


# Clinical Utility of Rush Venom Immunotherapy: Current Status

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**Abstract:** Hymenoptera venom allergy (HVA) is the leading cause of anaphylactic reactions in adults and the second most common cause in children. Venom immunotherapy (VIT) is used to elicit an immune tolerance against hymenoptera venom in allergic patients and is based on the administration of purified venom extracts regularly for defined periods. The protocols of administration include 2 phases: an up-dosing phase that incrementally reaches the final dose resulting in a protective effect, and a maintenance phase in order to obtain the sustained effect. The goal of this review is to detail the efficacy and the safety of the up-dosing phase also named rush. Pathophysiological mechanisms, indications of VIT and technical aspects of up-dosing protocol are also covered.

**Keywords:** hymenoptera, allergy, immunotherapy

## Introduction

Hymenoptera venom allergy (HVA) is the leading cause of anaphylactic reactions in adults.<sup>1</sup> In children, it is acknowledged as the second most common cause, after food-related anaphylaxis.<sup>2</sup> Such reactions are primarily due to stings by honeybees (*Apis*) and social wasps (*Vespula vulgaris*, *Vespula germanica*, and *Polistes dominula*, in particular). Insect stings by hymenoptera species are frequent with 56.6% to 94.5% of the general population stung at least once in their lifetime.<sup>3</sup> Insect stings also affect young children, in an Irish prospective longitudinal study, 6.8% of children had been stung by the age of 2 years, and 21.9% had been stung by the age of 5 years.<sup>4</sup>

Sensitization to hymenoptera venom (HV) (defined by the positivity of skin prick-tests and/or specific IgE) is widely observed in the general population. The prevalence ranges from 27% to 40% of adults, and up to 50% of children.<sup>5</sup> The prevalence of large local reactions (LLR), usually defined as swelling exceeding 10 cm of diameter that lasts >24 hrs, varies considerably from one study to another due to a non-uniform definition of LLR, different methodology of surveys, and different populations surveyed. In the general population, LLR ranges from 2.4% to 26.4%,<sup>6</sup> in children a prevalence of 19% has been reported.<sup>7</sup> In beekeepers, a high-risk group, prevalence ranges from 31% to 38%.<sup>8,9</sup> Currently, the risk of evolution of LLR to a systemic sting reactions (SSR) after re-sting is considered low, ranging from 5% to 15% in adults, and 2% to 4% in children.<sup>10–12</sup> The rate of self-reported SSR in European studies ranges from 0.3% to 7.5% in adults of the general population.<sup>13</sup> There is less reported SSR in children, rates range from 0.15% to 3.4%.<sup>13–15</sup> Systemic sting reactions can be life threatening, with an estimated death rate of 0.03 to 0.48/1,000,000 inhabitants per year.<sup>3</sup>

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## History of Venom Immunotherapy

Reports of HVA can be found in the annals of history, the description of an anaphylactic response by Pharaoh Menes (2600 BC) to a wasp sting is thought to be the first documented anaphylactic death to HV.<sup>16</sup> For centuries the management of HVA was rudimentary, with no noticeable progress for millennia. Detailed descriptions of HV stings started to appear in publications of the eighteenth and nineteenth century, describing what is now referred to as anaphylaxis.<sup>17</sup>

The first notable date regarding therapy was in 1925, when Dr Braun reported the effective use of immunotherapy in a bee allergic patient. In the report, Dr Braun described snipping off the posterior 1/8 inch of the Bee's body and grinding it up, extracting it in saline, and filtering the solution, demonstrating a positive skin test response and then using the same material to perform immunotherapy. In the following 40 years, a plethora of publication reinforced the efficacy of whole-body extract (WBE) for immunotherapy to Hymenoptera.<sup>18</sup>

In the 1970s, a second revolution took place, with the first purified venoms for desensitization. A publication from 1974 reports a successful case of immunotherapy using purified bee venom to treat a 4-year-old child with HVA.<sup>19–21</sup>

## Pathophysiological Mechanism of Venom Immunotherapy

Initial sensitization to HV involves priming of allergen-specific T helper type 2 (Th2) cells resulting in the production of interleukin-4 (IL-4) and IL-13, and also CD40 ligand signaling. This cytokine signaling and ligand binding drives immunoglobulin-E (IgE) production by B cells.<sup>22</sup> The resulting IgE binds mast cells and basophils via high-affinity FcεRI receptors expressed on their surface.<sup>23</sup> Upon subsequent HV exposure, antigen mediated IgE/FcεRI crosslinking on the surface of sensitized cells triggers the release of pre-formed mediators contained in cytoplasmic granules, such as histamine, resulting in the development of a type I hypersensitivity reaction.<sup>24–26</sup>

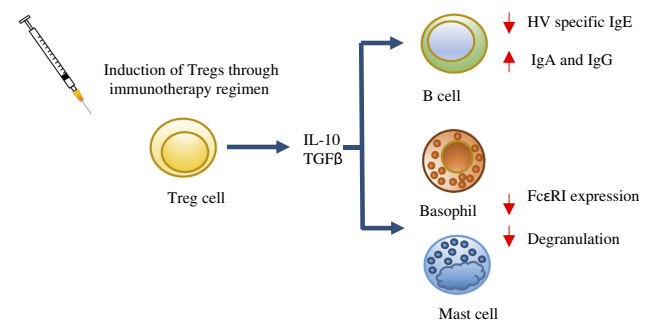
The goal of venom immunotherapy (VIT) is to elicit a healthy immune response in HV allergic patients. Acquired tolerance is characterized by several mechanisms including changes to allergen-specific T and B cell responses and higher mast cell and basophil activation thresholds.<sup>27,28</sup> The early response to VIT is characterized by desensitization

and subsequent decreased mediator release from mast cells and basophils.<sup>28–30</sup> The rapid up-regulation of the histamine type 2 receptor, which has a suppressive effect on FcεRI-mediated activation and degranulation, has been proposed to contribute to early desensitization,<sup>31</sup> as have changes in FcεRI expression;<sup>32</sup> however, underlying mechanisms need to be further elucidated in order to better explain early desensitization events.

As allergen dosing increases, the next key event in the development of a healthy immune response is a change in T cell subset ratios.<sup>33</sup> Research into beekeepers has shown that continuous exposure to high doses of HV suppresses allergen-specific T cell subsets and drives the switch towards IL-10 and Transforming growth factor beta (TGFβ) secreting regulatory T cells (Tregs).<sup>31</sup> These soluble mediators are key regulators of immunological processes in peripheral tolerance to allergens.<sup>34</sup> Interleukin-10 and TGF-β drive the switch in B cell antibody (Ab) production away from IgE towards the non-inflammatory isotypes IgA and IgG.<sup>35,36</sup> This switch in Ab production from IgE to IgA to IgG<sub>4</sub> is a key feature of long-term tolerance. Immunoglobulin-G<sub>4</sub> competes with IgE for allergen, blocking allergen-IgE complexes to prevent the degranulation of mast cells and basophils.<sup>37</sup> Interleukin-10 also plays a direct role in inhibiting mast cell degranulation through signaling inhibition and also reducing FcεRI expression and function<sup>38</sup> (Figure 1).

## Indications of VIT

Reactions following hymenoptera stings include physiological local reactions, related to the composition of venoms (histamine, serotonin, bradykinin, etc.), and allergic reactions. The latter can be divided into LLR at the sting site, which are the most common manifestation of HVA, and systemic reactions, ranging from isolated cutaneous



**Figure 1** Mechanisms of immunotherapy. The switch from allergen-specific Th2 cells to Tregs is a key event during venom immunotherapy. Tregs secrete IL-10 and TGFβ; these mediators suppress the degranulation of mast cells and basophils and reduce FcεRI expression and function. IL-10 and TGFβ also inhibit IgE production by B cells and drive the switch to the non-inflammatory isotypes IgA and IgG.

reaction (e.g., urticaria) to SSR, which are the most severe (Classifications of reactions are detailed in Table 1).

Venom immunotherapy is indicated in children and adults following a SSR, exceeding generalized skin symptoms, with a documented sensitization to the venom of the culprit insect via skin prick tests and/or specific serum IgE tests and/or the basophil activation test.<sup>39–43</sup> Concerning moderate SSR (i.e., SSR confined to generalized skin symptoms), VIT is recommended in adult patients if the quality of life is impaired.<sup>40,44,45</sup> When faced with this clinical situation it is also necessary to identify risk factors for relapse, and factors aggravating the severity of a possible recurrence (e.g., mastocytosis).

Generally, patients with repeated LLR are reported as having minimal risk of progressing to SSR. VIT is not typically recommended for these patients.<sup>46,47</sup> Nevertheless, a recent prospective study indicates a risk of 24% SSR in adults and children after an initial LLR.<sup>48</sup>

**Table 1** Definitions and VIT Indications for Each Type of Reaction

Type of Reaction	Definition	VIT Indication
Local reaction	Inflammatory reaction <10 cm of diameter.	No
LLR	Swelling exceeding 10 cm of diameter, that lasts >24 hrs.	To be discussed with the context and allergic tests
Moderate systemic reaction	Generalized skin symptoms (including flushing, urticaria, and angioedema).	Possibly, in adult, if impaired quality of life or risk factors associated.
SSR	Anaphylaxis, or shock and loss of consciousness, or even cardiac or respiratory arrest.	Yes
No sensitization	Type I allergic reaction without any sensitization highlighted.	No
Other situations	Unusual reactions (not type I immediate reactions) such as thrombocytopenic purpura and vasculitis, rhabdomyolysis, or renal failure after multiple stings	No

The risk of SSR was reported to be higher in cases of skin test reactivity to *Apis mellifera* or *Vespula* species (OR 2.1 and 3.8, respectively), if positive at 0.001 µg/mL concentration (OR 13.4 and 16.5, respectively). For the authors, an accurate diagnostic workup may be considered in LLR, particularly skin tests. If skin tests are positive at low dilutions, VIT may be performed because of a high risk (24%) of developing SSR if re-sting occurs particularly in at-risk population. However, more studies are warranted to clarify the place of VIT in LLR.

Scenarios when VIT should not be considered include: the lack of sensitization to insect venom during skin prick tests or the absence of specific IgE. In patients that are sensitized to insect venom but have not experienced a SSR, VIT should not be considered. Additionally, VIT should also not be considered in the context of unusual reactions that are not attributed to type I hypersensitivity reactions such as thrombocytopenic purpura and vasculitis, rhabdomyolysis, or renal failure after multiple stings<sup>3</sup> (see Table 1).

Typically, the diagnosis of HVA has been based on skin tests and specific IgE to WBE. However, recently component-resolved diagnosis (CRD) has been developed in which venom allergen proteins, instead of WBE, are now used to characterize sensitization in patients.<sup>49</sup> Venom allergen proteins are produced by genetic engineering using insect cells.<sup>50</sup> The available CRD data on HV in clinical practice are presented in Table 2. There are limited benefits of adding recombinant allergens to improve the detection of Hymenoptera venom-allergic patients.<sup>49</sup> One of the most important disadvantages of WBE is the underrepresentation of allergens that are present in low abundance. This may lead to the failure to detect sensitization in some cases.<sup>51</sup> Regarding the high amount of Api m 1

**Table 2** Available Component-Resolved Diagnosis of Venom Hymenoptera in Clinical Practice

Bee Venom Proteins	Vespula Venom Proteins	Polistes Venom Proteins
Api m 1	Yes v 1	Pol d 1
Api m 3	Yes v 4	Pol d 5
Api m 4	Yes v 5	
Api m 6		
Api m 7		
Api m 8		
Api m 9		
Api m 10		
Api m 11		

and Api m 4 in WBE, which represent together 62% of the dry weight, CRD does not improve detection rates. However, the use of WBE allergens in low abundance, such as Api m 3 or Api m 10, may lead to underdiagnosing the severity of venom allergy.

## Venom Immunotherapy: Technical Aspects and Up-Dosing Protocols

Although early case studies carried out VIT using WBE, VIT is now practiced with industrially produced venom extracts with the specific allergen composition standardized. When the culprit hymenoptera has been identified and allergy diagnosis confirmed, venom extract can be administered, subcutaneously, following standardized protocols. These protocols always include 2 phases: an up-dosing phase that incrementally reaches the final dose resulting in a protective effect, and a maintenance phase in order to obtain the sustained effect.

This final dose may be reached within a few weeks to months (in outpatient clinics), days or hours (ultra-rush or cluster protocols including several injections a day) depending on the protocol. These protocols include administered doses and cumulative doses (Table 3 describes some published administration protocols).<sup>52–57</sup> In the published literature describing VIT protocols, clinical characteristics of the patients are disparate, and the number of patients is sometimes low. Considering its brevity and simplicity, Birnbaum's protocol is used as a reference in our department. The data in Table 3 may help to determine the most appropriate protocol for other teams to adopt. In case of toxicity or reaction to an ultra-rush protocol, our department utilizes a protocol with a slow administration among those presented in Table 3.

The data suggest that sustained tolerance is achieved more effectively using long-way protocols compared to ultra-rush protocols.<sup>39</sup>

## At-Risk Populations

Recent data suggest that 5 to 15% of anaphylactic reactions to venom hymenoptera show signs of potential mastocytosis. Systemic mastocytosis may be evoked and diagnosed during hymenoptera allergy care by serum tryptase dosage and cutaneous examination.<sup>58</sup> These patients often show a very low specific IgE level. Mastocytosis and serum tryptase level over 20 µg/L are associated with higher risk of adverse events in VIT in vespid allergy.<sup>39</sup> The REMA score can help to identify,

with a 90% predictive value, patients with a clonal mast cell disorder when at least 2 criteria are met.<sup>59</sup> Efficacy is potentially lower with relapses after stopping VIT. Life-long therapy is recommended in patients with mastocytosis. Up-dosing is not necessary except in adverse events during VIT. Ultra-rush protocols seem to be well tolerated in patients with mastocytosis<sup>60</sup> and VIT is considered safe.<sup>39</sup>

In beekeepers, treatment with bee venom is the most important risk factor for systemic adverse events with VIT. Upgrading maintenance dose and long-life treatment should be considered in the bee-keeping population.<sup>39</sup>

Regarding current guidelines, VIT should not be initiated during pregnancy; however, if ongoing VIT is well tolerated this may be continued.<sup>39</sup> In children below 5 years of age, VIT should only be considered in the event of a SSR and when the child is likely to be co-operative. VIT is not recommended in patients with active multi-system autoimmune disorders. Nevertheless, VIT is recommended in patients with organ-specific autoimmune disorders and patients with cardiovascular disease providing that the underlying disease is stabilized, and in high-risk venom-allergic patients with malignant disease as long as the disease is stable or in remission.

## Effectiveness of Venom Immunotherapy

The main goal of VIT is to prevent a relapse of systemic reaction in a context of hymenoptera re-sting. This treatment is mainly considered as a preventive treatment. Evaluation of efficacy can be challenging especially when the patient undergoing VIT has not been exposed to HV since the last clinical visit.

Two meta-analysis studies have evaluated the effect of VIT on the risk of systemic reaction to a sting. Meta-analysis conducted by the Cochrane database pooled the results from 6 studies (392 patients).<sup>41</sup> A subsequent systemic allergic reaction to a sting was observed in 3 out of 113 (2.7%) participants treated with VIT compared to 37 out of 93 (39.8%) untreated patients. The risk ratio was established at 0.10 [95% confidence interval (CI) 0.03 to 0.28]. Suggesting the risk of a systemic reaction to a sting decreases by 90% with VIT. In a more recent meta-analysis, 17 studies were retained for the final analysis.<sup>40</sup> The authors concluded that VIT was beneficial with a substantial reduction of the risk of subsequent SSR (OR=0.08, 95% CI 0.03 to 0.26).

**Table 3** Examples of Injection Schedule Published for VIT

Day	Time (min)	Birnbaum <sup>52</sup>	Laurent <sup>53</sup>	Sturm <sup>54</sup>	Vander Zwan <sup>55</sup>	Roll <sup>56</sup>	Malling <sup>57</sup>
		Dose ( $\mu\text{g}$ )	Dose ( $\mu\text{g}$ )	Dose ( $\mu\text{g}$ )	Dose ( $\mu\text{g}$ )	Dose ( $\mu\text{g}$ )	Dose ( $\mu\text{g}$ )
1	0	0.1	0.001	0.001	*	0.1	0.02
	30	1	0.002		5	1	0.1
	60	10	0.004	0.01	20	10	0.2
	90	20	0.008		30	20	0.6
	120		0.01	0.1	60		1
	150	30	0.02		100	30	
	180		0.04	0.2			
	210	40	0.08			50	
	240		0.1	0.4			
	270		0.2				
	300		0.4				
	330		0.8				
	360		1				
	390		2				
2	0		1	0.8			
	60			1			
	90		2				
	120			2			
	180		4	4			
	240			6			
	270		8				
	360		10				
420		20					
3	0		20	8			
	60			10			
	120			20			
	180		40	40			
	240			60			
	420		50				
4	0		100	80			
	60			100			
7	0					100	1
	30						1.6
	60						2
	90						4
	120						8
14	0					100	8
	30						12
	60						16
	90						20
	120						40
15	0	50					
	30	50					
21	0						40
	30						80
	60						120

(Continued)

**Table 3** (Continued).

Day	Time (min)	Birnbaum <sup>52</sup>	Laurent <sup>53</sup>	Sturm <sup>54</sup>	Vander Zwan <sup>55</sup>	Roll <sup>56</sup>	Malling <sup>57</sup>
		Dose ( $\mu\text{g}$ )	Dose ( $\mu\text{g}$ )	Dose ( $\mu\text{g}$ )	Dose ( $\mu\text{g}$ )	Dose ( $\mu\text{g}$ )	Dose ( $\mu\text{g}$ )
	90 120						160 200
45		100					

**Notes:** \*The initial dose of venom was a factor of 10 40- measured every half hour. The threshold for the venom in the skin – that is, amount of venom that provoked a reaction – was estimated, and the initial dose of venom was a factor 10 below the 30 –6 threshold. The venom was injected subcutaneously in both upper legs. The amount of venom was increased 10-fold up to 1 mcg.

Venom immunotherapy is recognized as the only treatment that can potentially prevent further SSR. Its effectiveness ranges from 77% to 84% of patients treated with honeybee venom, and in 91–96% of patients receiving vespid venom.<sup>61,62</sup> The difference between honeybee and vespid has not been fully elucidated. It has been speculated that the amount of venom delivered by a honeybee sting is more important and some patients allergic to honeybee venom are sensitized to protein present in a low amount of immunotherapy solution.<sup>63,64</sup>

In the European Academy of Allergy and Clinical Immunology (EAACI) guidelines, beyond the benefit of VIT in preventing SSR, the authors highlight VIT also improves quality of life.<sup>39</sup> In patients with an allergy to HV, 80% declared a significant improvement in health-related quality of life after a sting challenge test.<sup>65</sup> Disease-specific quality of life was also shown to be improved in a meta-analysis study with a risk difference of 1.41 (95% CI 1.04–1.79).<sup>40</sup>

These data take into account the whole treatment with immunotherapy and do not focus on the build-up phase. As explained above, several schedules are used in the build-up phase to reach the maintained dose. The efficacy of the build-up phase in terms of efficacy has not been extensively studied. After rush immunotherapy, a decrease in skin-test sensitivity has been observed.<sup>66</sup> However, no study has yet identified a relevant difference in skin test reactivity between tolerant subjects and patients with relapses.<sup>67,68</sup> Sting challenges are considered the gold standard for the assessment of VIT efficacy, but the challenges are feasible only in specialized centers. Only one study to date had focused on the efficacy of rush VIT, the authors report interesting data on response to sting challenge after the build-up phase.<sup>69</sup> Bee venom-allergic patients who underwent conventional or rush VIT were challenged with a live bee sting within 1 week after reaching the 100  $\mu\text{g}$  maintenance dose. Among the 107 patients, 79 (73.8%) agreed to

be challenge, 70 (88.6%) tolerated the challenge with no reaction. Only 4 (5.1%) patients developed a transient rash. Five (6.3%) presented a mild-to-moderate systemic reaction and 4 were given an increased dose of VIT (200–250 $\mu\text{g}$ ) and tolerate further challenges.

To our knowledge, the effectiveness of the different schedules used in the build-up phase have never been compared. Studies have only focused on the safety of VIT schedules.

## Safety of Venom Immunotherapy

The most important objective of the build-up phase is to reach the maintenance dose with no reactions. As described above, several schedules can be employed in the build-up phase. The safety of the build-up phase is high as the maintenance dose is reached in 96.6% of patients with a rush protocol<sup>70</sup> and 97.5% of patients with an ultra-rush protocol.<sup>56</sup> A systemic reaction was shown to occur in patients receiving a 3-day protocol with a frequency ranging from 10.9% to 29.6%.<sup>70–72</sup> A local reaction has been described in 42.3% of patients receiving a 3-day protocol. Regarding the ultra-rush protocol, systemic reactions range from 7% to 22%.<sup>56,73–75</sup> The vast majority of systemic reactions are mild and do not need medication.<sup>76</sup> However, life-threatening anaphylaxis and fatal anaphylaxis have been described,<sup>77</sup> and the build-up phase should be managed by trained health care professionals able to start resuscitation if needed. Uncontrolled asthma, a prior history of SRs, administration of SCIT injections during peak pollen season, and delay in administration of epinephrine are recognized factors of fatal reaction to VIT.<sup>78,79</sup> Reactions to immunotherapy are not restricted to the build-up phase and may appear during the maintenance phase. An increase in observed reactions during the build-up phase compared to the maintenance phase has been described (1.5% vs 2.4%).<sup>72</sup> However, this is still debated and some authors described

an increased risk of fatal reactions during the maintenance phase.<sup>78</sup>

Potential adverse reactions from VIT are difficult to predict. In a prospective study carried out on 680 patients, index sting reaction grade III or IV, and female sex were not identified as risk factors of a reaction needing an emergency intervention.<sup>80</sup> Bee VIT clearly increases the risk of reactions compared to vespid venom.<sup>70,74,80</sup> Before VIT, measurement of baseline serum tryptase concentration should be used to identify patients with a high risk for side effects. Moreover, mastocytosis is a significant determinant for VIT failure.<sup>62</sup> Conventional protocols are less likely to result in a reaction needing an emergency intervention<sup>80</sup> compared to ultra-rush protocols which have been shown to increase the frequency of adverse reactions.<sup>80</sup> It should be acknowledged that several studies have suggested that an ultra-rush protocol may be associated with less adverse reactions compared to rush or conventional protocols; however, the cumulative effect was not comparable between the schedules.<sup>52,81</sup>

Beta-blockers had been considered to increase the risk of a systemic reaction during VIT particularly in patients with cardiovascular diseases.<sup>82</sup> However, two large studies,<sup>80,83</sup> and a position paper published by the EAACI<sup>84</sup> suggest beta-blockers are no longer to be considered as contra-indicated in VIT. Although angiotensin conversion enzyme inhibitors (ACEI) were previously associated with systemic reactions during VIT, the EAACI has now recommended that ACEI therapy can be continued during VIT as long as the patient is informed about possible risks.<sup>39</sup> Any use of anti-hypertensive drugs has been identified as a significant risk factor of systemic reactions to VIT.<sup>80</sup> However, in a retrospective study that focused on patients with cardiovascular diseases, cardiovascular medication did not impair the safety and/or the efficacy of VIT.<sup>85</sup> Surprisingly, reaction rates were lower in patients taking any kind of cardiovascular medication or an ACEI. Patients taking anti-hypertensive drugs should be evaluated carefully before starting VIT, based on an individual risk/benefit assessment.

Pre-treatment with antihistamines reduces large local reactions and systemic reactions and should be used in clinical practice 1 or 2 hrs before starting VIT.<sup>86</sup> In rare cases, VIT is associated with severe systemic reactions with conventional protocols. Pre-treatment with omalizumab has been used in case reports and case series with interesting effects.<sup>87-89</sup> In patients with severe systemic reactions to VIT, omalizumab was not associated with

a reaction when administered concomitantly with VIT. The regimen of omalizumab administration varies between studies and so a typical regimen of administration cannot be referenced.

## Maintenance Dosing and Long-Term Evaluation of Venom Immunotherapy

Once the maintenance dose has been reached, venom extract must be injected regularly in order to obtain long-term effects.

The maintenance dose is typically 100 µg of the culprit venom (equivalent to 2 honeybee stings or 5 wasp stings). Some specific cases require an increase to 200 µg: patients who experience anaphylaxis under ongoing VIT, beekeepers and other high-risk populations. Intervals of 4 to 6 weeks between injections are recommended in the EAACI guidelines: 4 weeks during the first year, 6 during the second year and 8 weeks between 3 and 5 years, intervals may be extended to 3 months however no effect has been demonstrated when intervals are extended to 6 months.

Venom immunotherapy duration of 3 years may be sufficient in most cases with mild reactions; however, 5 years of VIT are associated with more successful long-term effectiveness. The EAACI guidelines also recommend considering life-long treatment in patients that experience a severe initial systemic reaction or systemic adverse events during VIT. Honeybee venom-allergic patients with a high risk of stings, such as beekeepers should also carry out lifelong VIT to prevent relapse.

Effectiveness may reach a 97 to 98% protection with a better score in vespid VIT than in honeybee.<sup>39</sup>

## Conclusion

Venom immunotherapy is effective for patients with HVA. It is the only causal and preventive treatment with respect to potential future sting reactions. Hymenoptera venom allergy indications are well codified. The build-up phase relies mainly on the ultra-rush protocol. Venom immunotherapy should be carried out for 3 to 5 years, or life-long in high-risk populations.

## Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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