Venom Immunotherapy

A Guide for Clinical Immunology/Allergy Specialists

This document supersedes information contained in the older 2014 ASCIA Allergen Immunotherapy Manual. It has been updated by the ASCIA Immunotherapy Working Party and extracted into this separate Guide. ASCIA Immunotherapy Working Party members are listed on the ASCIA website. ASCIA resources are based on published literature and expert review.

ASCIA health professional document references are at www.allergy.org.au/hp/papers

Abbreviations

CCD	Common carbohydrate determinants
GMP	Good manufacturing practice
IDT	Intradermal test
IgE	Immunoglobulin E
IgG	Immunoglobulin G
JJA	Jack Jumper Ant
MCT	Mast cell tryptase
PBS	Pharmaceutical Benefits Scheme, AU
Pharmac	Pharmaceutical Management Agency, NZ
QOL	Quality of life
SCIT	Subcutaneous immunotherapy
sIgE	(allergen) specific IgE
SPT	Skin prick test
SR	Systemic reactions
TGA	Therapeutic Goods Administration, AU
VIT	Venom immunotherapy

CONTENTS

1. AIMS OF VENOM IMMUNOTHERAPY (VIT)

In most patients allergic to insect venom, VIT reduces, but does not eliminate, the risk of having systemic allergic reactions (anaphylaxis) to insect stings.

The aims of VIT are therefore to:

- Reduce the risk of anaphylaxis from venomous insect stings, thereby reducing risk of death or long term sequelae of anaphylaxis.
- Reduce acute medical care due to anaphylaxis.
- Improve quality of life (QOL) in people at risk of anaphylaxis from insect stings.
- Obviate the need to carry an adrenaline (epinephrine) autoinjector in some cases.

2. PATIENT AND ALLERGEN ASSESSMENT AND SELECTION

The primary indication for VIT is a history of systemic allergic reaction including anaphylaxis to a bee, wasp or JJA sting. Adults (defined here as 16 years and over) who have generalised cutaneous reactions only, without systemic features (such as Brown grade 1 allergic reactions), should be considered for VIT. The natural history of venom allergy suggests a risk of progression to more severe allergic reactions with future stings.

Identification of the insect that caused the reaction is critical in selecting the right venom for VIT. Sensitisation to the suspected venom should be established, and if there is uncertainty, screening for sIgE to all likely venoms should be carried out.

Baseline mast cell tryptase (MCT) should be checked in all subjects with history of sting anaphylaxis since elevated baseline tryptase is a major risk factor for hypotensive anaphylaxis, even in the absence of overt systemic mastocytosis.

3. INDICATIONS

Disease-related indications

Confirmation of the diagnosis with a positive skin test or blood test for allergen specific IgE is required. VIT is not usually indicated for the following:

- **Generalised cutaneous reactions to stings/bites** e.g. urticaria (hives).

  Adults have a possible risk of more severe reactions with future stings, so VIT may be considered in some cases. Patient age, geographical location, access to medical care, occupation, risk of re-sting, and co-morbidity should all be considered when deciding to commence VIT.
- **Large local reactions** (LLR) to stings/bites. Small series of VIT have demonstrated that around 50% of patients have reduced severity, but VIT is not routinely recommended.

Other factors to consider for patient selection

- Children (under 16 years of age) who have had exclusively cutaneous reactions without systemic features may not require VIT because the natural history is towards reduced reaction severity with future stings.
- Where anaphylaxis has been followed by a tolerated sting, VIT is not excluded because reactions can be variable.
- Comorbidities, concurrent medications and other factors which might increase the risk of VIT are not contraindications to VIT. These factors increase the danger of field stings, and alter the risk or efficacy of the use of adrenaline. Cautious VIT is generally the preferred option.
- Factors such as patient age, remoteness of residence and work and access to medical care, occupation, risk of re-sting, and local prevalence of stinging insect may be considered.
- In the case of JJA allergy, moving to an area where ants are not known to be prevalent, and avoidance of such areas, may remove the need for VIT.
- People with mast cell disorders and sting allergy often lack cutaneous features (at baseline and in acute reaction). The presence of mastocytosis or a mast cell disorder strengthens the indication for VIT, but is also a risk factor for adverse reactions to VIT.

4. CONTRAINDICATIONS AND PRECAUTIONS

Absolute contraindications

- Inability to give informed consent.
- Current or planned pregnancy (contraindication to initiation of VIT only).
  - While there is no evidence that VIT is teratogenic, the major reason for not initiating VIT during pregnancy is the risk of anaphylaxis, the effects of which could be dangerous to the foetus (hypotension with reduced placental perfusion, hypoxia, uterine contractions).
  - Pregnancy is not a contraindication to continuation of maintenance VIT; patients who become pregnant during maintenance VIT can continue, since the major risk is during the initiation/up-dosing phase. This information should be given to female patients of childbearing age.

Malignancy, immunodeficiency or autoimmunity are not contraindications for VIT.

There is no published evidence that these factors alter VIT efficacy, and there is no evidence that VIT exacerbates the above conditions.

Special considerations/precautions

- **Unstable or poorly controlled asthma** is a significant risk factor for severe reactions to VIT. Asthma should be under optimal control before VIT is commenced.
- **The use of beta-blockers** (especially non-selective beta blockers), may impede the management of anaphylaxis. When initiating VIT in a patient taking these medications the following issues should be considered:
  - Patients with cardiovascular disease who are allergic to venomous insect stings are at high risk of fatal anaphylaxis if stung.
  - Withdrawal of the beta-blocker may increase the risk of fatality in some patients with cardiovascular disease.
  - VIT may proceed in patients on beta-blockers if appropriate precautions are taken. This includes the availability of glucagon (which has an inotropic effect independent of beta receptors) for treatment of anaphylaxis, in addition to adrenaline.
- **The use of ACE-inhibitors** may be associated with a greater risk of more severe anaphylaxis in VIT. However, cessation of ACE-inhibitors may place the patient at greater risk of cardiovascular disease, and the risk/benefit ratio of proceeding with VIT should be considered. Replacement of ACE-inhibitors with alternative medications, such as angiotensin II receptor blockers (ARBs), may be considered, as there is no evidence that ARBs are associated with increased risk.
- **Advanced age and severe co-morbidity** such as cardiovascular and respiratory disorders may influence the safety of VIT but the same conditions increase the risk of fatal anaphylaxis from field stings.
- **In patients with arm lymphoedema** (e.g. after cancer surgery), injections should not be administered on the affected side.

5. DESCRIPTIONS OF INSECTS AND STINGS

Bees:

- **Apis mellifera** (honeybee) is prevalent in Mediterranean climates with a high density of horticultural activity. Sting reactions to honey bee are most frequent in hot dry conditions. South Australia has the highest rate of hospitalisations attributed to honeybee stings. In Australia and New Zealand the honeybee is the only insect that leaves a stinger.
- **Bombus spp** (bumble bee) is limited to Tasmania and New Zealand. It is not aggressive and most stings occur during very heavy occupational exposure (such as in glass houses). Its venom cross reacts substantially with honeybee venom, but it is not known whether honeybee venom VIT is effective in treating clinical allergy to bumble bee stings.
- **Apis cerana**, (Asian honeybee) is a recent invader. Some cross reactivity is expected but it is unknown whether VIT using Apis mellifera venom is effective.
- **Native bees** are often solitary, non-aggressive and less likely to sting. However, allergic reactions have been described. Venoms are not available and cross reactivity is unknown.

Vespids:

- Vespula spp (e.g. European wasps/yellow jacket) look similar to honeybee and some Polistes wasps. They are frequently found in sites rich in garbage. Vespula spp appear to prefer cool climates and prevalence is influenced by eradication programs. They are capable of recurrent stings, delivering relatively small doses of venom per sting.
- Paper wasps (Polistes and Ropalidia) account for many sting related deaths. Their inverted cone nests may be seen under eaves or in sheds. Appearance is variable, but in general they have a narrow thorax, and legs that hang in flight. They seek small insects as prey.
- Vespa (hornet) venoms are not currently available for clinical use.
- Vespid venoms are substantially cross-reactive.

Ants:

- Myrmecia pilosula, commonly known as Jack Jumper Ant (JJA) or Hopper Ant appears to be a dominant cause of sting reactions in native bushland across Australia.
- JJA has characteristic colouring (black body, yellow to red extremities), hopping movement and leaps at, and stings upon sighting movement in its territory.
- Due to the ability to climb and leap from vegetation and sting through clothing, any part of the body is a target. JJA also wander long distances from their nests.
- There is significant cross reactivity of the venoms of M. pilosula sibling species.
- Other Myrmecia of similar appearance and behaviour are M. nigrocincta which differs in having a red thorax and is found in bushland in costal NSW and QLD. Its venom differs significantly from that of M. pilosula spp. Between Perth and Margaret River occurs M. ludlowi which differs from M.pilosula in the colour of the hind legs and in its venom.
- Larger Myrmecia species, such as inch ants and bulldog ants, are distributed widely in Australasia, including some nearby Pacific islands and a species introduced to New Zealand. They have adapted to diverse environments and are defensive in behaviour unless disturbed. Many are nocturnal. Venoms have significant cross reactivity with other inch ant venoms, but only low level cross reactivity with JJA venoms.
- Green head ants (Rhytidopnera metallica) are small climbing ants that are a significant cause of sting allergy in some regions. Venoms are not currently available for clinical use.
- Imported fire ants (Solenopsis invicta) were introduced to Queensland. In contrast to Myrmecia species, they are very small (2-6mm length) but build large, environmentally destructive nests and often sting in mass. Venom appears unrelated to JJA venom. Whole body extracts that contain venom may be effective for VIT and have been imported. Australia access is available through TGA SAS B.

6. DIAGNOSTIC ASSESSMENT

Serology

In vitro sIgE tests are widely available for venoms of *Apis mellifera (honeybee)*, *Vespula spp (common or European wasp or Yellow jacket), Vespa spp. (hornet* which is highly cross reactive with *Vespula spp* venoms), and *Polistes spp (paper wasp)*.

A test for sIgE to JJA (*M.pilosula spp)* and "inch ant- bulldog ant" venoms (*M. pyriformis, M. forficata, M. nigriceps*) representative of most or all of the venoms allergens of "inch ants" encountered in southern Australia is now available at IMVS, Adelaide, South Australia.

Sensitivity of in vitro sIgE varies from approximately 70-80% for *M. pilosula* venoms, approximately 80% for Vespula venoms to approximately 93% at best for *Apis mellifera* venom. Specificity can be considered under serological specificity or clinical specificity. The latter is poor with a substantial minority of exposed subjects with no history of systemic allergic reaction having positive tests.

The natural history of venom allergy is variable and in some cases may resolve over time. In a patient with a distant (>10 years) history of a SR to a sting, a negative sIgE to the responsible insect implies a low risk of SR on subsequent stings.

Venom Skin Testing

The main indication for IDT to venoms is a recent history of immediate generalised allergic reaction to a venom if the sIgE test is negative or equivocal.

IDT should be performed in patients with a history of reaction to a vespid sting using the venom extract planned for VIT. It is necessary to demonstrate that there is sensitivity to the derived venoms in the mixture proposed for VIT.

It is considered that venom skin testing is more sensitive than *in vitro* specific IgE and even in that case the "false negative" subjects for the two techniques differ. In a patient with a reliable history of sting allergy, but negative results for in vitro specific IgE tests, this should be followed by skin testing.

Basophil activation tests (BAT) are being developed in some laboratories but are not yet available for routine diagnostic use.

7. VENOM CROSS-REACTIVITY

Cross reactivity has two important implications:

- Patients allergic to one insect may be allergic to the cross-reactive insect even without prior stings from that insect (may apply between some ant species, some wasp species but not between bees and wasps).
- Interpretation of test results, in which case in-vitro patterns of cross-reactivity may overestimate clinical cross-reactivity risk (in some cases there may be in-vitro cross-reactivity between IgE to bee and wasp venoms).

Bees

Venoms of Apis and Bombus genus are significantly cross reactive; cross reactivity with native bees is unknown. There is limited cross-reactivity between Apis and Vespid venoms but less than within vespids. There is no known cross reactivity with ant venoms.

Bee and vespid venoms contain CCD that can result in serological false positive *in vitro* tests in atopic subjects with pollen allergy, but are not considered an important source of clinical reactivity. If specificity of an *in vitro* test is in doubt, especially if there are positives to several potential offenders, there are several approaches:

- Reciprocal cross absorption with venoms prior to in-vitro sIgE testing.
- sIgE to recombinant venom specific allergens; these tests avoid problems posed by CCD and other cross reactive components. Sensitivity is low, at least in the case of honeybee venom, but they are considered to have excellent specificity. A positive to r Api m1, r Ves v5 or r Pol d 5 is therefore strong evidence of true sensitisation to respectively, *Apis mellifera, Vespula spp or Polistes spp* venom but a negative result does not exclude the same. Recent studies suggest that better sensitivity will follow with addition of other recombinants such as r Api m 2, 3 and 10 and r Ves v 1 to test panels.
- Venom skin testing - convincing data on how much this excludes cross reactivity is lacking.
- Basophil activation tests (BAT) offer promise for improved sensitivity and specificity. They are claimed to predict clinical responses to venom better than traditional diagnostic tests, but need standardisation before routine application and are not currently available for routine clinical use.

Vespids

There is significant venom cross reactivity between vespids, and less cross reactivity with honey bee venom.

Ants

There is some cross reactivity across the *Myrmecia* genus but cross reactivity between JJA and “inch-bulldog ants” is very limited. It has been shown that cross reactivity between “inch-bulldog” ants in southern Australia is such that a mix of “inch ant- bulldog ant” venoms (*M. pyriformis, M. forficata, M. nigriceps*) will detect specific IgE in vitro to venoms of nearly all inch ants found in southern Australia.

There is no significant known cross reactivity between venoms of *Myrmecia, Rhytidoponera or Solenopsis* species, or between any of these venoms and bee or vespid venoms.

Serum with high total IgE (2,000-20,000 kU/L) does not produce significant false positive JJA venom sIgE test results. It appears that CCD reactivity is irrelevant to JJA venom.

8. AVAILABLE PRODUCTS

For current availability of the TGA registered, PBS and Pharmac subsidised Albey or Hymenoptera products, refer to the ASCIA website www.allergy.org.au/members/insect-allergy

Honeybee (*Apis mellifera*) venom

Yellow jacket (*Vespulsa spp*.) venoms

- Contains venoms of several Vespula species. In Australia these are referred to as European wasps and in Europe and Phadia catalogue as common wasps. The Australian species are *Vespula germanica* and Victoria also has *Vespula vulgaris*.

Paper wasp (*Polistes spp*.)

- Contains venoms of several northern Hemisphere paper wasp species. In Australia there are more than 30 species of paper wasps, including imported Polistes species and indigenous species, some of which belong to the Ropalidia genus.
- This venom mix should be used for subjects with a history of immediate systemic allergic reactions to paper wasp sting with skin test reactivity to this venom.
- Some patients have experienced anaphylaxis from local paper wasp stings yet have negative skin tests to Albey polistes venom; they should not undergo VIT with this product because they will not be protected.

Restricted TGA status, no PBS subsidy: JJA Venom

- JJA venom for diagnostic and therapeutic use is prepared at Royal Hobart Hospital (RHH) under TGA cGMP as an Active Pharmaceutical Ingredient. This license allows for distribution to approved hospital pharmacies in other states for re-formulation and use within the same hospitals under TGA SAS B conditions. SAS B approval also allows for venom to be transported in a ready to use product, where re-formulation at the local site is unavailable. Availability requires signed patient consent, SAS B approval, and a signed agreement between the prescriber, treating hospital and RHH.
- Whole body extract of imported fire ant, *Solenopsis invicta*. has been possible in the past. Current availability would need to be checked before ordering.

Not available

- Venoms of larger *Myrmecia spp*; (inch ants or bulldog ants).
- Venoms of *Rhytidoponera spp* (greenhead ants).
- Venoms of *Vespa spp* (hornets).

Case reports show that anaphylaxis may rarely occur from mosquito, tick and March fly bites. However, VIT is not currently available for these insects and arachnids.

9. EFFICACY AND OUTCOMES

When evaluating the literature, outcomes may be influenced by variables such as the type of insect, the maintenance dose (50 or 100mcg of venom), duration of VIT, severity of index reactions, and age of the population.

- Overall, VIT is very effective in reducing the risk of systemic reactions from insect stings as demonstrated by a 2012 Cochrane meta-analysis of seven studies (n=392 subjects). After the achievement of maintenance dose, the level of protection from severe anaphylaxis during VIT is (approximately) >95% (wasp) and >90% (bee). Most patients will experience local reactions only if stung during VIT. Honeybee VIT is generally less protective than vespid or JJA VIT, providing shorter duration of protection following cessation of treatment and more chance of systemic reactions with re-stings.
- North American studies have indicated that three to five years after the completion of VIT, the chance of a systemic reaction is approximately 10% per sting with a cumulative relapse rate approaching 20% after 15 years after treatment is stopped. These subsequent reactions are usually milder than pre-treatment reactions.
- With regards to initiation protocols, there is conflicting evidence if the modified rush regime is associated with increased adverse events. A large randomised comparative study using JJA VIT, found much higher serious reaction rates on ultra-rush versus clustered semi-rush regime. However, accelerated schedules (rush or ultra rush) for bee and wasp venom initiation are widely used in clinical practice in Australia and New Zealand. These schedules may be more feasible for patients who live in remote or rural areas, who have minimal access to local allergy specialist expertise.

10. TREATMENT SETTING AND FOLLOW-UP

A clinical immunology/allergy specialist diagnoses insect venom allergy and reviews management strategies including supervision of VIT initiation. Stable maintenance dosing may be undertaken in General Practice. Regular clinical review is to be undertaken by the clinical immunology/allergy specialist, often every 6-12 months, for the duration of treatment.

Patients undergoing VIT should carry their adrenaline autoinjectors when attending VIT.

Most people tolerating maintenance VIT can be considered likely to be protected from dangerous reactions to stings whilst maintenance therapy continues. There is still some risk (reported between 5-20%) of a systemic reaction to a sting/bite during maintenance VIT. Reactions are usually milder than before treatment, and are rarely severe.

It is important to note that:

- The reaction to stings is the only true test of efficacy of VIT.
- Deliberate sting challenge is not routinely undertaken due to incomplete sensitivity.
- Blood tests (venom specific IgE, blocking IgG) and skin tests do not provide reliable information about protection from sting anaphylaxis.

After a period at maintenance doses it may be reasonable to advise a patient that it is no longer necessary to carry an adrenaline autoinjector, since the risk of a dangerous reaction is low. Factors which will influence this advice include:

- Tolerance of a sting during maintenance VIT.
- Mild to moderate severity of index reaction.
- Urban location.
- Absence of significant co-morbidity.

Conversely it is appropriate to advise continuation of maintenance VIT beyond the standard three to five year duration (including lifelong), in cases of particularly high risk, such as:

- Original reaction extremely severe, such as prolonged hypotension, loss of consciousness, life-threatening respiratory involvement.
- Geographical isolation, living alone, outdoor occupations.
- Co-morbidities (cardiovascular or respiratory disease, mast cell disorders).
- Adverse reactions during VIT.

Tolerance of a sting during VIT provides additional reassurance to remove the requirement to carry an adrenaline autoinjector. However, venom delivery varies markedly so that tolerance of one sting does not guarantee tolerance of future stings. Stings following completion of VIT may be associated with re-sensitisation, hence caution is required if risk factors such as those listed above are high.

Failure to tolerate a field sting during VIT, or a SR to a dose of VIT, implies inefficacy of treatment and a higher maintenance venom dose (such as 150 – 200mcg for bees or wasps) may be considered.

Patients undergoing VIT should be reviewed prior to cessation of VIT to consider potential need for prolongation of VIT, and whether an adrenaline autoinjector should continue to be carried.

11. TEMPLATES

The following templates are available on the members sections of the ASCIA website www.allergy.org.au/members/allergen-immunotherapy

- Sample SCIT dosing schedule template.
- Sample patient consent form template.
- ASCIA SCIT Treatment Plan.
- Up-dosing schedules bee venom semi-rush.
- Up-dosing schedules bee venom ultra-rush.
- Up-dosing schedules Jack Jumper Ant (JJA).