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Information
FOR HEALTH PROFESSIONALS

Position Statement
Jack Jumper Ant venom immunotherapy

Summary points

1. Insect venom immunotherapy (VIT) is the injection, under the skin, of gradually increasing doses of insect venom. VIT starts with a very tiny dose that is gradually increased. This process causes a change in how the immune system responds to the venom.
2. There is a high level of scientific evidence to show that VIT prevents severe allergic reactions (anaphylaxis) to insect stings, with the aim of preventing morbidity and death. More than 30 years experience has found it to be effective, well tolerated, safe when administered in appropriate settings and associated with an improvement in quality of life for patients.
3. Different insect venoms are associated with different risks of allergic reaction to the VIT injections themselves. In this regard, Jack Jumper Ant (JJA) VIT appears to be similar to honeybee VIT.
4. Any clinical service that is competent to deliver honeybee VIT is also competent to deliver JJA VIT. The same protocols used to administer honeybee VIT can be applied to JJA VIT.
5. The protocols of administration associated with the lowest risks of allergic reactions to VIT are the slower outpatient ("conventional" and "semirush") approaches.
6. Accelerated inpatient approaches ("rush" and "ultrarush") may be used, but these present higher risks of allergic reactions. Patients offered accelerated inpatient treatment should be carefully selected so as to exclude those at greatest risk of decompensating during a reaction.
7. There is a risk of allergic reactions to VIT injections. Emergency procedures and experience with treating anaphylaxis must be in place for the treatment of these reactions. *This applies to all forms of injection immunotherapy, not just JJA VIT.*
8. JJA VIT is unique because the JJA is found only in Australia. The number of patients affected on a worldwide basis is therefore small. This presents a problem for the manufacture and supply of venom extract because there is no “economy of scale”.
9. At present, JJA venom is only available as an Active Pharmaceutical Ingredient (API), i.e. in concentrated form. This restricts its use to allergy services that are able to manage formulation, storage and dispensing on-site.
10. Where there are limited resources for providing JJA VIT, allergy services should prioritise available treatment places for patients that (i) have had documented hypotensive or hypoxaemic reactions requiring emergency medical treatment, and (ii) have an ongoing risk of accidental stings.
11. ***VIT for flying insects (honeybee, European wasp, paper wasp) is widely used in Australia and is considered to be “standard of care”. ASCIA considers that JJA VIT for patients with a history of anaphylaxis to JJA stings should likewise be considered a standard of care.***

Extent of the problem

The prevalence of insect venom allergy and the species of insects responsible vary significantly depending on sting exposure rates. In highly urbanised areas, venom allergy prevalence and presentation rates may be relatively low, but in rural areas and highly exposed populations the prevalence of previous systemic reactions to stings can approach 3-4%, with around half of these experiencing relatively severe reactions satisfying criteria for a diagnosis of anaphylaxis.[1, 2] In an urban emergency department (ED), 17-30% of presentations of anaphylaxis are due to insect stings,[3-5] but in rural populations, up to 60% of all cases of anaphylaxis may be due to insect stings.[6] For any given species of insect the prevalence of allergy correlates closely with annual accidental sting exposure rate for that particular insect.[2]

The Australian ant *Myrmecia pilosula* or Jack Jumper Ant (JJA) is highly aggressive and responsible for a majority of cases of anaphylaxis in areas where the ant is prevalent. In two Tasmanian studies, the prevalence of allergy to JJA was 2.7% with around 1% of the population suffering severe potentially life-threatening reactions (anaphylaxis).[2] Tasmanian ED presentation rates of anaphylaxis for JJA are twice that for honeybees (HB).[4]

JJA are also found in South Australia, Victoria, New South Wales, the Australian Capital Territory and Western Australia, although in mainland Australia the distribution of JJA is patchy. A national study of ant venom allergy supported by serological diagnosis found that JJA are the predominant cause of ant venom anaphylaxis in south-eastern Australia with "hot spots" of JJA sting allergy around Adelaide and on the outskirts of Melbourne and nearby rural areas. More sparsely distributed cases were identified in south-eastern New South Wales and in the south of Western Australia around Albany.[7] A postal survey of adults in four rural Victorian electorates published in 1998 found a prevalence of systemic reactions to ant stings of 2.4%, of which the majority were relatively severe and likely to satisfy criteria for a diagnosis of anaphylaxis.[8] The prevalence of anaphylaxis to JJA in adults in this study was 1.7%, which is comparable with the finding of a 1% overall population prevalence (adults and children, the later having a lower prevalence of sting allergy) in Tasmania.

Efficacy and effectiveness of JJA VIT

There have been three controlled clinical trials assessing the efficacy of venom immunotherapy (VIT) compared to treatment with placebo and/or whole body extract for preventing sting anaphylaxis.[9-11] The study of JJA VIT was of the highest standard (randomised, double-blind, and placebo-controlled). The results of these three trials are remarkably consistent with one another and are summarised in **Table 1**. These studies prove that VIT in severely allergic people is highly effective for preventing anaphylaxis, reducing the risk of sting reactions from 60-75% to 0-25%. It is also notable that in the few that experienced a reaction to sting challenge after immunotherapy, these reactions were always less severe than the reactions experienced prior to receiving VIT.

Since completing an initial randomised controlled trial,[11] the Tasmanian Jack Jumper Allergy Program has continued to monitor the real-world efficacy or "effectiveness" of JJA VIT (unpublished data - S Brown, June 2012). Of 478 patients receiving maintenance JJA VIT between January 2002 and March 2012, 132 subjects experienced a total of 218 accidental stings. Systemic reactions occurred in only 6/132 (4.5%) subjects. None were severe, 2 were moderate (with gastrointestinal or respiratory symptoms) and 4 were mild (skin only). One reaction was treated with adrenaline. Of the 478 started on JJA VIT in Tasmania since 2002, 95 (20%) have stopped prematurely. The decisions to stop treatment were attributed to adverse reactions in 29 (6% of those started on JJA VIT), inconvenience of treatment schedule in 37 (8%) and moving interstate in 17 (4%). The remainder stopped for a variety of reasons including planned pregnancy (unknown risks of VIT), inter-current illnesses and/or a perception of reduced or absent risk of further JJA stings.

This data is consistent with a large, long-term multicentre study of honeybee (HB) and vespid/wasp VIT from North America, where 410/1410 (29%) had stopped VIT by the end of the three-year study period; 114 failed to reach maintenance dose (reasons not specified - presumably because of reactions to treatment in most cases) and of those who achieved maintenance but dropped out later, 23 stopped treatment due to reactions.[12]

An impact of VIT on reducing mortality due to insect venom anaphylaxis is expected but has not been established. This is because it has not been feasible to undertake an adequately powered study comparing VIT with no VIT, which would be prohibitively large and likely to be confounded by behaviour according to treatment allocation. It is clear, however, that VIT has a significant impact by improving quality of life by enabling people to continue to reside, work, and undertake recreational activities in areas where there is a risk of accidental stings.[13, 14]

Table 1. Controlled trials of VIT

Study	Design	Comparison treatments	Primary outcome measure	Results
Hunt 1978[9]	Randomised, single-blind, adults with a history of honeybee or vespid anaphylaxis	Placebo, whole body extract (WBE), venom immunotherapy (VIT)	Sting challenge as soon as maintenance dose established	Systemic reactions to sting challenge in 7/12(58%), 7/11(64%) and 1/18(6%) in placebo, WBE and VIT groups respectively.
Muller 1979[10]	Open label, allocation method not stated, adults with a history of honeybee anaphylaxis	Whole body extract (WBE), venom immunotherapy (VIT)	Accidental stings and serological (IgG) changes during first year of treatment	Significant increases in antigen-specific IgG in VIT but not WBE group. Systemic reaction in 9 (75%) of 12 WBE patients accidentally stung versus 3 (25%) of 12 VIT patients accidentally stung (all of which were less severe than previous reactions).
Brown 2003[11]	Randomised, double-blind, adults with a history of jack jumper ant (JJA) anaphylaxis	Placebo, venom immunotherapy (VIT)	Sting challenge as soon as maintenance dose established	Systemic reactions to sting challenge in 21/29 (72%) versus 0/23 in placebo and VIT groups respectively (blinded phase) and 2/64(3%) for all after VIT including the crossover phase. Sting challenge reactions were cutaneous only, in subjects who had previously had hypotensive sting anaphylaxis prior to JJA VIT.

Treatment schedules and adverse reactions to treatment

A range of treatment schedules can be used to initiate VIT and are well described in the scientific literature. Faster dose increases (rush and ultrarush schedules) are given in a hospital environment and are designed to reach a protective maintenance dose as soon as possible. Slower dose increases (semirush and conventional schedules) are more suitable for outpatient practice. For JJA VIT, the semirush and ultrarush approaches to treatment initiation have been comprehensively assessed in two randomised controlled trials of semirush *versus* placebo,[11] and ultrarush *versus* semirush.[15]

Reported systemic reaction rates during VIT vary between 0% and 67% and are difficult to interpret because of a lack of standardised definitions and reporting, variable use of antihistamine premedication, variable baseline allergy severity of subjects (and reporting of same), variations in age, gender balance, and comorbidities of the populations being treated, and variations in treatment schedules and insect species to which patients were allergic.

The two clinical trials of JJA VIT have used prospectively applied definitions of adverse reactions based on data that has been carefully collected by dedicated research staff. Objective systemic reactions of any grade (including mild flushing) were classified as adverse reactions and hypotensive reactions were defined by strictly applied blood pressure criteria. Furthermore, there was little doubt as to the species responsible for each patient's allergy. By comparison, other reports of adverse reactions to VIT in the setting of honeybee and

vespid allergy have included one or more of; retrospective review of notes, voluntary reporting by non-research staff, and patients that may not have been allergic to the respective venom species (for example multiple treatments for cases where there is uncertainty as to whether the primary sensitisation is to honeybee or vespid).

Table 2 provides a comparison of reaction rates during the initiation of VIT in studies that have included a substantial number of JJA or HB VIT treatments, as these are of most relevance to Australian clinicians. Although systemic reactions overall appear to be more common during JJA VIT, these are mostly mild. Overall, the need for *emergency intervention* is similar for JJA VIT and HB VIT. Whatever venom is used, the risk is greater where VIT is given by rapid rush/ultrarush schedules, compared to the slower semirush and conventional VIT schedules. Combined data from the two JJA VIT studies indicates a risk (per patient treated) of 13% for treatment with adrenaline and 2% for hypotensive anaphylaxis during semirush VIT. The corresponding risks during ultrarush JJA VIT are 24% and 12% respectively.

Based on these studies, ASCIA recommends that slower outpatient (conventional or semirush) schedules should be the "default" option for JJA VIT unless there is are compelling reasons to use a rush/ultrarush approach. Before using a rush/ultrarush schedule, patients should be informed of the higher risk. This is particularly important if there are significant comorbidities and/or advanced age, when a severe reaction could be life threatening.

Whatever VIT approach (conventional, semirush, rush or ultrarush) is used, the treating clinician must be adequately experienced, equipped and prepared to provide emergency treatment for severe anaphylaxis. This applies to all forms of injection immunotherapy, not just JJA VIT.
Any clinical service that is competent to deliver HB VIT is also competent to deliver JJA VIT. The protocols used to administer HB VIT can be applied to JJA VIT.

Table 2. Adverse reactions during VIT

Study	Venom	Schedule	Number or percentage of subjects experiencing one or more reactions
Brown 2003[11]	JJA	Semirush	22/64(34%) experienced one or more systemic reactions ranging from mild to severe. 8 subjects (12%) were treated with adrenaline. 2 subjects (3%) had a severe reaction with hypotension.
Brown 2012[15]	JJA	Semirush	12/42 (29%) experienced one or more systemic reactions ranging from mild to moderate. 6 subjects (14%) were treated with adrenaline. No subject had a severe reaction with hypotension.
		Ultrarush	32/49 (65%) experienced one or more systemic reactions ranging from mild to severe. 12 subjects (24%) treated with adrenaline. 6 subjects (12%) had a severe reaction with hypotension.

Rueff 2010[16] *Multicenter study (Europe)*	HB	All types	Overall, 33/207 (16%) required "emergency intervention" (unspecified). The study also found that ultrarush initiation was associated with more than twice the risk of reactions than conventional treatment, irrespective of venom type. The paper did not give absolute risk in HB ultrarush versus HB semirush but these are probably in the order of 20-25% and 5-10% respectively.
	Vespid	All types	Overall 24/473 (5.1%) required "emergency intervention" (unspecified).
Lockey 1990[12] *Multicenter study (North America)*	HB	Conventional	90/224 (40%) reactions, ranging from mild-severe.
	Vespid	Conventional	28/234 (12%) reactions, ranging from mild-severe.
Westall 2001[17]	Mainly HB	Rush	26/73 (35%) had one or more reactions. 25 (34%) were mild. 11 (18%) were treated with adrenaline. 7 (9.5%) were moderate. 3 (4%) were severe.
Muller 2008[18]	HB	Ultrarush	14/54 (25%) had objective reactions.

Children, pregnant women, older adults, and people with significant comorbidities

The efficacy and safety of VIT in children has been established for HB and Vespid venoms, however little data is available for older adults and patients with comorbidities. There is no published data specifically on the use of JJA VIT in children, although children were included in a comparison of semirush and ultrarush initiation.[15] As of June 2012, the Tasmanian Jack Jumper Allergy Program had initiated JJA VIT in 59 patients less than 14 years and 26 patients more than 65 years old, including a number with significant respiratory and cardiovascular comorbidities (unpublished data - S Brown, June 2012).

ASCIA recommends that any clinicians providing JJA VIT to children, pregnant women, older adults and people with significant comorbidities should carefully assess the risk/benefit of JJA VIT and collaborate with the Tasmanian Jack Jumper Allergy Program to monitor treatment tolerability, safety and effectiveness in these groups.

Maintenance dose, maintenance dose intervals and duration of therapy

For routine JJA VIT treatment, ASCIA recommends standard HB dosing protocols, as used and shown to be effective in the first study of JJA VIT. Ongoing studies are exploring whether lower maintenance doses and longer maintenance intervals can be used without compromising protection from JJA stings. There is, as yet, no data specific to JJA VIT regarding duration of therapy. The Tasmanian Jack Jumper Allergy Program offers patients a minimum of 5 years maintenance therapy. Indefinite ongoing treatment (for as long as a risk of accidental stings persists) is offered to those with a history of severe (life-threatening) sting reactions with hypotension or hypoxaemia, high baseline mast cell tryptase, or severe adverse reactions to VIT.

Patient selection

The same criteria used to select patients for HB VIT should be applied to JJA VIT. That is, patients with a history of systemic allergic reaction to a sting plus evidence of JJA sIgE (positive testing by either skin testing or serum CAP) are eligible.

JJA sIgE CAP assays are available through SA Pathology (Flinders Medical Centre, Bedford Park, SA 5042) but are only 80% sensitive compared to intradermal skin testing.[19] Intradermal skin testing with JJA venom is performed in the same way as for HB venom.[11]

Where patient demand for treatment is greater than service capacity, it is recommended that patients be prioritised so that those who have had life-threatening reactions with hypotension or hypoxaemia (rather than reactions which left untreated *might* have become life threatening) and who have a significant ongoing risk of accidental stings are offered treatment first. Patients who have had a severe reaction with hypotension or hypoxaemia should be considered at highest risk, as these people have the greatest risk of a severe reaction when stung again.[2, 20] If previous reactions occurred without physiological monitoring, high risk historical features suggestive of hypotension and/or hypoxaemia are confusion, collapse, unconsciousness and incontinence.[4] It is important to base risk on the *worst* prior reaction, because reaction severity typically fluctuates with severe reactions followed by several milder or even no reaction to sting(s), and then a severe or even lethal one thereafter.[2, 21]

Special issues

1. Venom supply

As JJA venom is not commercially available, there are a number of special considerations and processes that must be followed prior to supply of JJA venom for VIT.

Venom for JJA VIT is produced by the Tasmanian Jack Jumper Allergy Program at the Royal Hobart Hospital. At this time, it is only available as an Active Pharmaceutical Ingredient (i.e. concentrate), and as such requires further formulation/processing before it is suitable for use as a therapeutic or *in vivo* diagnostic (i.e. skin testing) agent.

The use of JJA venom for VIT should be discussed with the Jack Jumper Allergy Program at the Royal Hobart Hospital to ensure that (i) sufficient venom will be available for an ongoing supply to complete at least 5 years maintenance therapy before treatment starts; (ii) the treating site has access to the necessary facilities for venom storage and formulation, and (iii) the necessary procedures are followed. Prior to using JJA venom for VIT, approval to use the venom must be obtained from the Therapeutic Goods Administration under the Special Access Scheme (www.tga.gov.au/hp/access-sas.htm). A category B approval is required, and this documentation must be forwarded to the Jack Jumper Allergy Program prior to venom being supplied. Prescribers must complete a Prescriber Agreement acknowledging the potential risks of using JJA venom (a proforma can be obtained from the Jack Jumper Allergy Program) and have written approval from the relevant committee at their hospital that approves the use of unregistered drugs.

JJA venom is supplied as a concentrated solution in Water for Injection and labelled with the concentration of venom protein (in mg/mL unit). This solution can be stored at -18°C but is ideally stored at -80°C. This JJA venom will need to be further formulated to a 1100 microgram/mL solution in 22% sucrose under aseptic conditions (i.e. in a laminar flow hood). At this concentration, JJA venom is stable for 12 months -18°C and 4°C. Care should be taken not to repeatedly freeze-thaw solutions. Immediately prior to use, JJA venom solution should be diluted to 100 microgram/mL with JJA venom-compatible diluent solution. At this concentration JJA venom is stable for 7 days at 4°C. 10-fold dilutions may be prepared from the 100 microgram/mL solution. 10 µg/mL solutions are stable for 24 hours at 4°C, but more dilute solutions should be used immediately and then discarded.[22]

2. Further research

Although the evidence base supporting JJA VIT should be considered equivalent to that which supports *honeybee, European wasp, paper wasp* VIT, ASCIA recognises the special limitations imposed on JJA VIT by the small market volume. Ongoing clinical research is encouraged to investigate the use of smaller doses of JJA venom, immunological adjuvants and pharmaceutical research to investigate more stable formulations for distribution and supply to clinicians.

3. Equity

Australian Commonwealth and State Governments currently fund the provision of honeybee, European wasp, and paper wasp VIT. In the interests of equity for JJA allergic people, ASCIA recommends that Governments

provide ongoing funding for hospitals in each affected state to provide JJA VIT alongside VIT for other species of insect.

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Website: www.allergy.org.au
Email: projects@allergy.org.au
Postal address: PO Box 450 Balgowlah NSW Australia 2093

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