Task Force Report

AAAAI/ACAAI Joint Venom Extract Shortage Task Force Report

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PREFACE

This report has been developed to provide guidance for clinicians who provide venom immunotherapy services to affected patients. The intent is to provide clinicians information about the developing shortage of Hymenoptera venoms to assist them in making decisions about the appropriate care for their patients.

The recommendations made by this task force are voluntary and are intended to be strictly temporary in response to an unexpected shortage of Hymenoptera venom extracts. The recommendations will no longer be relevant when the venom supply returns to normal. The recommendations are based on objective clinical and scientific evidence where available, and on clinical experience and expertise where necessary (as identified in the text). We have extensively examined the available evidence related to these issues in the hope of finding solutions. We have made these recommendations with the understanding that some measures are needed to mitigate the venom shortage that likely will exist for some period of time. For situations in which we have a low level of confidence in making recommendations, we have refrained from doing so. Our recommendations are being offered to achieve the most benefit with the lowest potential harm or burden to individual patients.

As is the case with our Practice Parameters, we are proposing management recommendations for typical or prototypic patients with Hymenoptera venom allergy who are receiving or are candidates to receive venom immunotherapy. We have strived to identify special circumstances that may influence medical decisions; however, no set of recommendations can include all the myriad variations in patients and circumstances that may exist in a specific situation. For these reasons, it is important for providers who manage patients with Hymenoptera venom allergy to consider these recommendations as appropriate on the basis of their best medical judgment, with input when appropriate from the patient.

This report is not intended to replace physician judgment with respect to individual patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. The ultimate judgment regarding the propriety of any specific treatment must be made by the physician in light of the individual circumstances presented by the patient. Accordingly, the recommendations in this report are voluntary and advisory.

Since October 2016, ALK Laboratories has notified its customers that it is unable to fill orders for Hymenoptera venom extracts. All their venom products are affected by manufacturing delays. No specific information is available, and it is not clear how long it will take to restore normal production and distribution. An extended delay (1-2 years) has occurred in similar situations in the past. HollisterStier (HS) Allergy has indicated that it is doing everything possible to equitably distribute the available venom and to ramp up production of the venoms to help deal with the shortage. However, we expect that increased production will take time to reach the market.

The lack of availability of Hymenoptera venoms from 1 of the only 2 suppliers in the United States has created 2 kinds of problems: the need to change suppliers and/or the need to manage the reduced availability because demand now exceeds supply.

CHANGING SUPPLIERS

For prescribers of ALK venoms, there is a need to change suppliers. Prescribers will need to assess whether substitute products are interchangeable or whether dose adjustments are appropriate. There are slight differences between HS and ALK venoms. These differences can be due to differences in the species of insects used or due to differences in the standardization process. There are no differences in the species used for honeybee or hornet venoms. Both yellow jacket and Polistes wasp venoms are actually mixes of several species of Vespula or Polistes, and the

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species that are used (and the ratio of species) are not exactly the same between the 2 sources. Comparison of the specifications of the 2 suppliers shows that all the species used in HS venoms are present in ALK venoms. As such, the change from ALK to HS should not expose the patient to any new species. Also, both suppliers have, in the past, made infrequent adjustments in the proportions of the species used.

The standardization of vespid venoms is based on phospholipase and hyaluronidase content. Differences between suppliers should be minimal for honeybee venom, but these are not the major allergen (ves v 5) in vespid (Vespula and Polistes) venoms. As a result, it is possible that a slight difference in potency (of ves v 5) could exist between vespid venoms from different suppliers. So for those venoms in particular, it might be prudent to reduce the dose initially when changing suppliers, as is normally recommended when changing batches or suppliers of non-standardized allergen extracts for immunotherapy.

The clinician must determine, on the basis of each individual patient's history, duration of treatment, and known risk factors, whether and how to make any dose adjustments. On the basis of the limited margin of variability in standardized allergen extracts, the prescribing physician may consider reducing the first dose of a new venom by 25% to 50% and, if tolerated, resuming the planned dose schedule on subsequent injections. That approach is consistent with common treatment plans recommended for inhalant allergen immunotherapy when changing batches or suppliers, and is consistent with the manufacturers' recommendations for venom extracts. The degree of dose adjustment and the subsequent build-up schedule may depend on how long the patient has been on maintenance venom immunotherapy (VIT), and whether they have any of the known high-risk factors. For example, a patient who has been on maintenance VIT for 4 years, has never had any adverse reactions, and has no high-risk factors might need no dose reduction, or could resume full dose after a single reduced dose of 75 μg. However, a patient who has been on maintenance dose for 8 months, had a systemic reaction during build-up, or has other known risk factors might warrant a 50% dose reduction and several steps to build back up to 100 μg (similar to when a fresh batch of inhalant allergen immunotherapy is started). Although that level of caution may not be needed, it should be considered for some patients. These examples illustrate the range of possible scenarios that clinicians should consider when changing the supplier of venom treatment extracts, but they are not meant as specific treatment recommendations. It is noteworthy that venom shortages, changes in venom species mixes (in both ALK and HS products), and changes in venom suppliers have all occurred before without any observed problems or unusual adverse events.

VENOM SHORTAGE

For prescribers of any venoms, the other important issue is how to best manage patients when there is a shortage of venom. The shortage can be viewed at the level of the individual practice and at the national level. To be able to adequately treat those with the greatest need, all allergists should consider measures to conserve venom.

There are 4 strategies to be considered:

- extending the maintenance interval;
- decreasing the maintenance dose;
- suspending or restricting treatment in patients with the lowest risk of severe reaction to stings; and
- developing strategies to minimize wastage.

An overriding theme in the application of these recommendations is the need to stratify patients according to the known high-risk factors for severe reactions to stings. Adjustments of dose or interval (but not both) may be suitable for some patients, but not others. As described in the 2016 practice parameter update, those risk factors include very severe historical sting reaction, systemic reactions during VIT (to a sting or injection), elevated basal serum tryptase level, beekeepers (honeybee allergy), unavoidable frequent exposure to stinging insect, use of beta blocker or angiotensin-converting enzyme inhibitor medications, age, and underlying cardiovascular or other remarkable medical conditions.[1]

There usually is minimal flexibility for patients on the initial treatment VIT build-up, but for patients on maintenance treatment the prescriber may consider adjusting the interval or the dose. The risk of those adjustments is likely small in patients on established maintenance VIT. The protection achieved during VIT is relatively durable. For example, it has been noted that when VIT is stopped after 3 to 5 years, the risk of reaction to a sting has been reported to be minimal until more than a year off treatment.[2] The current Practice Parameters suggest the safety and efficacy of maintenance intervals of 4 weeks for 12 to 18 months, then 6 weeks for 12 to 18 months, then 8 weeks for 12 to 18 months, and 12 weeks thereafter (current standard duration in Table I). There is published evidence for this recommendation,[3-7] and the clinical experience in thousands of patients over the past 30 years has shown this approach to be quite successful. Patients who are already eligible to extend the interval on the basis of these standard recommendations should ideally do so. During this venom shortage, the practitioner may consider accelerating this schedule (eg, 9-12 months at each interval). That would mean that patients on VIT for 18 to 24 months could be on an 8-week interval, and possibly 12 weeks by 3 years of VIT (temporary recommendations in Table I). For patients who require or elect long-term treatment (beyond 5 years), further extension to 16 weeks may be considered,[8] although 6-month intervals were found to be less reliably effective.[9]

Another option could be to reduce the maintenance dose to 75 μg or even 50 μg on a temporary basis. There is good evidence to support the recommendation that children who are receiving 100 μg may be safely reduced to a 50 μg maintenance dose.[10,11] In adults, the optimal maintenance dose has been less clear. For honeybee VIT, the 100 μg dose is considered a minimum, and is associated with full protection (no systemic reaction to a sting) in almost 85% of patients. With vespid venoms, 50 μg was reported to be as effective as 100 μg by some authors[12] and not by others.[13] There are insufficient data to determine the optimal dose with these venoms. The dose used in all controlled clinical trials of VIT was 100 μg.[14-16] In patients on established maintenance VIT *with no high-risk factors*, a reduction in dose is likely to provide sufficient protection for a limited period of time; this is not based on any evidence or experience, and may not be appropriate for patients who are in one of the above-mentioned high-risk groups.

The third strategy to consider is to suspend or restrict VIT in the patients with the lowest risk of severe reaction to stings.

TABLE I. Temporary measures (during venom shortage) to consider to increase maintenance interval for VIT

Maintenance dose interval (wk)	Current standard duration (mo)	Temporary recommendation (mo)
4	12-18	9-12
6	12-18 (total = 24-36)	9-12 (total = 18-24)
8	12-18 (total = 36-54)	9-12 (total = 27-36)
Move to 12	After 36-54	After 27-36

On the basis of evidence presented in the 2016 practice parameter update, both adults and children with cutaneous systemic reactions do not require VIT (unless there are mitigating high-risk factors). There are many adults who began VIT on the basis of previous recommendations for treatment of cutaneous reactors, who may not require VIT under current guidelines, and might now be considered for discontinuation. There may also be children with cutaneous reactions, and large local reactors, who are receiving VIT because of quality-of-life or personal preference considerations, who might now be considered for discontinuation (after thorough discussion with the patient). Also, there are patients who are receiving VIT longer than 5 years based on quality-of-life and personal preference rather than high-risk factors. Eligible patients who have deferred the decision on discontinuing VIT should be asked to reconsider the possibility of stopping if the risk of severe reaction is very low. Another way to conserve venom would be to reduce the number of venoms being administered. Some patients might be adequately treated with a single vespid venom instead of mixed vespid venom. Based on the likely culprit for their reaction and the frequency of exposure, honeybee VIT might be suspended in some patients with primary vespid venom allergy.

The fourth strategy to consider is to prevent wastage of venom. It might be helpful to use only multidose vials because with single-dose vials there is often a portion that is discarded. Venom extracts are generally stable for 12 months from the date of reconstitution. Although skin testing accounts for only about 1% of the venom supply, we could conserve a little venom by using *in vitro* serum specific IgE tests as the initial diagnostic intervention, and perform skin testing only if necessary. HS has already reduced the production of venom skin test products.

CONCLUSIONS

The measures recommended above should be considered in every patient in the hope of conserving the national supply of venom for all who need it. The prescriber should evaluate these options on a case-by-case basis, having an open discussion with patients and inviting them to express their values and preferences, with due consideration of the known high-risk factors for severe reactions to stings. It is also important to note that these recommendations are meant to be temporary. It is the opinion of this task force that they are likely to be safe and effective for a limited period of time, and we make them with the understanding that the previously published treatment recommendations will be resumed as soon as possible. The recommended measures for which there is the best evidence are as follows: discontinuation of VIT in patients for whom it is optional ("not required" according to the Practice Parameters); extension of the maintenance interval within the standard guidelines (Table I); and reduction of dose to 50 μg in children. In many patients, further extension of the maintenance interval (Table I) is likely to be safe and effective for a limited period of time based on very limited evidence. The task force welcomes comments and feedback. We also encourage the reporting of any suspected adverse events that arise after adjustment of the VIT regimen.

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