

ORIGINAL ARTICLE

Review of venom immunotherapy at a regional tertiary paediatric centre

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Aim: Bee stings can result in allergic reactions, including anaphylaxis. Venom immunotherapy (VIT) is a definitive cure for bee venom allergy, but controversy surrounds whether accelerated protocols are safe in children. Our primary aim was to assess the safety profile of ultra-rush bee VIT compared with conventional bee VIT at a regional paediatric tertiary centre. We also sought to evaluate the impact of both approaches on time and resource use.

Methods: Data were collected retrospectively from 14 patients with bee venom allergy who were treated with ultra-rush or conventional bee VIT between 2013 and 2021 at John Hunter Children's Hospital. We compared VIT-associated adverse reactions and use of resources in both these groups.

Results: Overall, six patients received ultra-rush bee VIT and eight patients received conventional VIT. The ultra-rush group had a lower rate of systemic reaction (16%) compared with the conventional group (25%). One patient from the conventional group required adrenaline. Ultra-rush patients require fewer injections over a shorter time and fewer hospital visits to complete the protocol. Travel distance for families was significantly reduced.

Conclusion: At our regional paediatric tertiary centre, ultra-rush bee VIT was a safe treatment option for children with bee venom allergy. It has many advantages over a conventional approach, especially for patients living in regional or remote areas.

Key words: anaphylaxis; bee venom; immunotherapy.

What is already known on this topic

- 1 Venom immunotherapy reduces the risk of anaphylaxis in children with severe venom allergy.
- 2 The duration of time to complete different updosing protocols can vary, for example, conventional (months) or ultra-rush (days).

What this paper adds

- 1 Ultra-rush venom immunotherapy is safe in Australian children.
- 2 Its advantages include fewer injections, fewer hospital visits and less travel, especially important to consider for patients living in regional and remote communities.
- 3 Ultra-rush VIT should be offered to all children who have experienced venom anaphylaxis in centres with clinical expertise and can be safely conducted on a paediatric ward.

It is common for children to be stung by insects such as bees, wasps, and ants. Most sting reactions are mild, but a small proportion (<1%) result in systemic IgE mediated symptoms such as urticaria, wheezing or hypotension. In Australian children, insect stings are the second leading cause of anaphylaxis after food allergens.¹ In addition to severe allergic reactions, affected children and their parents may experience significant anxiety and a reduced quality of life.²

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Venom immunotherapy is a definitive treatment for bee and wasp venom allergy. It can reduce the risk of severe allergic reactions from a future sting from 60–70% to <5%.³ VIT begins with an initial updosing protocol followed by ongoing maintenance dosing over a period of 3 to 5 years. Years after discontinuation of therapy, the benefits of VIT persist.⁴ Bee venom immunotherapy is commercially available in Australia with the cost government-subsided via the PBS (Pharmaceutical Benefits Scheme).

While the efficacy of VIT in children is undisputed, controversy surrounds optimal dose escalation. A typical conventional updosing protocol may involve 15 incremental, injectable doses of venom delivered over 15 weeks.⁵ In contrast, accelerated updosing protocols are delivered over the course of hours to days. Ultra-rush VIT protocols are the fastest of these. For example, a cumulative venom dose of 101.1 mcg divided into six, incrementally dosed, subcutaneous injections that can be delivered over

3.5 h on day 1, followed by 100 mcg divided into two subcutaneous injections on day 15 and finally a single 100mcg injection at day 45.⁶ In comparison to conventional VIT, ultra-rush has the advantage of fewer injections and more rapid attainment of protection. However, there are potential downsides. Studies in adults have reported increased rates of adverse reactions associated with accelerated protocols.⁷ Few studies have investigated the safety and overall use of ultra-rush bee VIT in children in Australia. As a result, some centres deliver ultra-rush VIT in a costly intensive care setting, due to perceived risk of severe reactions.

We recently switched from a conventional to an ultra-rush updosing protocol for bee VIT, providing us with a unique opportunity to directly compare the two approaches in our patients. Since our centre serves metropolitan, regional, and remote areas, many families travel long distances to access our services. We hypothesised that the ultra-rush approach would be beneficial to those who live far from the hospital.

We thus aimed to compare the safety profile of ultra-rush versus conventional VIT at our regional tertiary paediatric centre. Our secondary aim was to evaluate the time and resource utilisation for both approaches. Finally, we explored the feasibility of providing ultra-rush VIT on a paediatric ward.

Methods

Patients

Data were collected retrospectively from medical records of patients with bee venom allergy who were treated with bee-venom immunotherapy (VIT) between 2013 and 2021 at John Hunter Children's Hospital, one of the three tertiary paediatric hospitals in New South Wales, Australia. Ethics was obtained (Authorisation Number: AU202110-15) prior to review of records.

Patients included in the study met the following criteria:

- 1 History of immediate severe systemic reaction to honey bee sting (defined by cardiovascular, respiratory or gastrointestinal involvement).
- 2 Elevated serum-specific immunoglobulin E (IgE) to bee venom.
- 3 Parental consent for VIT.

Venom immunotherapy protocols

The conventional and ultra-rush VIT protocols are shown in Table 1. Conventional VIT was undertaken in a paediatric outpatient clinic setting, while ultra-rush was offered only in the paediatric intensive care unit (PICU). For both groups, the majority of patients received standard age-based doses of oral antihistamine prior to receiving immunotherapy injections that contained honey bee venom (Albey bee venom, Stallergenes Australia Pty Ltd). Before starting the ultra-rush protocol, children had an intravenous cannula inserted. If there was a history of asthma, peak flow readings were measured. Injections were given by a Paediatric Allergy Clinical Nurse Consultant, who also performed frequent observations. When a VIT-associated reaction occurred, the Paediatric Allergy Specialist was consulted to decide whether

Table 1 Conventional and ultra-rush updosing protocols

Conventional protocol		Ultra-rush protocol	
Timing	Dose (mcg)	Timing	Dose (mcg)
Week 1	0.1	Day 1	
Week 2	0.2	0 h	0.1
Week 3	0.4	0.5 h	1
Week 4	0.8	1 h	10
Week 5	1	1.5 h	20
Week 6	2	2.5 h	30
Week 7	-	3.5 h	40
Week 8	4		
Week 9	8	Day 15	50, 50
Week 10	-	Day 45	100
Week 11	20		
Week 12	40		
Week 13	80		
Week 14	100		

h, hours; mcg, micrograms.

it was safe to continue with the protocol and whether treatment was required.

Safety

Data on adverse reactions and treatments given were obtained from the medical record. Adverse reactions were classified as local or systemic. The severity of systemic reactions was graded using a system described by Mueller,⁸ detailed in Table 2.

Time and resource use

Medical records and hospital VIT protocols were examined to calculate the number of injections received by patients during each updosing protocol. We recorded the duration of time and number of hospital visits between starting and completing VIT. We then calculated the total distance travelled by patients and their families when attending the hospital for immunotherapy and compared it to the estimated time and distance for the alternate treatment regimen.

Table 2 Severity of systemic allergic reactions based on Mueller⁸

Grade	Description
Grade 0	Large local reaction larger than 10 cm
Grade 1	Generalised urticaria, pruritus, nausea
Grade 2	Vomiting, angioedema, dizziness, sensation of tightness
Grade 3	Dyspnoea, stridor, wheezing, fear of dying, weakness, drowsiness
Grade 4	Hypotension, cyanosis, respiratory or circulatory arrest

Table 3 Patient characteristics for conventional and ultra-rush groups

Baseline characteristics	Conventional	Ultra-rush
Median age in years (IRQ)	8 (3.5)	7.3 (4)
Male sex (%)	6/8 (75)	5/6 (83.3)
Ethnicity		
Caucasian	6/8 (75)	5/6 (83.3)
Aboriginal and/or Torres Strait Islander	2/8 (25)	1/6 (16.7)
Concurrent atopy		
Asthma	1/8 (12.5)	1/6 (16.7)
Allergic rhinitis	1/8 (12.5)	0
Eczema	1/8 (12.5)	0
Food Allergy	1/8 (12.5)	0
Other risk factors		
Previous bee sting anaphylaxis (%)	8/8 (100)	6/6 (100)
Parent beekeeper (%)	1/8 (12.5)	1/6 (16.7)
ssIgE bee elevated >0.3kU/L (%)	8/8 (100)	6/6 (100)
Baseline tryptase <11 ng/mL	3/3 [†] (100)	6/6 (100)

[†] Tryptase available for three patients in conventional group. E, kU kilounit; IRQ, interquartile range; ng, nanogram; ssIgE, serum-specific immunoglobulin E.

Results

Patient characteristics

In total, 14 patients received honeybee venom immunotherapy between 2013 and 2021 with six patients receiving ultra-rush VIT and eight patients conventional VIT. There were no differences between the groups at baseline (Table 3). Both groups had a predominance of male patients. All patients had an elevated serum-specific IgE for honey bee venom. Baseline tryptase levels were performed on nine (64.3%) of 14 patients, none of which were elevated.

Table 4 VIT-associated reactions

Protocol	Most severe reaction	Dose eliciting reaction (mcg)	Treatment needed
Conventional			
Patient 1	Local reaction	0.1	AH
Patient 2	Local reaction	0.1	AH
Patient 3	No reaction		
Patient 4	Grade 0 (large local reaction >10 cm)	80	AH, analgesia
Patient 5	Local reaction	2	AH
Patient 6	Local reaction	1	AH
Patient 7	No reaction		
Patient 8	Grade 3 (urticaria, wheezing)	80	Adrenaline, AH, glucocorticoid
Ultra-rush			
Patient 9	No reaction		
Patient 10	No reaction		
Patient 11	Local reaction	10	AH
Patient 12	Grade 3 (urticaria)	30	AH
Patient 13	No reaction		
Patient 14	No reaction		

AH, antihistamine; mcg, micrograms.

Safety

All VIT-associated reactions are shown in Table 4. Of 14 patients, 11 patients experienced none or localised reactions only. The rate of systemic reaction was 16.6% in the ultra-rush group and 25% in the conventional group. Systemic reactions were seen in three patients, all of which occurred within 30 min of an injection. One patient in the conventional group required adrenaline. There were no Grade 4 reactions.

Time and resource use

The majority of patients (13/14; 93%) completed the updosing schedule. One patient in the conventional group decided to discontinue therapy due to a severe reaction. In total, 149 injections were delivered to patients. When compared to conventional patients, ultra-rush patients completed their updosing protocol over a shorter time period (6 vs. 14 weeks), had fewer hospital visits (3 vs. 12) and fewer injections (9 vs. 12) as shown in Figure 1a. Additionally, there was a cumulative distance savings of 9792 km for the six patients in the ultra-rush group (Fig. 1b).

Discussion

Some studies in adults have shown accelerated schedules such as ultra-rush to have increased rates of VIT-associated systemic reactions compared with conventional approaches.⁷ There have been surprisingly few studies to explore if this is the case in children. A number of European studies indicate that systemic ultra-rush VIT-associated reactions in children are less frequent than typically reported in adults, ranging between 2.7% and 16.6%.^{6,9–11} These findings are similar to our study, where 16.6% of ultra-rush patients had a systemic reaction. Children enrolled in these European studies shared similar age and gender characteristics to our patients. However, factors such as ethnicity or provoking insects are likely to vary.

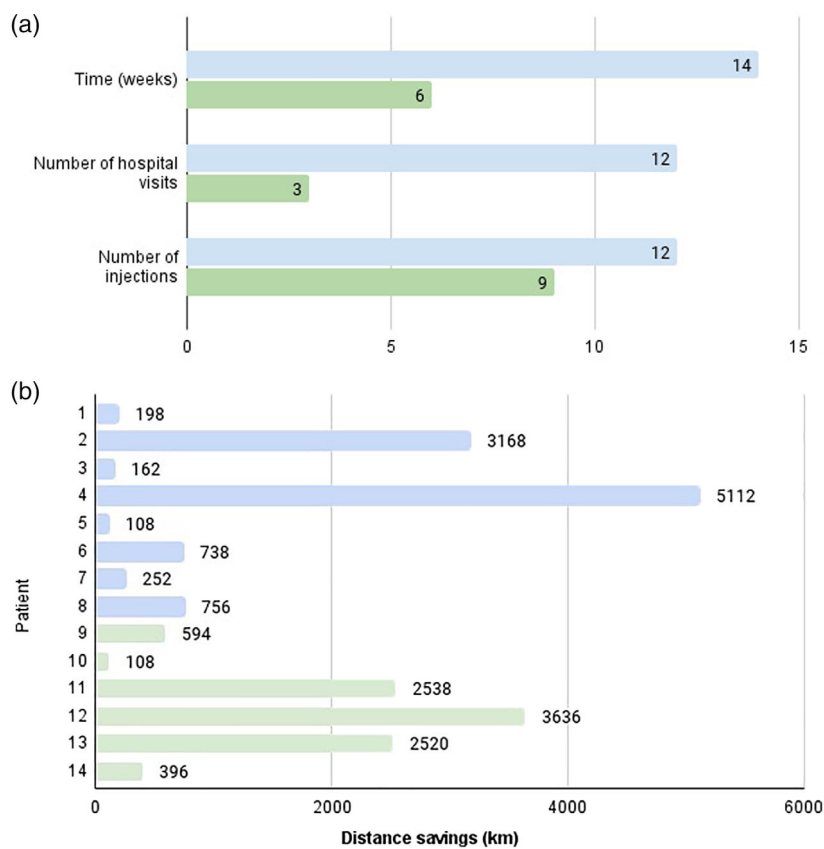


Fig. 1 (a) Time, hospital visits and number of injections required for conventional and ultra-rush uposing protocols: (■), Conventional; (■), Ultra-rush. (b) Distance savings associated with ultra-rush uposing protocol: (■), Potential savings for conventional group; (green box), actual savings for ultra-rush group.

In Australia, two studies have shown a wider variability in the rate of systemic reactions to ultra-rush VIT. Houliston¹² retrospectively examined 82 children treated with modified honey-bee ultra-rush VIT and reported a lower rate of systemic reaction of 10%. The modified protocol was not provided. Additionally, the final maintenance dose used in this study was 50 mcg, lower than the 100 mcg dose used in our institution's protocol as well as recommended in international venom immunotherapy consensus guidelines.¹³ For this reason, the results are not directly comparable. A second smaller report by Mackey¹⁴ described 19 patients undergoing 2-day ultra-rush VIT and identified a significantly higher rate of systemic reaction (47.4%). The reasons for the higher rate are not clear. Little information was provided regarding pre-medication of patients or other risk factors, such as elevated basal tryptase levels.

For years, conventional VIT has been the uposing schedule of choice for paediatric patients. Despite its popularity in both the United Kingdom¹⁵ and United States,¹⁶ a conventional approach requires considerable time and resource commitment by both families and health-care providers. A weekly outpatient appointment and repeated injections are required until the final maintenance dosage is reached. There are also additional disadvantages for the patient and family such as longer delays in achieving protection from stings and increased burden of additional injections.

Our centre serves a major metropolitan area, several large regional centres, as well as a number of smaller rural areas and remote communities within its referral catchment area. As a result, repeated long distance journeys to and from the hospital pose a cumulative burden for families. Compared to densely populated

urban areas, remote and regional communities are disproportionately impacted, making it difficult for them to access tertiary care.

Our study is the first to quantify the considerable time, resource and travel savings offered by ultra-rush VIT compared with slower conventional protocols. We provide proof of the special benefits afforded to patients and families who live far from our hospital. Individual families in the ultra-rush group saved between 162 and 5112 km of travel each over the course of their treatment and avoided nine additional hospital visits. If all 14 patients had received ultra-rush, a cumulative saving of 20 286 km of travel could have been achieved. Importantly for families, reduced travel burden translates into fewer days off from school for patients, fewer days at work for parents, and less disruption to routine.

It has been a common practice to administer accelerated protocols to children in intensive care units due to the perceived increased risk of severe reactions. This subsequently increases the cost of delivering ultra-rush VIT as well as burdening highly specialised, costly hospital facilities. While some studies utilised intensive care,⁹ we reviewed several studies that delivered ultra-rush VIT in unspecified hospital settings^{10,11} or in outpatient clinics instead.^{6,12} International¹³ and national¹⁷ guidance on choosing an optimal care setting for ultra-rush VIT delivery is lacking and as a result, it falls to individual allergy centres to make this decision mindful of local circumstances and limitations. An unpublished survey of 10 venom immunotherapy centres in Australia and New Zealand found that 83.7% of the centres that offer ultra-rush VIT to children do so on a paediatric ward (personal communication). To our knowledge, there has been no ultra-rush VIT-associated mortality in children in any setting, intensive care or otherwise, reported in the literature. We estimate

that providing ultra-rush VIT on a paediatric ward at our institution instead of in intensive care would be associated with major direct and indirect health-care cost savings, though these calculations were beyond the scope of this study.

Our study's limitations include its small size, retrospective study design and missing baseline tryptase data for a small number of patients. Despite these issues, this study adds to the literature demonstrating the safety of ultra-rush bee venom immunotherapy in Australian children.

Conclusion

This study demonstrates that ultra-rush bee VIT is a safe treatment option for children with bee venom allergy. When compared with conventional approaches, we found that ultra-rush VIT is a better option for patients and families, particularly those in remote and regional communities. Advantages included less travel and hospital visits, fewer injections and a shorter time to therapeutic maintenance dosing.

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