic sting reactions. Venom immunotherapy is also recommended in adults with only generalized skin reactions as it results in significant improvements in quality of life compared to carrying an adrenaline autoinjector. This guideline aims to give practical advice on performing venom immunotherapy. Key sections cover general considerations before initiating venom immunotherapy,

evidence-based clinical recommendations, risk factors for adverse events and for relapse of systemic sting reaction, and a summary of gaps in the evidence.

KEYWORDS
Hymenoptera venom allergy, anaphylaxis, venom immunotherapy, safety, effectiveness

1 | INTRODUCTION

This guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on Venom Immunotherapy (VIT) and is part of the EAACI Guidelines on Allergen Immunotherapy (AIT). This guideline aims to provide evidence-based recommendations for the use of VIT in children and adults. The primary audience is clinical allergists although these are also likely to be of relevance to all other healthcare professionals (e.g, primary care practitioners, emergency departments and other specialist doctors, nurses, and pharmacists working across a range of clinical settings) who may deal with insect venom-allergic patients. (Box 1) Development of this guideline has been informed by a formal systematic review and meta-analysis of AIT for hymenoptera venom allergy (HVA) with systematic review principles being used to identify additional evidence where necessary.[1]

Insect stings by hymenoptera species are very common with data indicating that 56.6%-94.5% of the general population has been stung at least once in their lifetime.[2] The most frequent clinical presentations of HVA are large local reactions (LLR) at the sting site and systemic sting reactions (SSR). A large local reaction has been defined as a swelling exceeding a diameter of 10 cm that lasts for longer than 24 h.[3] In SSR, 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 SSR. The rate of self-reported SSR in European epidemiological studies ranges from 0.3 to 7.5% in adults[4] and up to 3.4% in children.[4,5] LLRs occur in 2.4% to 26.4%[6] of the general population. Severe reactions are life threatening and have been attributed to fatalities. Although only 0.03 to 0.48 fatalities/1 000 000 inhabitants/year are reported,[2] hymenoptera sting mortality may have been underestimated due to unrecognized stings in unexplained causes of death. Patients with HVA are advised to carry an emergency kit comprising of an adrenaline autoinjector (AAI), H_1-antihistamines, and corticosteroids depending on the severity of their previous sting reaction(s). The only treatment that can potentially prevent further systemic sting reactions is venom immunotherapy (VIT), which is reported to be effective in 77%-84% of patients treated with honeybee venom,[7,8] in 91%-96% of patients receiving vespid venom,[7,8] and in 97%-98% of patients treated with ant venom.[9,10]

The systematic review suggested that VIT is effective in reducing subsequent SSR reactions in both children and adults and that this treatment modality can have a significant beneficial impact on disease-specific quality of life (QoL).[1] VIT proved to be safe, and no fatalities were recorded in the studies included in this review. The cost-effectiveness of VIT needs to be established. Modeling cost-effectiveness suggested that VIT was likely to be cost-effective in those at high risk of repeated systemic sting reactions and/or impaired quality of life. However, primary studies assessing the cost-effectiveness of VIT could not be identified.

2 | METHODOLOGY

This guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach,[11,12] an internationally recognized and accepted 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

BOX 1 Key terms

Allergen immunotherapy (AIT)	Repeated allergen administration at regular intervals to modulate immune response in order to reduce symptoms and the need of medication for clinical allergies. This is also sometimes known as allergen-specific immunotherapy, desensitization, hyposensitization, or allergy vaccination
Aqueous venom preparations	Lyophilized venom, which is reconstituted in (albumin-containing) saline diluent.
Depot venom preparations	Venom preparation adsorbed onto aluminum hydroxide or L-tyrosine.
Purified venom preparations	Venom preparations where irritant low-molecular components <1000 Dalton are removed.
Venom immunotherapy (VIT)	AIT where insect venom preparations are administered as a series of subcutaneous injections to eliminate systemic-allergic reactions after insect stings.

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 guideline is based on the systematic review, and they follow the methods and criteria applied.[1]

2.1 | Clarifying the scope and purpose of the guideline

The scope of this EAACI guideline is multifaceted, providing statements that assist clinicians in the optimal use of use of VIT in the management of patients with hymenoptera venom allergy and identifying gaps for further research.

2.2 | Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on VIT represented a range of 16 European countries and disciplinary and clinical backgrounds, including allergists, pediatricians, primary care practitioners, ophthalmologists, ear, nose, and throat (ENT) specialists, pharmacists, immunologists, nurses, and patient representatives. Representatives of immunotherapy product manufactures were given the opportunity to review and comment on the draft guideline as part of the peer review and public comment process. These comments were considered by the taskforce, and, where appropriate, revisions were made.

2.3 | 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 and meta-analysis of the evidence.[1] We continued to track evidence published after our systematic review and meta-analysis with a cutoff date of July 1, 2017, and, where relevant, studies were considered by the taskforce chairs. This evidence will formally be considered in the systematic review update that will precede the update of this guideline, which is scheduled for publication in 2022.

2.4 | Formulating recommendations

We graded the strength and consistency of key findings from these systematic reviews[1] to formulate evidence-based recommendations for clinical care by applying the GRADE process[13] (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, that is: (i) other systematic reviews on the subject to see whether 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 using an expert panel. 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.

2.5 | Peer review and public comment

A draft of this guideline was externally peer-reviewed by invited experts from a range of organizations, countries, and professional backgrounds. Additionally, the draft guideline was made available on the EAACI Web site 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 light of the feedback received. We will be pleased to continue to receive feedback on this guideline, which should be addressed to the corresponding author.

2.6 | Identification of evidence gaps

The process of developing this guideline has identified a number of evidence gaps which are prioritized.

2.7 | Editorial independence and managing conflict of interests

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

2.8 | Updating the guideline

EAACI plans to update this guideline in 2022 unless there are important advances before then.

2.9 | General considerations before initiating venom immunotherapy

2.9.1 | General indications

VIT is indicated in children and adults following a systemic-allergic reaction exceeding generalized skin symptoms with a documented

BOX 2 Assigning levels of evidence and recommendations [Oxford Centre for Evidence-based Medicine]

Level of evidence

Level I Systematic reviews, meta-analysis, randomized controlled trials

Level II Two groups, nonrandomized studies (e.g., cohort, case-control)

Level III One group nonrandomized (e.g., before and after, pretest, and post-test)

Level IV Descriptive studies that include analysis of outcomes (single-subject design, case series)

Level V Case reports and expert opinion that include narrative literature, reviews, and consensus statements

Grades of recommendation

Grade A - Consistent level I studies

Grade B - Consistent level II or III studies or extrapolations from level I studies

Grade C - Level IV studies or extrapolations from level II or III studies

Grade D - Level V evidence or troublingly inconsistent or inconclusive studies at any level

Strength of recommendations

Strong - Evidence from studies at low risk of bias

Moderate - Evidence from studies at moderate risk of bias

Weak - Evidence from studies at high risk of bias

Recommendations are phrased according to the strength of recommendation: strong: "is recommended"; moderate: "can be recommended"; weak: "may be recommended in specific circumstances"; negative: "cannot be recommended".

sensitization to the venom of the culprit insect with either skin prick tests and/or specific serum IgE tests and/or the basophil activation test (BAT). VIT should also be considered for adults with skin symptoms only but at high risk of re-exposure and/or impairment in QoL. VIT is not indicated if no sensitization to insect venom can be verified. Also, an incidental finding of sensitization to insect venom (e.g, using a multiplex system) in patients who have not had a SSR is not an indication for VIT. Furthermore, it is 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 0.8%-7% are expected to develop SSR in the future.[14-16] As patients with repeated LLRs have been reported to have a minimal risk for SSR,[17,18] VIT is generally not recommended in these patients. However, subcutaneous VIT has been shown to reduce the size and duration of LLR.[19] Therefore, VIT could be considered a treatment option in patients with recurrent, troublesome LLRs. Additional precautions should be taken to avoid insect stings during the build-up phase of VIT by following preventive measures such as not going barefoot, not eating outdoors, and avoiding gardening. Beekeepers should stop beekeeping until the maintenance dose is reached because of the increased risk of stings and consecutive SSR (Table 1).

2.10 | Absolute and relative contraindications and VIT in patients with special conditions

An European position paper on clinical contraindications has been published in 2015 tackling all relevant contraindications in detail.[20] In a recently published survey among 520 mainly European allergists, up to 47% had experience with administration of AIT in patients with risk conditions such as cardiovascular disease, taking ACEI or beta-blockers, malignant disease in remission, and autoimmune disease which previously had been considered as contraindications.[21] Problems were uncommon and mostly minor so we have reconsidered contraindications in VIT. Below contraindications are briefly described, and recommendations are given in Table 2.

2.10.1 | Cardiovascular disease

Fatality studies have shown that particularly elderly patients with HVA and pre-existing cardiovascular disease have an increased risk of dying from a sting.[22] Therefore, in contrast to respiratory allergies, VIT is commonly performed in elderly patients. Based on the risk/benefit profile, cardiovascular diseases *per se* are not a contraindication for VIT.[20]

2.10.2 | 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.[20] However, these patients may theoretically be at increased risk of more SSRs, and emergency treatment with adrenaline may be less effective. Elderly patients with HVA and cardiovascular disease treated with beta-blockers are considered to be particularly at high risk of severe SSR in the case of an insect sting.[23] Based on the risk/benefit profile, there is no contraindication for VIT in patients treated with beta-blockers.[20]

2.10.3 | Angiotensin-converting enzyme inhibitors (ACEI)

Studies with large number of patient participants conclude that treatment with ACEI does not affect the safety of VIT.[24,25] One study

TABLE 1 Recommendations: indications for VIT

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
VIT is recommended in adults and children with detectable sensitization and systemic sting reactions exceeding generalized skin symptoms	I (III for children)	A (B for children)	Strong to moderate for adults based on two low risk of bias SR.[1,131] Weak for children based on one high risk of bias CBA[15] and one high risk of bias RCT study that included children[87]	Carrying an AAI without VIT negatively impacts on health-related QoL	Dhami 2017[1] Boyle 2012[131] Golden 2004[15] Hunt 1978[87]
VIT is recommended in adult patients with systemic sting reactions confined to generalized skin symptoms if quality of life is impaired	I	A	Strong to moderate based on one low risk of bias SR[1] and two adult RCTs of moderate risk of bias[50,52]	Carrying an AAI without VIT negatively impacts on health-related QoL	Dhami 2017[1] Oude Elberink 2002 and 2009[50,52]
VIT can be recommended in adults with recurrent, troublesome LLR to reduce the duration and size of future LLR	II	B	Moderate/low based on one open, controlled trial of venom-allergic adults with LLR[19]	Cost/benefit profile should be considered for this indication. No pediatric data	Golden 2009[19]
VIT is not recommended in individuals with incidentally detected sensitization to insect venom and no clinical symptoms	IV	C	Weak based on one case series and expert consensus[18]	Asymptomatic sensitization is very common	Sturm 2014[18]
VIT is not recommended in patients with unusual reactions that do not represent immediate type systemic reactions	V	D	Weak, as no studies have focused on this. Expert consensus	Reactions of nonallergic nature following hymenoptera stings require neither diagnostic testing nor administration of VIT	Expert consensus

reported a higher risk for more severe SSR[26]; however, there is a growing base of evidence that indicates that ACEI do not increase the risk for severe SSR in untreated patients.[27-29] In univariate analyses, results are often confounded by patient's older age which has been shown to be a strong risk factor for more severe SSR.[27,29,30] One multicenter study reported that all patients on ACEI tolerated a sting challenge or field sting during VIT,[31] whereas in another study, patients taking ACEI had a higher risk for relapse.[32] However, the risk of ACEI may have been overestimated in certain studies due to the very small patients' group and highly selected patients with suggested cardiovascular comorbidity.[33] Therefore, ACE inhibitor therapy may be continued during VIT, but the patient should be informed about possible risks.

2.10.4 | Malignant neoplasia

AIT was safely administered in patients suffering concomitantly from vespid venom allergy and less advanced stage cancer in one small case series of four patients.[34] No controlled studies are available relating to the risk or effectiveness of AIT in malignant neoplasias.[20] Therefore, acute malignant neoplasias are considered a relative contraindication, even if there is no evidence on any unfavorable effects of VIT on tumor growth or the efficacy of chemotherapy. The benefits of VIT should be weighed against the possible burdens of the treatment and the activity of the tumor disease. To conclude, VIT can be recommended in high-risk venom-allergic patients when malignant disease is stable or in remission.

2.10.5 | Autoimmune disorders

Caution should be exercised when prescribing VIT to patients with multiorgan 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.[20] Organ-specific autoimmune disorders, such as diabetes mellitus, Hashimoto's thyroiditis, Crohn's disease, ulcerative colitis, and rheumatoid arthritis, are not considered a contraindication when the disease is stabilized, but concerns were raised that immune-suppressive medication could theoretically negatively influence the effectiveness of VIT.[35] Therefore, VIT can be recommended in patients with organ-specific autoimmune disorders when the underlying disease is stabilized.

TABLE 2 Recommendations: VIT in patients with special conditions

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
VIT can be recommended in patients with cardiovascular disease but the underlying disease should be stabilized before initiation	V	D	Weak based on reviews of expert opinions[20] and one case series study[23]		Pitsios 2015[20]
Beta-blocker therapy may be continued during VIT but the patient should be informed about possible risks	IV	C	Weak based on two case series studies[24,26] and expert consensus	Stopping beta-blocker may even harmful for some patients	Ruëff 2010[24] Ruëff 2009[26]
ACE inhibitor therapy may be continued during VIT but the patient should be informed about possible risks	IV	C	Weak based on two case series studies[24,25] and expert consensus		Stoevesandt 2014[25] Ruëff 2010[24]
VIT can be recommended in high-risk venom-allergic patients when malignant disease is stable or in remission	IV	C	Weak based on one case series study[34] and expert consensus		Wöhrl 2011[34]
VIT can be recommended in patients with organ-specific autoimmune disorders when the underlying disease is stabilized	V	D	Weak based on expert consensus	Immune-suppressive medication may negatively influence effectiveness of VIT	Expert consensus
VIT cannot be recommended in patients with active, multisystem autoimmune disorders	V	D	Weak based on expert consensus		Expert consensus
Treatment with MAOIs is not a contraindication for VIT but caution is recommended with the use of adrenaline	V	D	Weak based on case reports and expert consensus	MAOIs are nowadays rarely prescribed	Expert consensus
VIT in children below 5 years of age should only be considered in the event of severe sting reactions and when the child is likely to be cooperative	IV	C	Weak based on one case series[38] and expert consensus		Stritzke 2013[38]
VIT should not be initiated during pregnancy, but well-tolerated ongoing VIT can be continued during pregnancy	IV	C	Weak based on case series studies[39,40]		Schwartz 1990[40] Metzger 1978[39]
VIT may be recommended in patients with underlying systemic mastocytosis as it is safe and effective	IV	C	Weak based on two case series[45,47]	In few patients, side-effects can be more frequent and severe	Bonadonna 2008,[45] 2013[47]

2.10.6 | Monoamine oxidase inhibitors (MAOI)

The prescribing of MAOIs is now extremely limited, due to their wide range of dangerous drug-drug interactions.[36] The major concern with their use in the context of AIT is that they prevent the breakdown of sympathomimetic drugs; therefore, in the event of adverse events, emergency treatment with adrenaline could result in severe hypertension and/or tachycardia.[20,36] To conclude, treatment with MAOIs is not a contraindication for VIT but caution is recommended with the use of adrenaline.

2.10.7 | Children below five years of age

Generally, severe SSR is less frequent in children and appears to be rare in children of preschool age (<5 years).[37] In the rare event of a SSR, decisions should be made on an individual basis considering the risk of future severe systemic reactions. Successful VIT in children under four years has been reported;[38] as the age limit of five years is arbitrary, there are no specific concerns regarding children younger than five years and the same recommendations as in adults apply.

2.10.8 | 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.[39] During VIT, only two mild adverse events were observed in 43 pregnancies.[40] VIT appears to be safe in pregnant women, but data are scarce. Therefore, initiation of VIT is not recommended. Due to the high risk of relapse after early termination of VIT[41,42] and the low risk of

adverse events,[24,43] a well-tolerated ongoing VIT regime during pregnancy should be continued, using the tolerated VIT maintenance dose administered before pregnancy.

2.10.9 | Mastocytosis

Mastocytosis is a risk factor for both the development of HVA and for more severe SSR.[44] VIT is usually well tolerated by the majority of patients with underlying systemic mastocytosis,[45] although adverse events can occur more frequently.[46] 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.[47] Whether elevated serum tryptase levels alone increase the risk for adverse events is still a debated issue and robust data are scarce. One study showed a slightly elevated risk for adverse events,[24] whereas others did not identify a higher risk[25] which may be related to a very low overall rate in objective side-effects in all patients. Generally, there is no evidence from the literature that VIT should be performed indefinitely in patients with mastocytosis.[48] However, VIT may be less protective in patients with severe initial SSR and mastocytosis and/or elevated serum tryptase (>11.4 μg/L). Therefore, for safety reasons, it should be prolonged in those patients; it remains unclear whether it should be given lifelong or after which duration of treatment it should be stopped.

2.11 | Quality of life

For most patients, and their families, 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 HVA negatively influences QoL. This is particularly due to emotional distress of being alert during activities of daily living.[49] VIT improves QoL in vespid venom-allergic patients even when they do not experience a resting.[50] In a study where patients were offered a sting challenge after VIT, 80% of patients reported a significantly increased QoL after tolerating a sting challenge.[51] In contrast, therapy with the AAI alone was shown to negatively impact on health-related QoL,[50,52] a significantly increased burden for patients[53] and a higher level of anxiety and depression.[54] In contrast, more than 90% of patients perceived VIT as (extremely) positive,[53] with health and allergy-related QoL improving significantly during treatment,[50,52,55] dysfunctional beliefs decreasing,[55] and anxiety and depression levels, were the lowest among VIT-treated subjects.[54] In a randomized study evaluating dermal reactors, QoL was also impaired in these systemic reactors and VIT was also able to improve their QoL in contrast to the AAIs.[52]

2.12 | Venom immunotherapy: evidence-based clinical recommendations

2.12.1 | Available venoms

Venom of *Apis mellifera* and Vespula species is available throughout Europe, whereas venom of Polistes is accessible in those countries where allergy to Polistes *species* (e.g, *Polistes dominula* in Spain and Italy) most often occurs. The use of bumblebee venom would be preferable if the primary sensitization was induced by bumblebee stings.[56,57] Bumblebee venom for VIT is currently only available in some countries, for example, in Italy. Worldwide, also ant venoms are available, such as venom of *Myrmecia pilosula* (Jack Jumper Ant) in Australia.

2.12.2 | Preparation of venom

Throughout Europe, nonpurified aqueous, purified aqueous preparations, and purified aluminum hydroxide adsorbed preparations (so-called depot preparations) are used to perform subcutaneous VIT.[58] (Box 1) The efficacy is supported by studies using both sting challenge and 'in-field' stings.[58] The aqueous preparations can be used for build-up protocols including ultra-rush, rush, clustered and conventional, as well as for maintenance phase. Purified aluminum hydroxide adsorbed preparations are typically used for the conventional or clustered build-up and maintenance schedule. Treatment can be switched from aqueous to depot preparations following the rapid updosing phase.[59] Depot preparations seem to be associated with fewer local side-effects than aqueous preparations, but results may have been biased by the slower build-up phase with depot preparations.[60] Purified aqueous preparations cause smaller local reactions compared with nonpurified aqueous preparations.[61] A systematic literature review has documented a similar rate of systemic adverse events when depot and aqueous venom allergen preparations were used, but the difference between purified and nonpurified aqueous preparations was not taken into account.[62] A comparative study in honeybee venom-allergic patients indicates the superiority of the purified aqueous preparations over the corresponding nonpurified aqueous preparation under the same rush protocol in terms of systemic reactions during the build-up phase[63] (Table 3).

2.12.3 | Treatment with more than one venom

Selection of the correct venom preparation(s) is important to ensure optimal efficacy of VIT. Sensitization to venom of more than one hymenoptera species is common in insect venom-allergic patients,[64] and it can be difficult to determine whether this reflects double sensitization due to cross-reactivity of shared allergenic determinants or genuine multiple sensitization to more than one venom. However, in most of these cases, treatment with only one venom appears to be sufficient.[64] A major diagnostic problem is that currently available tests, such as skin testing, IgE determination including component-resolved diagnosis or the BAT, are not able to distinguish between asymptomatic sensitization and clinically relevant allergy with LLR and SSR.[18] However, if the initial sting reaction was severe and all allergy tests are almost equally positive to vespid and to honeybee venom, VIT with both venoms should be considered. As there is only limited cross-reactivity between honeybee and vespid venom and Vespula and Polistes venom, simultaneous injections with both

TABLE 3 Recommendations: preparation and venom dose, pretreatment with antihistamines, duration of treatment, carriage of adrenaline autoinjectors during/after VIT

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key reference
Purified venom preparations can be recommended as they have a lower frequency of local and systemic adverse events than nonpurified aqueous preparations	I	B	Weak to moderate based on one RCT of moderate/high risk of bias[63]		Bilo 2012[63]
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.	IV	C	Weak based on one case series study[64] and expert consensus		Stoevesandt 2013[64]
Two venoms can be administered simultaneously in the left and right arm, respectively. However, in the case of systemic adverse events, VIT should be continued with 30-minute intervals between injections	V	D	Weak based on expert consensus		Expert consensus
Pretreatment with H_1 antihistamines is recommended as it reduces large local reactions and to some extent also systemic adverse events	I	A	Strong to moderate based on four RCTs, two of them were of low risk of bias,[67,68] two of moderate risk of bias[65,66]		Müller 2008[68] Reimers 2000[67] Brockow 1997[66] Berchtold 1992[65]
It is recommended to administer a standard maintenance dose of 100 μg venom	II	B	Weak to moderate based on one CCT of moderate/high risk of bias[88]		Golden 1981[88]
If patients still react to field stings or sting challenges, a dose increase to 200 μg of venom can be recommended	IV	C	Weak based on one case series study[91]		Ruëff 2001[91]
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	V	D	Weak based on expert consensus[93]		Bonifazi 2005[93]
In the case of lifelong therapy, 12-week intervals may be still safe and effective	II	C	Moderate based one CCT[94] and one CBA[95] study		Simioni 2013[94] Goldberg 2001[95]
It can be recommended to perform VIT for at least 3 years. In patients with severe initial sting reactions, at least a 5-year treatment is recommended	IV	C	Weak based on case series studies[98,99,101]		Lerch 1998[99] Golden 1996[101] Reisman 1993[98]
Lifelong VIT may be recommended in highly exposed patients with bee venom allergy, patients with very severe initial sting reactions (Muller grade IV or grade III-IV according to Ring & Messmer), and patients with systemic side-effects during VIT as they are major risk factors for relapse	IV	C	Weak based on case series studies[8,31,98]		Ruëff 2013[31]; 2014[8] Reismann 1993[98]
During and after VIT, AAI cannot be recommended in patients with mild-to-moderate initial sting reactions without risk factors for relapse	V	D	Weak based on expert consensus		Expert consensus
During and after VIT, AAI may be recommended in patients at risk of multiple stings or with risk factors for relapse	V	D	Weak based on expert consensus		Expert consensus

venoms should be safe. This approach is common in the United States (US) and partly in Europe; however, no studies have examined this question (Table 3).

2.13 | Preventive pretreatment

In several double-blind, placebo-controlled trials, it has been shown that pretreatment with H_1 antihistamines improves the tolerability of VIT.[65-68] In detail, it was reported that levocetirizine decreased the rate of SSR[68] and fexofenadine decreased the rate of LLR and cutaneous SSR[67] (Table 3). Importantly, effectiveness of VIT was not negatively influenced.[68,69] Antihistamines were usually administered 1-2 h before the injections or sometimes twice daily. In case of repeated adverse events during updosing, pretreatment with omalizumab may be recommended.[70-72]

2.14 | Treatment protocols

VIT is performed by subcutaneous injections. VIT consists of an updosing phase and a maintenance phase, which 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 outpatient clinics.[73] In an effort to reach the maintenance dose faster, rush[73-77] and ultra-rush protocols[78-81] with several injections per day on consecutive days are performed in hospitals. Maintenance dose is reached either within a few hours or within a few days, respectively. Cluster protocols, with several injections per day usually 1-2 weeks apart, are also a quick alternative to conventional protocols.[82,83] Importantly, the risk of adverse events is not associated with the severity of initial reactions,[24,25,84] high venom-specific IgE levels, or skin test reactivity at low venom concentrations.[84,85] Conventional regimes appear to be best tolerated, while rush and ultra-rush protocols are more frequently associated with adverse events.[24]

2.15 | Updosing

The recommended starting dose in updosing protocols lies between 0.001 and 0.1 μg, but it has also 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.[86] A maximum dose of 100 μg venom allergen dose usually offers adequate protection against systemic-allergic sting reactions in the majority of venom-allergic individuals.[87–89]

2.16 | Maintenance dosing

A maintenance dose of 100 μg venom is significantly more effective than 50 μg.[88] This dose is equivalent to the dry weight of approximately two honeybee stings or five wasp stings[90] and has been adhered to as the recommended maintenance dose since the first controlled trial.[87] A further increased dose gives a better protection when needed.[91] 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.[91] An increased maintenance dose should also be considered in allergic populations at high risk of multiple stings, such as beekeepers[92] and in exceptional cases where patients have accumulated risk factors for treatment failure.

Although the European Medicines Agency (EMA) had no safety concerns regarding aluminum toxicity from their pharmacovigilance review of aluminum hydroxide in standard AIT, high dose VIT and lifelong therapy have not been specifically evaluated. As a precaution, where lifelong therapy is planned is can be undertaken with aqueous preparations. If a 200 μg dose is required for maintenance, half can be given as an aqueous preparation.

The interval for maintenance VIT with 100μg venom recommended by the manufacturers has been 4-6 weeks for aqueous preparations and 6-8 weeks for purified aluminum hydroxide adsorbed preparations (depot preparations). According to expert consensus, injections are usually given every four weeks in the first year of treatment, every six weeks in the second year, and in case of a five-year treatment every eight weeks from year 3-5.[93] Extending the maintenance interval to three months does not seem to reduce effectiveness or increase adverse events,[94-96] which could be relevant in terms of convenience and economic savings if lifelong treatment is necessary. As there is no specific study available for mastocytosis patients with severe initial SSR, caution should be used in extending the intervals to three months in those patients. A dose interval of six months did not provide suitable protection in honeybee venom-allergic patients[97] and is therefore not recommended for standard practice (Table 3).

2.17 | Duration of VIT

Termination after approximately one or two years leads to a relapse rate of 22%-27%.[41,42] Some studies have concluded that VIT for three years may be sufficient,[98] particularly in patients with only mild-to-moderate initial sting reactions.[98] Nevertheless, most of the studies concluded that a minimum of a five-year treatment is superior for long-term effectiveness.[99-102] Lifelong therapy should be considered in patients with severe initial SSR, systemic adverse events during VIT, and honeybee venom-allergic patients with high risk of future honeybee stings (Tables 3 and 4).

2.18 | Adherence

Adherence to VIT is high, possibly because of patients' perception of an unpredictable risk of life-threatening sting reactions. In a recent study, 95% and 84% of patients still continued VIT after three and five years, respectively.[103]

2.19 | Effectiveness

Treatment with ant venom is very effective as 97 to 98% are protected after VIT.[9,10] The effectiveness of honeybee and vespid VIT

TABLE 4 Recommendations: risk factors and management of side-effects, duration of treatment

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
It may be recommended that patients treated with bee venom and those on rapid updosing protocols should be closely observed for side-effects as they are at a higher risk of experiencing adverse events	IV	C	Weak based on case series studies[24,43]	The intake of beta-blockers or ACE inhibitors is not a risk factor for adverse events during VIT. Also most of the mastocytosis patients tolerate VIT well	Ruëff 2010[24] Mosbech 2000[43]
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 adverse events	IV	C	Weak based on case series studies[24,25,84]		Stoevesandt 2014[25] Ruëff 2010[24] Lockey 1990[84]
In case of VIT-related systemic adverse events during build-up phase, a temporary reduction of the venom dose (e.g, going one to two steps back in the protocol) may be recommended to avoid further adverse events	V	D	Weak based on expert consensus		Expert consensus
In case of repeated systemic adverse events during updosing, pretreatment with Omalizumab may be recommended	V	D	Weak based on case reports[70–71]		Stretz 2017[72] Kontou-Fili 2008[70] Schulze 2007[71]
In case of VIT-related LLR, it may be recommended to split dose in 2 injections or change injection site but not necessarily to reduce venom dose	V	D	Weak based on expert consensus		Expert consensus
Lifelong VIT may be recommended in patients who relapsed after stopping VIT	V	D	Weak based on expert consensus		Expert consensus
It may be recommended to avoid insect stings during build-up phase by abiding by preventive measures (e.g stop beekeeping) until maintenance dose is reached	V	D	Weak based on expert consensus		Expert consensus

is different and ranges from 77 to 84% for honeybee venom compared to 91 to 96% for vespid venom.[7,8] The underlying reasons are still unclear. It has been speculated that the amount of venom delivered by a honeybee sting is much larger and more consistent.[90] This may also explain the difference in the reaction rate to sting challenges, which has also been observed in untreated patients.[104–106] It also appears that the broad sensitization pattern in honeybee venom-allergic patients may play a role in the lower effectiveness of honeybee VIT.[107] For example, some patients are predominantly sensitized to Api m 10, which may be underrepresented in certain available honeybee venom preparations.[108,109] However, none of these studies included a patient analysis of molecular sIgE binding patterns to honeybee venom allergens before the start of VIT. Without such a specific IgE stratification aligned with the clinical outcome, the conclusions are of limited value. The specific preparation does not seem to have an impact on the effectiveness. The effectiveness of aqueous and purified aluminum hydroxide adsorbed preparations has been shown to be similar.[60,110]

2.20 | Effectiveness of VIT after updosing phase

Only one recent study has looked at how rapidly protection occurs. In honeybee VIT, 89% tolerated the sting challenge one week after reaching the maintenance dose in a 3- to 5-day rush protocol or a 3- to 4-month conventional protocol. Those patients who were not protected with 100 μg venom tolerated the sting challenge immediately after reaching the dose of 200μg.[89]

2.21 | Effectiveness during/after maintenance VIT

Most effectiveness data are obtained during VIT. Resting reaction rates of 0%-10% 1-5 years after discontinuation of vespid VIT have been reported.[100,101,111] Relapses after honeybee VIT are more frequent as 17% are reported to relapse one year after stopping VIT.[112] There are only few reports on the outcome following VIT withdrawal for more than five years, and there are 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,[98,99] while 15.8% after stopping honeybee VIT had resting reactions.[99] Another study compared relapse rates after four and approximately 10 years and reported relapse rates of 10.2% and 16.2%, respectively.[113] In children, the long-term outcome is superior compared to adults as only 5% with moderate-to-severe reactions relapsed after up to 20 years after stopping VIT.[15]

2.22 | Carriage of adrenaline autoinjectors during and after VIT

It is still a debated issue whether AAI should be carried during and after VIT, and it has also been difficult to reach a consensus on this topic. Most patients are protected after reaching the maintenance dose.[89] 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 AAI can negatively impact on health-related QoL[50,52] (Table 3). According to the EAACI position paper "Self-medication of anaphylactic reactions due to Hymenoptera stings", 13% of experts/authors would still prescribe an AAI to patients who initially only had generalized skin symptoms after discontinuation of 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.[114]

2.23 | Risk factors for systemic adverse events with VIT and relapse of SSR

2.23.1 | Risk factors for systemic adverse events with VIT

The frequency of systemic adverse events with VIT in large multicenter studies ranges from 8 to 20%.[24,43,84] Several risk factors for the occurrence of systemic adverse events have been described. Most of the studies include only small numbers of patients and provide conflicting data. The most important risk factor is treatment with honeybee venom. It has been consistently reported that there is a 3.1- to sixfold higher risk for systemic adverse events due to treatment with honeybee venom.[24,77,86] Rapid dose increase during the build-up phase is a weaker, but nonetheless established risk factor.[24,43] Mastocytosis and/or elevated serum tryptase was initially considered as risk factor for adverse events. 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),[24] whereas another study performed in honeybee venom-allergic patients did not.[85] A study performed in patients with mastocytosis concluded that VIT is safe and efficacious,[47] confirming previous data.[45] Although still a debated issue, ACE inhibitors and beta-blockers are not considered to be independent risk factors for adverse events.[23–25] Importantly, severe initial sting reactions,[24,25,84] positive skin tests at low test concentrations and high specific IgE levels[25,84,85] are not regarded as risk factors for adverse events (Table 4).

2.23.2 | Management of adverse events during build-up phase of VIT

Adverse events are generally mild and adequately respond to standard anti-allergic treatment.[20,36] In the case of systemic adverse events, a common procedure during build-up phase is reducing the allergen dose (going one to two steps back in the protocol) and then continuing with the second last well-tolerated dose of VIT. If not yet considered, premedication with H_1 antihistamines should be established. When systemic adverse events prevent reaching the maintenance dose, premedication with omalizumab may be an option. Currently, case reports and a case series have documented the usefulness of omalizumab[70-72,115] but there is also one negative report[116] (Table 4).

2.24 | Risk factors for relapse of SSR

2.24.1 | Age and type of venom

As already mentioned above, children generally have a more favorable prognosis than adults[15] and patients who were treated with honeybee venom had a higher risk for relapse compared to those who were treated with vespid venom.[98,99,113]

2.24.2 | Severity of reaction prior to VIT

Two studies reported a higher relapse rate in patients who have had a severe SSR before VIT.[98,100] In the larger study, relapses were observed in 4% with mild but 14% with severe pretreatment reactions.[98] Other studies concluded that the grade of the SSR prior to VIT was not relevant to the probability of a relapse.[112,117] Although it is still controversial whether severe initial SSR is a risk factor for relapse, it has been agreed that those patients are at greater risk for severe SSR when they relapse.[118]

2.24.3 | Systemic adverse events during VIT

Patients who developed systemic adverse events during VIT showed a relapse risk of 38%, while those who did not, only had a 7% risk.[112] Two more studies reported similar results (46% vs 8% and 16.4 vs 5.4%, respectively).[32,102]

2.24.4 | Mastocytosis/elevated serum tryptase levels

A large multicenter study could not detect an association between higher baseline tryptase and therapy failure,[31] and 86% of 50 mastocytosis patients were protected after initiation of VIT.[47] However, one study indicated that patients with tryptase >20 μg/L and/or mastocytosis in the skin had a 2.7-fold higher risk for therapy

failure.[32] Available data are scarce and heterogeneous but it appears that mastocytosis is not a strong general risk factor for relapse but should be considered as risk factor in individuals with severe initial SSR.

2.24.5 | ACEI

While in one multicenter study, all patients on ACEI tolerated a sting challenge or field sting during VIT,[31] another study reported a higher risk for relapse in patients taking ACEI.[32] However, the risk of ACEI might have been overestimated due to the very small patients' group and highly selected patients with suggested cardiovascular comorbidity.[33]

2.25 | Procedures to monitor VIT

Many attempts have been made to identify biomarkers to monitor AIT. In peripheral venous blood samples of treated patients, there are significant changes of venom-specific T-cell populations, secreted cytokine patterns, and immunoglobulin levels but these are not appropriate to estimate the individual risk for relapse of SSR. The sting challenge remains the gold standard in identifying unprotected patients (Table 5).

2.26 | Sting challenges/field stings

Performing sting challenges is still the most reliable method and gold standard to monitor the effectiveness of VIT. VIT is effective immediately after reaching the first maintenance dose.[89] Therefore, if feasible, sting challenges should be performed as early as possible to identify those who are not protected with the maintenance dose of 100 μg. If sting challenges cannot be performed, information about field stings may be helpful. However, the risk of misidentification of the stinging insect and the nonstandardized sting procedure reduce reliability.[112]

The reproducibility of sting challenges, at least for diagnostic purposes, is a debated issue. A study on 129 patients revealed that in 95% of patients, a diagnostic sting challenge provided a good

TABLE 5 Recommendations: monitoring of VIT

Recommendations for individuals with venom allergy	Evidence level	Grade of recommendation	Strength of recommendation	Other considerations	Key references
In adults, a sting challenge can be recommended as the most reliable method to evaluate effectiveness of VIT	IV	C	Weak based on case series studies[101,117]		Van Halteren 1997[117] Golden 1996[101]
If no sting challenge can be performed, it may be recommended to record outcomes of field stings to evaluate effectiveness of VIT	V	D	Weak based on expert consensus		Expert consensus
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	IV	C	Weak based on case series studies[99,100,112]		Lerch 1998[99] Müller 1991[112] Keating 1991[100]

TABLE 6 Gaps in evidence

Gaps	Plan to address	Priority
Optimal duration of VIT in children and adults (e.g, 3 vs 5 years or longer)	RCTs	High
Evaluation of biomarkers such as sting challenges, component-resolved diagnosis, and BAT (inhibition) in assessing the clinical efficacy of VIT	Prospective studies	High
Identification of biomarkers for the risk assessment for side-effects and relapse	Prospective studies	High
Comparison of different VIT updosing schedules, maintenance doses, and maintenance intervals in adults/children in terms of efficacy both short and long-term	RCTs	High
Safety and efficacy of VIT in patients taking antihypertensive drugs (beta-blockers, ACEI)	Observational studies	High
Safety and efficacy of VIT in patients with elevated serum tryptase/mastocytosis verified by sting challenges	RCTs	High
Comparison of purified and nonpurified bee venom preparations in respect of safety and efficacy verified by sting challenges	RCTs	High
Safety of the simultaneous application of two or more venoms during updosing and maintenance phase	RCTs	High
Value of VIT on health-related quality of life compared to AAI in children and their parents	RCTs	Medium
Assessing the cost-effectiveness of VIT	Cost-effectiveness analysis of RCT	Medium
Safety of VIT in adults and children with concomitant disease such as cardiovascular disease	Observational trials	Medium

prediction of tolerance for subsequent field stings.[119] On the other hand, it has been shown that 21% of patients not treated with VIT, who initially tolerated a sting challenge, had systemic symptoms after a second challenge.[120] The reliability of early sting challenges to monitor effectiveness of VIT appears to be high,[121] although repeated sting challenges during three to five years after treatment identified 8%-10% of patients who relapsed.[101,117] Importantly, tolerated sting challenges can improve health-related QoL, especially in patients reporting high impairment of health-related QoL before the sting challenge.[51] Thus, sting challenges should not only be seen in the context of evaluating effectiveness but also in terms of fostering individual belief in disease-specific safety.

2.27 | Specific IgE and IgG4 levels

It has been repeatedly shown that specific IgE levels to the respective venom decrease during VIT after an initial rise during the first months of treatment[60,121]; they usually remain low even after stopping VIT.[117] VIT is associated with a significant increase in specific IgG antibodies that has initially been suggested as a marker of effectiveness[122]; these immunological changes induced by VIT were also reported in honeybee venom-allergic children.[123] The subclass of IgG antibodies is usually restricted to IgG1 and IgG4.[121] However, after stopping VIT, specific IgG starts to decrease[99,124,125] and patients appear to be protected by a mechanism independent from venom-specific IgG.[122] Taken together, available data do not support the use of specific IgE, specific IgG, or specific IgG subclasses or

BOX 3 Summary

- VIT is recommended in children and adults with detectable sensitization and systemic sting reactions exceeding generalized skin symptoms
- VIT is recommended in adult patients with systemic sting reactions confined to generalized skin symptoms if quality of life is impaired
- VIT is not recommended in individuals with incidentally detected sensitization and no systemic symptoms
- Patients with severe initial sting reactions, high skin test reactivity, and high venom-specific IgE levels are not associated with a higher risk of adverse events
- Pre-treatment with H_1 antihistamines is recommended as it reduces large local reactions and to some extent also systemic adverse events
- VIT should be performed for at least three years. In patients with severe initial sting reactions, at least a five-year treatment is recommended
- Lifelong VIT may be recommended in highly exposed patients with honeybee venom allergy, patients with very severe initial sting reactions (Muller grade IV or grades III-IV according to Ring & Messmer), and patients with systemic side-effects during VIT as they are major risk factors for relapse
- All available diagnostic tests, including determination of venom-specific IgE, IgG, BAT response, and allergen-blocking capacity, are not able to estimate the individual risk for relapse
- Sting challenges are the most reliable method to evaluate effectiveness of VIT

BOX 4 Key messages for primary care practioners about referral to allergy services for venom immunotherapy

- Venom immunotherapy is very effective in preventing future systemic reactions to honeybee, wasp, and ant stings
- Refer patients to an allergist with experience in venom immunotherapy for assessment as below. If unsure on review, seek advice from your local allergy centre
- Venom immunotherapy is recommended in individuals with
  - systemic sting reactions exceeding generalized skin symptoms
  - generalized skin symptoms only (including urticaria/angioedema) if quality of life is impaired
- Venom immunotherapy is not recommended in individuals with
  - only local reactions, including large ones (defined as a swelling exceeding a diameter of 10 cm lasting longer than 24 h)
  - incidentally detected sensitization and without any systemic allergic symptoms
- A careful personal history should be taken (culprit insect, characterization of sting reactions, emergency, and concomitant medication) and, if possible, venom-specific-IgE should be determined before patients are referred to an allergist
- Negative test results are possible in patients with insect venom allergy. If there were clear symptoms of anaphylaxis after a sting, patients should be referred to an allergist
- Large local reaction typically develops within 24 h and should be treated with oral antihistamines and corticosteroids but not oral antibiotics. No further follow-up is needed.
- Quality of life is impaired in many patients who only carry an adrenaline autoinjector and do not receive venom immunotherapy

TABLE 7 Barriers and facilitators to implementation, audit criteria, and resource implications of recommendations

First-line intervention: VIT for venom-allergic individuals	Barriers to implementation	Facilitators to implementation	Audit criteria	Resource implications
Venom immunotherapy is highly clinically effective in adults and children with moderate-to-severe allergic reactions to hymenoptera stings	Failure to recognize severe allergic reactions (anaphylaxis) following hymenoptera stings Lack of knowledge among patients, caregivers, and professionals about the availability of venom immunotherapy Concerns about side-effects The hope that allergic reactions will subside with time or symptomatic treatments only (e.g, AAI, antihistamines/glucocorticosteroids)	Education and training of emergency care doctors, general practitioners, and other physicians on venom allergy and its grades of severity Information about need of follow-up visits with clinical allergists for diagnosis and management of venom allergy Information sheets for patients and caregivers	Proportion of adults and children with moderate-to-severe SSR who are treated with VIT Proportion of adults and children who experience relapses and/or side-effects while on VIT	Venom allergen immunotherapy (VIT) needs to be prescribed by clinical allergists and made available to patients. Patient education about self-treatment with adrenaline (AAI) before starting VIT is important and requires availability of trainer devices
VIT is recommended in adult patients with systemic sting reactions confined to generalized skin symptoms if quality of life is impaired	Lack of knowledge among physicians, including clinical allergists about the indication of venom immunotherapy in these circumstances	Education and training of physicians and allergy specialists Information sheets for patients	Proportion of patients experiencing impairment of QoL when venom allergy is confined to skin only who are treated with VIT	Education and training of both physicians and patients Cost/benefit profile needs to be established
Lifelong VIT can be recommended in highly exposed patients with bee venom allergy, patients with very severe initial sting reactions (Muller grade IV or grade III-IV according to Ring & Messmer), and patients with systemic side-effects during VIT as they are major risk factors for relapse.	Lack of resources (professional and financial) Adherence to lifelong VIT unrealistic	Provision of insurance cover for lifelong VIT within Europe Education and training of clinical allergists Education of patients in terms of sting exposure risk behavior; Patient leaflets, smartphone "shot" reminder apps, etc.	Proportion of patients who adhere to lifelong (or prolonged, that is, > 5 years) VIT and proportion of patients consecutively tolerate hymenoptera stings	Equipment of specialized allergy centers with skilled staff for successful administration of VIT Safety measures in place to minimize side-effects in high-risk patients
Pretreatment with H_1 antihistamines is recommended as it reduces large local reactions and to some extent also systemic adverse events	Lack of knowledge among healthcare professionals regarding pretreatment Reluctance of patients Additional costs for healthcare system	Education of healthcare professionals, and patients	Proportion of patients with VIT who have antihistamine pretreatment	Prescription of antihistamines to be taken by patients prior to VIT
AAI during and after VIT is recommended only in patients at risk of multiple stings or with risk factors for relapse	Lack of knowledge among healthcare professionals in terms of (non) prescribing AAI Risk behavior and misconception of patients	Education of healthcare professionals and patients	Proportion of high-risk patients carrying and administering intramuscular (AAI) during or after VIT	Time to educate and train physicians and patients

even ratios can be used as predictors for protection during and after VIT in the individual patient.

2.28 | Intradermal testing

Similar to the decline of specific IgE levels during VIT, intradermal test end point concentrations usually decrease from before to after VIT.[99,101] No study has been able to identify a relevant difference in skin test reactivity between tolerant subjects and patients with relapses.[99,100,112] Moreover, patients with negative intradermal tests have been reported to have significant relapse, a few with near-fatal reactions.[102,113]

2.29 | Basophil activation test (BAT)

Allergen-specific basophil response remains positive[126] or even unchanged[125] during VIT. However, basophil responses at submaximal allergen concentrations are markedly decreased after VIT in tolerant subjects and this decline seemed to be associated with the induction of tolerance.[125,127] Also the measurement of basophil threshold sensitivity to anti-FcεRI stimulation has been proposed to monitor an early protective effect of VIT.[128] BAT inhibition with sera of treated subjects correlated well with effectiveness of AIT in grass pollen-allergic patients[129] but this has not yet been shown in patients with HVA.

2.30 | 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.[130] One study measured the serum inhibitory activity of VIT-treated vespid venom patients.[124] 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 specific IgG4 levels were again reduced in patients who stopped VIT several years ago.[124]

Despite of the availability of new methods such as the BAT and the ELIFAB, most of the parameters cannot precisely distinguish between patients who are protected from future SSR and those who are at risk. Currently, it is not possible to estimate the individual risk for relapse of SSR with any of the currently available parameters (Table 5).

3 | SUMMARY, GAPS IN THE EVIDENCE, AND FUTURE PERSPECTIVES

The EAACI Taskforce on VIT has developed this guideline as part of the EAACI AIT Guidelines initiative. The guideline has been informed by a formal systematic review and meta-analysis of VIT.[1] The guideline provides evidence-based recommendations for the use of VIT for patients with LLR and SSR. A summary of the guideline is provided in Box 3, and key messages for primary care practitioners are given in Box 4. The recommendations should be of value to all healthcare professionals involved in the management of patients with HVA.

There are a number of areas in this guideline where low risk of bias evidence is not available. The primary gaps are highlighted here and in Table 6. There is a major gap in the evidence 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 anecdotal findings, an important number of children do not outgrow allergic reactions to insect stings.[15] Additionally, the effect of VIT in children and their parents on health-related QoL should be investigated further. In adults, there is need for studies with sufficient power to evaluate risk factors for adverse effects during VIT or for treatment failure. There is also minimal data in the elderly population particularly for patients with cardiovascular disease. Additionally, we need cost-effectiveness and cost utility studies to use in discussions with healthcare funders. Biomarkers to predict effectiveness of VIT and to identify treatment failure are also urgently needed.

Despite all these gaps, we have clear evidence for the clinical effectiveness of VIT for patients with SSR. Potential barriers and facilitators for the implementation of these recommendations are described in Table 7. 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 highly effective and is likely to be cost-effective, and that patients and patient support groups are aware of this approach.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

GJ Sturm and EM Varga jointly chaired the EAACI Guideline on VIT and initially drafted the manuscript. H Mosbech, MB Bilò, CA Akdis, D Antolín-Amérigo, E Cichocka-Jarosz, R Gawlik, T Jakob, M Kosnik, J Lange, E Mingomataj, D Mitsias, M Ollert, JNG Oude Elberink, O Pfaar, C Pitsios, V Pravettoni, F Ruëff, BA Sin, I Agache, E Angier, S Arasi, MA Calderón, M Fernandez-Rivas, S Halken, M Jutel, S Lau, A Muraro, GB Pajno, R van Ree, G Roberts, D Ryan, R Gerth van Wijk were members of the taskforce who were involved in conceptualizing the guidelines and critically reviewed guideline drafts. S Dhami, H Zaman, and A Sheikh provided methodological support to the taskforce. O Spranger was the patient group representative. All the authors satisfied the international authorship criteria with further details in Table 1 of the online repository. This guideline is part of the EAACI Guidelines on Allergen Immunotherapy, chaired by Antonella Muraro, and coordinated by Graham Roberts.

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