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Updates and Recent Advances on Venom Immunotherapy

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Abstract

Purpose of Review Venom immunotherapy has been utilized to treat Hymenoptera venom allergy since the 1920s. Over the last century, significant advances in the fields of immunology and genetics have led to improvements in the practice of venom immunotherapy. This review encompasses recent advances in the use of venom immunotherapy to provide precise, patient-centered care.

Recent Findings Research about the mechanism of action of venom immunotherapy continues to highlight the modification of both the innate and adaptive immune systems. Molecular techniques have allowed for the identification of specific venom allergens to improve the diagnostic accuracy and safety of venom immunotherapy. Research continues to support the safety of accelerated schedules which can impact the cost, adherence, and quality of life for patients receiving this treatment modality. Finally, significant advances have led to the elucidation of risk factors that place patients at risk for reactions during and after venom immunotherapy. Creation of risk profiles for venom-allergic patients can thus inform the process of immunotherapy in order to provide personalized and precise care.

Summary Significant progress in the use of venom immunotherapy makes the practice a dynamic and active field for continued research. Future research needs to build on these recent advances to continue to optimize and enhance this life-saving treatment.

Abbreviations

ACE-I	Angiotensin-converting enzyme inhibitor
BAT	Basophil activation test
CVD	Cardiovascular disease
EMI	Extended maintenance intervals
HαT	Hereditary alpha tryptasemia
HVA	Hymenoptera venom allergy
IFA	Imported fire ant
ILIT	Intralymphatic immunotherapy
IT	Immunotherapy
JJA	Jack jumper ant
LLRs	Large local reactions
MCD	Mast cell disease
MD	Maintenance dose
MOA	Mechanism of action
OR	Odds ratio
QOL	Quality of life
RR	Relative risk
sBT	Serum basal tryptase
sIgE	Specific IgE
SM	Systemic mastocytosis
SR	Systemic reaction
Treg	Regulatory T cell
VIT	Venom immunotherapy
WBEs	Whole body extracts
Wt/vol	Weight/volume

Introduction

Venom immunotherapy (VIT) is the single-best and only disease-modifying treatment modality for Hymenoptera venom allergy (HVA) which affects up to 3% of adults and 0.8% of children [1, 2]. The first report of specific immunotherapy (IT) to treat HVA is credited to Braun in 1925 who used venom to treat a bee-allergic patient [3]. Despite a 1956 seminal article by Mary Hewitt Loveless on the efficacy of venom sacs for testing and treatment of HVA, the use of whole body extracts (WBEs) continued until the 1970s [4]. It was not until the publication of two case reports of recurrent anaphylaxis in patients treated with WBEs that the efficacy of WBEs finally came into question [5, 6]. This led to the pivotal placebo-controlled trial published in 1978 proving that VIT was superior to WBEs in the treatment of HVA [7]. Following this trial, and 2 other supportive trials, the U.S. Food and Drug Administration approved venom extracts for the diagnosis and treatment of Hymenoptera allergy in 1979. Interestingly, stinging ant allergy is currently treated with both venom extracts (e.g., jack jumper ant allergy (JJA)) in Australia and WBEs (e.g., imported fire ant allergy (IFA)) in the USA.

This review will focus on recent advances in the use of IT to treat venom hypersensitivity to include a review of its purported mechanisms of action (MOA), commercial venom extracts (Table 1), indications and efficacy of treatment, and mitigating factors for adverse reactions. Figure 1 shows the factors

Table 1. Current extracts, starting and maintenance doses for venom, and whole body extract immunotherapy

	Flying Hymenoptera	Imported fire ant (IFA)
Extracts	Venom	Whole body
Standardization	Yes	No
Single venom	Honeybee (*Apis mellifera*) Yellow jacket (mixture of 5 *Vespula* species) White-faced hornet (*Dolichovespula maculata)* Yellow hornet *(Dolichovespula arenaria)* Wasp (mixture of 4 *Polistes* species)	Red IFA (*Solenopsis invicta)* Black IFA (*Solenopsis richteri)*
Mixtures	Mixed Vespid: yellow jacket, white-faced hornet, yellow hornet	Mixture of red IFA and black IFA
Starting dose	0.001 to 0.01 µg for single venom extracts 0.003 to 0.03 µg for mixed Vespid extract	0.05 mL of a 1:100,000 weight/volume concentration
Maintenance Dose	100 µg for single venom extracts 300 µg for mixed Vespid extracts	0.5 mL of a 1:100 weight/volume concentration

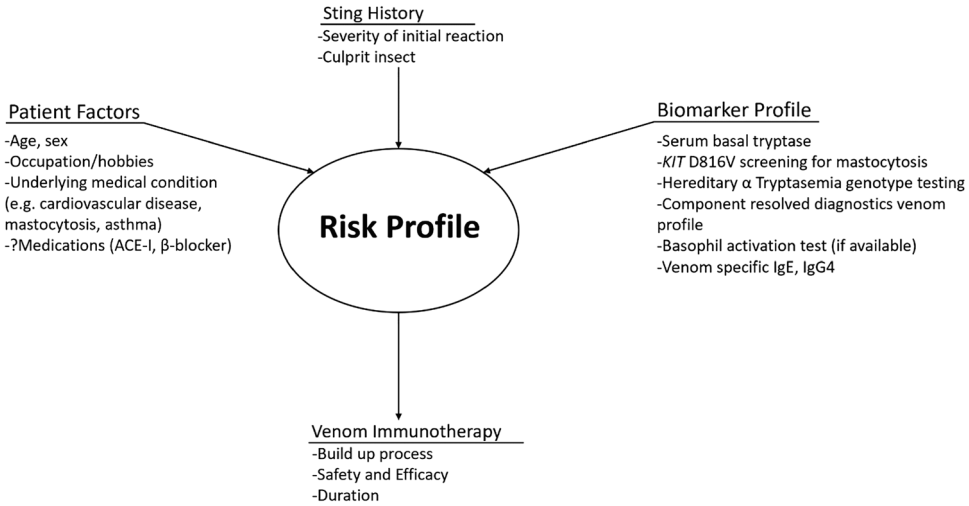

Fig. 1 Example of factors influencing the risk profile for venom immunotherapy

that impact the risk profile for VIT. We also provide a brief review on the current state of stinging ant allergy treatment. Despite the advances that the field of venom allergy and VIT have experienced, we recognize and discuss remaining unmet needs throughout the text and summarize these in Table 2.

Venom Immunotherapy

Mechanism of Action

While the exact mechanism of action of VIT has not been fully elucidated, studies point to modifications of both the innate and adaptive immune responses. VIT-induced modulation of the innate immune system includes

Table 2. Current and future unmet needs

Consistent biomarker for efficacy and side effect risk of venom immunotherapy (VIT)
Availability of extracts that contain all relevant allergens for diagnostic and therapeutic use for a given region and culprit insect
Natural history of large local reactions elucidated for different regions/populations and culprit insects
Novel delivery modalities and schedules for VIT to ensure cost-effectiveness, adherence, and improved quality of life
Data for specific patient populations (e.g., pediatrics, pregnant women, elderly with cardiovascular disease) as it pertains to optimal dosing, schedules, and duration of VIT
Analysis of current reimbursement models for VIT and long-term sustainment/availability of this treatment modalities

transient decreases in plasmacytoid dendritic cells and changes in Toll-like receptor 2 expression on myeloid dendritic cells which are speculated to suppress the allergic immune response [8]. Early suppression of basophil activation mediated by the histamine 2 receptor is seen within hours of VIT [9]. Subsequent changes include the induction of peripheral tolerance via the upregulation of regulatory T cells (Treg) and regulatory B cells that produce interleukin 10 leading to T cell anergy, suppression of IgE production, and induction of venom-specific IgG4 [10, 11]. VIT is associated with an early increase in venom-specific IgE (sIgE) followed by a decrease of sIgE over years and increased production of venom-specific IgG and IgG4 antibodies [12–14]. These latter antibodies are postulated to play an important role in the efficacy of VIT by inhibiting IgE-mediated allergen presentation, IgE signaling through the high-affinity FcεRI receptor, and by their binding to the inhibitory FcγRIIb receptor. The presence of venom-specific IgG, however, has not been consistent at predicting VIT effectiveness [14, 15]. Measurement of the blocking activity of venom-specific IgG has shown promise via the use of a facilitated allergen binding assay [12, 16]. As inhibitory function wanes after discontinuation of VIT, a sustained decrease in venom sIgE may provide an alternative mechanism for protection during and after VIT completion [12]. This is supported by the finding that tolerant beekeepers show a similar profile of low to absent venom sIgE [17]. A study describing levels of sIgE, IgG, and IgG4 after 1–29 years of VIT, however, did not show that these parameters where predictive of sustained clinical tolerance [18•]. Most recently, the use of immunological profiles in tolerant beekeepers has identified high levels of CTLA-4^{+} Treg and Helios^{-} Treg populations as novel and potential biomarkers for tolerance [19, 20].

Allergens

Standardized venom allergen extracts have been approved for diagnostics and treatment for over 40 years in the USA. In Europe, VIT is conducted with the use of non-purified aqueous, purified (dialyzed) aqueous, and aluminum hydroxide adsorbed (also known as a depot) preparations. The U.S. commercial extracts are available as single venoms to the honeybee (*Apis mellifera*),

wasp (mixture of 4 *Polistes* species), yellow jacket (mixture of 5 *Vespula* species), and 2 American hornet extracts (*Dolichovespula arenaria and D. maculata*) [21]. A mixed extract is also available that contains equal parts of yellow jacket, white-faced, and yellow hornet species. Table 1 summarizes available venom extracts in the U.S. Extracts are standardized to phospholipase A2 in the case of honeybees and hyaluronidase for Vespids.

Cross-reactivity patterns follow entomological family relationships although the presence of species' unique allergens poses an issue in the diagnosis and treatment of HVA. In the case of *V. squamosa*, which has unique allergenicity, manufacturers were permitted to add this venom to Vespid extracts starting in 1980 to account for its limited cross-reactivity with other *Vespula* venoms. Another example of limited cross-reactivity is seen between *A. mellifera* and other native Apids such as the bumblebee (*Bombus*) and sweat bee (*Halictidae*). The Mediterranean wasp, *Polistes dominula*, prominent in southern Spain and Italy, is also found extensively in the USA. It shows incomplete cross-reactivity with the wasp species included in commercial extracts and thus requires its own venom extract currently only available in some areas of Europe [22, 23]. This implies that treating providers need to be aware that missing or underrepresentation of relevant allergens in an extract may impact the diagnostic accuracy and efficacy of VIT. To that end, the use of molecular techniques has allowed for the continued identification of specific allergens and the creation of recombinant allergens to assist with the issue of underrepresented allergens in venom extracts [24]. Finally, it is important to note that procurement of venom extracts requires a trained and skilled work force to ensure that the correct species are captured and delivered for processing to allergen laboratories [25]. Availability of the various species required for the *Vespula* and *Polistes* extract mixes varies seasonally and annually. As they are the cornerstone of HVA management, any disruption to the availability of extracts can place a significant strain on the practice of VIT as was seen in the most recent allergen shortage due initially to production problems and subsequently to a loss of a manufacturer in the USA and Canada [26].

Indications and Contraindications

VIT is indicated to prevent the risk of systemic reactions (SRs) to flying Hymenoptera. The decision to conduct diagnostic tests and to offer IT relies on the clinical history of insect-triggered anaphylaxis. Patients who experience large local reactions (LLRs), defined as erythema and edema 10 cm or larger contiguous to the sting site, are likely to experience LLRs with subsequent stings. In these patients, the risk of insect-triggered systemic symptoms is less than 10% in adults and 2% to 7% in children [27–29]. Because this risk is deemed to be low, current guidelines do not recommend testing or treatment with VIT in these patients [30]. Shared medical decision-making should be considered for patients who experience recurrent LLRs affecting the quality of life (QOL) or who have frequent unavoidable exposures. A recent prospective study by Bilò et al. challenges this paradigm as up to 24% of their cohort with histories of LLRs went on to experience SRs with a subsequent venom sting [31]. Skin test reactivity to *A. mellifera* and *Vespula* species as well as having a

positive skin test at a 0.001 µg/mL concentration were risk factors for systemic symptoms in these patients [31]. Additional studies in other countries and different populations are needed to confirm these results and standardize management.

Patients who experience systemic cutaneous symptoms, defined as generalized flushing, pruritus, and urticaria (with and without angioedema) that is not contiguous with the sting site, have approximately a 10 to 15% risk of recurrent symptoms though < 3% chance of more severe symptoms with a subsequent sting [29, 32–34]. Similar to the management of patients with LLRs, patients with systemic cutaneous symptoms do not require testing or VIT treatment, though both can be considered in cases of significant morbidity, impaired QOL, or frequent unavoidable exposure. Patients who experience anaphylaxis to Hymenoptera stings characterized by the acute onset of multi-organ involvement such as cutaneous, respiratory, gastrointestinal, or cardiovascular symptoms have a 40 to 70% risk of recurrence with future stings and thus should undergo testing and evaluation for the presence of venom sIgE [35]. The sole definitive indication for VIT is a patient with a clinical history of insect-triggered anaphylaxis who has evidence of venom sIgE. The decision to offer VIT to other patient groups (e.g., those with LLRs or systemic cutaneous reactions after insect stings) requires shared medical decision-making to ensure the goals of treatment are clear.

Provided that the decision to start VIT is based on a correlating clinical history and evidence of positive sIgE, there are no absolute contraindications to VIT. Patient-specific factors that need to be considered include underlying medical conditions (e.g., mast cell disease (MCD), cardiovascular conditions) which may be associated with increased side effects to VIT. Screening patients for factors that may place them at increased risk for side effects or risk for relapse should be done prior to the start of VIT. Figure 1 shows the factors that need to be considered when assessing a patient's risk profile for immunotherapy to include patient-specific factors, the initial sting history, as well as biomarkers for risk that should be addressed. A patient's risk profile will then inform the process of immunotherapy such as the build-up process, mitigating factors, and duration of VIT.

Efficacy

Markers for the efficacy of VIT may be distinct from those of aeroallergen immunotherapy. For instance, VIT is not associated with an increase in TGF-β production which may be related to the differences in the route of exposure. Another difference is the onset of clinical improvement. In the case of VIT, decreased basophil and mast cell activity likely mediated through the histamine 2 receptor is key for early induction of tolerance [9, 36].

VIT can reduce the risk of anaphylaxis to flying Hymenoptera to < 5% though its efficacy may be lower in certain populations [7, 29]. For example, the culprit insect may impact the effectiveness of VIT such as in honeybee allergy where VIT effectiveness is only 75 to 85% [37]. There are several theorized explanations for this difference such as the relative venom dose from a sting (50 µg for honeybee vs 2–20 µg for Vespids). Another explanation for this difference may lie with the lack of equal representation of all relevant

allergens such as Api m 10 in the extracts used for testing and for VIT [38, 39]. The use of component-resolved diagnostics to elucidate individualized venom sensitization patterns may function as a biomarker for risk stratification [40].

VIT is recommended for 3 to 5 years with the latter providing better protection. In individuals deemed to be at high risk for relapse (e.g., honeybee allergy, SRs to VIT injections, recurrent anaphylaxis despite maintenance dose VIT), indefinite therapy should be considered. VIT in MCD patients has a lower efficacy of 75% and is a significant risk factor for relapse [41]. For these reasons, MCD patients should be considered candidates for lifelong therapy [41, 42]. The impact of VIT on QOL should also be considered as it may influence adherence and long-term efficacy (see QOL discussion below).

Maintenance Dose and Initial Dosing Schedules

VIT prescriptions typically include all allergens that test positive on skin testing or serologic tests. Historically, the limit of detection for sIgE has been 0.35 kUa/L, but technological advances have allowed for a lower limit of detection to 0.1 kUa/L in most laboratories. However, only limited data exists that supports the utility of using lower cut-offs in HVA patients [43]. Because discordance may exist between skin testing and serologic testing, the two testing techniques are best thought of as complementary. A recent study confirms the discordance of the two modalities and questions the optimal order of the tests in order to avoid missing allergens from a VIT prescription [44•, 45•].

Starting VIT doses is generally 0.001 to 0.01 µg, although equal safety was demonstrated for a starting dose of 1 µg [30, 46]. Increasing doses are delivered until a maintenance dose (MD) of 100 µg for single Hymenoptera allergens, and 300 µg for mixed Vespid extracts is reached. Data for the use of lower MDs in adults has been mixed; however, in pediatric patients, the use of a 50 µg MD has been shown to be efficacious [47–50]. Increased maintenance doses (200 to 300 µg) have been used in patients who experience repeat reactions at the standard MD [30, 51]. A maintenance dose of 200 µg has also been suggested for beekeepers at risk for multiple stings [52]. A pilot study that utilized an initial dose of 100 mcg and 4 monthly 100 µg doses was shown to be safe and protective [53]. This confirmed the observation 41 years earlier that 100 mcg rarely causes SRs [7]. Dosing schedules include conventional, modified rush, rush, and ultra-rush protocols. The time to MD varies for each of these protocols with conventional build-up taking the longest amount of time (months) compared to semi-rush (weeks), rush (days), and ultra-rush (hours) protocols that build a patient up to MD in shorter times. Rush protocols have been shown to be safe and effective even in high-risk patients such as those with repeated systemic reactions to initial VIT, beekeepers, those with systemic mastocytosis (SM), and in patients with fire ant anaphylaxis [54–61].

After the MD is reached, doses are spaced out to monthly injections for 12 to 18 months with consideration for 6-to-8-week dosing intervals thereafter. Studies examining the use of extended maintenance intervals (EMI) to 12 weeks have shown efficacy and safety [62, 63]. An EMI of 6 months was not shown to be protective in honeybee-allergic patients, though a more recent study using progressively prolonged intervals showed effectiveness after an EMI of 20 weeks [64, 65].

Adverse Side Effects and Risk Factors

The adverse side effects of VIT are mostly local or LLRs. SRs to VIT occur in 5 to 15% of patients but are usually mild, with < 5% requiring treatment with epinephrine [66••]. Severe reactions are characterized by many different signs and symptoms, including any combination of urticaria and angioedema, bronchospasm, edema of the large airway, hypotension, or other clinical manifestations of anaphylaxis. The most serious anaphylactic reactions involve the cardiovascular and respiratory systems and are potentially life-threatening [30]. Previously reported risk factors for severe anaphylaxis to VIT include serum basal tryptase (sBT) levels above 8 ng/mL, Vespid allergy, older age, and male sex [30, 67]. Underlying medical conditions that should be considered as risk factors during VIT include pregnancy, hereditary alpha tryptasemia (HαT), MCD, and honeybee allergy.

Other than sBT, there are no consistent or validated biomarkers for predicting VIT adverse reactions or VIT failure, but several tests show promise. The basophil activation test (BAT), for instance, measures basophil reactivity via flow cytometry. In patients on VIT, BAT sensitivity has been shown to be predictive of side effects during therapy and risk for relapse after therapy [68, 69]. Increased risk of SRs during honeybee VIT occurred in patients with increased basophil allergen CD63 activation compared to a group without SRs in a prospective study [70]. The BAT, however, is still of limited clinical use given its requirement for specialized laboratories and lack of standardization.

Elevated sBT levels are predictive of side effects and relapse after VIT [30, 67]. While a normal sBT is defined as a value < 11.4 ng/mL, the updated manufacturer's directions for use describe the 95th percentile for sBT as 8.2 ng/ml [71]. Recent studies point to the notion that sBT levels should be interpreted on a continuum. For example, levels > 8 ng/mL have been associated with severe sting anaphylaxis [72, 73]. Even more concerning is the finding that patients with tryptase levels of 4 to 7.5 ng/mL have an intermediate risk of severe reactions [74].

The association between HVA and HαT must be taken into account when using an sBT level as a biomarker. HαT is a genetic trait caused by increased α-tryptase-encoding copies at *TPSAB1* resulting in elevated sBT levels. HαT affects an estimated 5 to 7% of Western populations and is one of the most common causes of elevated sBT levels in these individuals [75•, 76, 77]. A HαT prevalence of 9% was seen in a cohort of HVA patients with severe anaphylaxis which requires additional study in different populations [78••]. HαT is associated with Mueller grade IV venom anaphylaxis (relative risk (RR) 2.0; $P < 0.05$), and among patients with SM, concomitant HαT is associated with increased risk for systemic anaphylaxis (RR 9.5; $P = 0.007$) [78••]. In HαT, the elevation in sBT is proportional to the number of increased α-encoding *TPSAB1* genes. A proposed correction formula (basal tryptase level divided by 1 plus the extra copy number of α tryptase genes) takes this concept into account [79••]. Finally, the presence of the *KIT* D816V mutation has also been used to screen for MCD and risk stratify patients with HVA and normal sBT levels [80•].

Although a recent study showed a lower prevalence of MCD among the U.S. population compared to Europe, that study was highly susceptible to reporting bias [81]. The incidence of side effects during VIT in mastocytosis patients has been noted in up to 18.9% [82]. Interestingly, in those with MCD and HVA, tryptase level is not necessarily correlated with the severity of VIT SRs [67]. Increased MDs, rush regimens, and biologics such as omalizumab have been used successfully in MCD patients to overcome SRs to VIT or field stings after MD is reached [83–86]. The U.S. and European guidelines recommend considering extended or lifelong VIT for patients with MCD and/or elevated sBT levels [30, 52].

Older age is a risk factor for severe allergic reactions to Hymenoptera venom stings [87–89]. However, there is a paucity of data on whether older patients have an increased risk of SRs on VIT. In a retrospective, single-center, observational cohort study, Chapsa et al. showed patients older than 40 years had significantly more severe allergic reactions to Hymenoptera venom stings compared with younger patients, but this group showed no increase in systemic reactions during the initiation of VIT [87]. Further research is needed in this population to assess the risk of SRs during VIT.

The impact of antihypertensive medications such as ACE-I or β-blockers on VIT risks has remained a question for decades. Previous studies have been inconsistent in their findings of the risk that antihypertensives may pose in venom-allergic patients, likely due to underpowering and variable treatment of confounders. The most important confounder is the presence of cardiovascular disease (CVD) in these patients which is difficult to isolate. A recent meta-analysis showed that β-blockers and ACE-Is increased the severity of anaphylaxis but not the incidence of new anaphylaxis cases. However, when they looked at the association between CVD and severity of anaphylaxis, the odds ratio (OR) for CVD was more than threefold higher than the pooled OR for β-blockers and more than fivefold higher than the OR for ACEIs [90]. In an open, prospective, observational, multicenter trial, Sturm et al. showed in 1425 enrolled patients that neither β-blocker nor ACE-I use increased the frequency of systemic adverse reactions during VIT nor led to more severe anaphylaxis reactions at the initial sting. Moreover, results suggest that these drugs do not impair the effectiveness of VIT [91••].

In the case of pregnancy, limited data exists that points towards the safety of VIT during pregnancy [92]. Current guidance regarding VIT in pregnancy includes deferring build-up to include not initiating VIT on a pregnant patient [30]. The risk for SRs with VIT in pregnancy is estimated to be 5% for the build-up phase and 0.1% during maintenance VIT [92]. Hypothetically, shifting the immune response from Th2 to Th1, VIT could be associated with early placental dysfunction and recurrent pregnancy loss [93]. Nevertheless, there are case reports of successful pregnancies both during build-up and during maintenance VIT [92, 94–96]. A recent case report highlights successful in-vitro fertilization and embryo transfer while on a lowered MD of VIT in a patient who had hypotensive Vespid hypersensitivity and recurrent miscarriages on VIT [97]. Shared decision-making is still recommended in this unique patient population.

In a survey of allergists, 42% of respondents felt comfortable with VIT in children as young as 5 years old [98]. In a retrospective study of 107 children from one center, VIT appears to be safe and protective against severe reactions after

re-sting though pre-existing asthma was identified as a risk factor for SRs and LLRs during VIT [99]. There are several studies showing that pediatric patients do well on rush and ultra-rush VIT protocols without an increase in SRs. In a retrospective study comparing 71 children and 981 adults on VIT, the overall rate of VIT-induced anaphylactic reactions was higher in children than in adults (6.9 vs 2.5%, $P = 0.046$) [100]. They found that honeybee VIT and using a 5-day build-up protocol (vs a 3-day protocol) was associated with an increased risk of VIT-induced anaphylaxis. In a prospective, observational study across 3 centers, ultra-rush VIT protocols reaching 100 µg in 3.5 h were studied in 207 children and 134 adults. Only 3.7% of children developed SRs on the ultra-rush VIT protocol [101]. Risk factors for SRs identified in this study were having a history of more severe field sting reactions prior to VIT and honeybee allergy compared to Vespid allergy [101]. Field stings after discontinuing VIT were more common in children but less likely to result in anaphylaxis compared to older children and adults [102].

Omalizumab can be considered to mitigate the risks of repeated SRs to VIT, although this constitutes an off-label use of the drug. There are numerous case reports of patients with repeated reactions to VIT who successfully reached maintenance VIT using 150 to 300 mg omalizumab before VIT and after maintenance was reached [51, 83, 84, 103–105]. However, omalizumab has not been universally successful in overcoming repeated SRs to VIT, and some patients had recurrent SRs when omalizumab was discontinued [103, 106, 107].

Adherence

Adherence to VIT remained high (61%) during the COVID-19 pandemic, compared to 30% who delayed VIT restart, and 9% who discontinued VIT during the pandemic [108]. A study of real-life compliance with allergen immunotherapy in pediatric patients showed that VIT was associated with a higher rate of non-adherence when compared to patients receiving IT to treat asthma and allergic rhinitis though logistics likely played a role due to long-distance commute and frequency of injections [109]. Many factors can affect adherence to fire ant and venom immunotherapy [110••].

VIT improves the QoL for HVA patients [111]. Of patients receiving VIT, 91.5% were (extremely) positive about their treatment, and 85% would choose VIT again [112]. In a cross-sectional study of 3 QoL validated questionnaires, 142 patients with a honeybee or yellow jacket hypersensitivity showed trends toward improved QoL during and after VIT and had increased confidence after a sting challenge done 6 to 18 months after VIT was started [113•]. A long-term, up to 29 years, post-VIT analysis reveals that patients who tolerated re-sting without anaphylaxis after cessation of VIT had a substantially improved QoL [18•].

Cost/cost-Effectiveness

When one manufacturer stopped production of venom extracts in the USA, this caused a significant bottleneck as allergy practices had to rely on the remaining venom extract manufacturer for venom extracts resulting in a

national shortage. Ninety-five percent of responders on a survey reported that the supply chain disruptions affected patient care; 36% and 20% thought that this impact was "a moderate amount" and a "great deal," respectively [114]. The increased demand also led to increased pricing for venom extracts which necessitated advocacy from multiple allergy organizations for increased reimbursement for VIT. A Portuguese study showed a doubling in their rate of patients who refused VIT after the National Health Service removed the 50% cost reimbursement to patients in 2011 [115]. In another modeling study, VIT for honeybee and wasp venom allergy was only likely to be cost-effective from an English NHS perspective for very high-risk groups likely to be exposed to multiple exposures to venom per year [116, 117]. Although of limited evidence, modeling suggested that VIT was likely to be cost-effective in those at high risk of repeated systemic sting reactions and/or impaired QOL [111]. An interesting mathematical modeling study showed that in an idealized 30-year-old patient who is on maintenance VIT without a history of SRs to VIT, has excellent adherence, strong contextual knowledge and high health literacy, that home VIT may be cost-effective [118]. This study was modeled after pandemic conditions where there was restricted non-essential travel and medical appointments. This concept will need further study owing to the risk profile that VIT is associated with. Current reimbursement models for VIT in the USA have led some practices to stop offering this service as the cost can become prohibitive. Further studies that specifically address reimbursement models for VIT are needed to fully elucidate this very important issue.

Stinging Ant Immunotherapy

It is commonly believed that *Solenopsis invicta* (red IFA) and *Solenopsis richteri* (black IFA) began their migration through the southern USA upon disembarkation from South American cargo ships in the 1920s. Today, IFA endemic areas span from Florida to California. IFA is a significant cause of insect-triggered anaphylaxis in endemic areas with a high rate of stings annually. Both species-specific and mixed species (*S. invicta* and *S. richteri*) non-standardized IFA WBEs are available for the diagnosis and treatment of allergic individuals. IFA WBEs were shown to contain significant amounts of venom antigens in the 1980s [119]. Since then, IT with IFA WBEs has been shown to be effective. Freeman et al. performed a retrospective study of 65 patients treated with IFA WBEs. Only 2.1% of those treated with IFA WBEs IT had anaphylaxis to a field sting, compared to 6 untreated patients who all had anaphylaxis to field stings [120]. Indications for IFA WBEs are the same as for patients allergic to flying Hymenoptera. Patients with IFA-triggered anaphylaxis who have evidence of IFA sIgE via skin testing or serology would qualify as candidates for IFA IT. As with VIT, fire ant IT can be considered in patients who experience LLRs and systemic cutaneous reactions to IFA after shared medical decision-making. As there are no large studies on IFA IT to date, much remains to be answered regarding the indications, utilization, and efficacy of IFA IT.

IFA IT typically starts at a concentration of 0.05 mL of a 1:100,000 weight/volume (wt/vol) extract with the typical MD target of 0.5 mL of a 1:100 wt/vol extract. The build-up process for IFA IT follows the same protocols as with flying Hymenoptera VIT. There is literature to support that patients can safely undergo IFA WBEs IT using 1- and 2-day rush protocols, thereby enabling the patient to be protected sooner [57, 58]. Similar to Hymenoptera VIT studies, omalizumab has been used for pretreatment in IFA-allergic patients who had previously failed to reach maintenance [121]. Accelerated protocols have also proven safe and effective for patients with IFA hypersensitivity and MCD [122]. The optimal duration of IFA IT is not well defined though a survey study noted no difference in field sting outcomes in patients receiving less than 3 years of IFA IT compared to those who received more than 3 years of treatment [123]. More data are needed to fully elucidate the optimal duration of IFA IT. Adherence to IFA IT may be problematic as noted in a recent prospective study which showed that inconvenience was the cause for IT discontinuation in almost a third of patients [124•].

There are many other stinging ant species in the world that are known triggers for allergic reactions; however, much is still unknown given a lack of commercial extracts to test and treat for these other stinging ants [125, 126]. In Australia, there are four groups of stinging ants that can trigger anaphylaxis [127]. Stings from the JJA, *Myrmecia pilosula*, account for 65 to 90% of stinging ant anaphylaxis in southeastern Australia and Tasmania [127, 128]. Interestingly, JJA IT utilizes JJA venom since the early 2000s when Brown et al. showed its effectiveness in a double-blind, placebo-controlled crossover study [129]. Currently, MD for JJA VIT is not standardized and ranges from 50 to 100 µg. A subsequent study showed that a 50-µg dose had lower side effects, but its effect on treatment efficacy is unknown [130].

Recent Advances

There have been novel modalities reported for delivering VIT. The use of an infusion pump to administer 3 increasing doses to reach MD showed SRs in 33% of the patients [131]. In a randomized, double-blind placebo-controlled trial for honeybee venom, sublingual IT significantly reduced the extent of LLRs [132]. Intralymphatic IT (ILIT) was studied in honeybee allergic patients in a pilot study which suggested the safety and efficacy of this treatment modality [133]. However, in a follow-up, randomized, dose-comparison study, a significant number of adverse reactions both with ILIT and with sting challenge testing necessitated the pause of the trial [133]. Each of these modalities needs further study with larger patient groups to evaluate safety and cost-effectiveness compared to subcutaneous IT. Finally, there is a study that showed dermal microemulsion of Api m 1 provided protection in the Api m 1-allergic mouse model [134]. Human studies are needed to replicate these findings and provide an additional treatment modality for HVA.

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Declarations

Ethical Approval
All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Conflict of Interest
The authors declare no competing interests.

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•• Of major importance

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