

Prevention of anaphylaxis with ant venom immunotherapy

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Purpose of review

Worldwide, eight genera of ants have been associated with sting allergy. Until recently only whole ant body extracts have been used for immunotherapy. The purpose of this review is to examine recent advances in the understanding of ant venom allergy and treatment using venom immunotherapy.

Recent findings

Public health problems due to severe ant sting anaphylaxis are not confined to the imported fire ant of North America.

Pachycondyla sennaarensis (samsun ant), *Pachycondyla chinensis*, and *Myrmecia pilosula* (jack jumper ant) also appear to pose notable threats. The risk to humans from a particular species probably depends on complex interactions between likelihood of human contact, insect aggression, efficiency of the venom delivery apparatus, and venom allergenicity. The highest population prevalence of clinical ant sting allergy so far (3.0%) was reported from south-eastern Australia, due mainly to *M. pilosula*. Prospective follow-up of untreated people suggests that those older than 30 years with a history of severe reactions (respiratory compromise or hypotension) will benefit most from venom immunotherapy. Whereas the efficacy of ant whole body extract immunotherapy remains to be proven, ant venom immunotherapy has been demonstrated to reduce the risk of systemic reactions to *M. pilosula* from 72% to 3%. Although a simple method of venom extraction has been developed, small market size means that the treatment may never become widely available.

Summary

Ant venom immunotherapy is feasible and highly efficacious. However, the limited geographical distribution of each species presents a major challenge to making venom extracts available for clinical use.

Keywords

anaphylaxis, ant sting, whole body extract, venom immunotherapy

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Abbreviations

IFA imported fire ant
JJA jack jumper ant
VIT venom immunotherapy
WBE whole body extract

Introduction

Until recently the medical literature on ant sting allergy has focussed on imported fire ant (IFA) infestations in North America, for which treatment has been with whole body extract (WBE) rather than pure venom [1]. However many other species are important worldwide and in Australia, pure ant venom extract has been tested in the first double blind randomized placebo-controlled study of venom immunotherapy [2•]. We will review recent studies of ant venom allergy and immunotherapy that provide a framework for further developing, testing, and applying immunotherapies for allergy to stinging ants.

Epidemiological considerations

When planning an immunotherapy program, an understanding of ant sting allergy epidemiology and natural history is required. It cannot be assumed that the results of studies in one species will apply to others.

Causative species

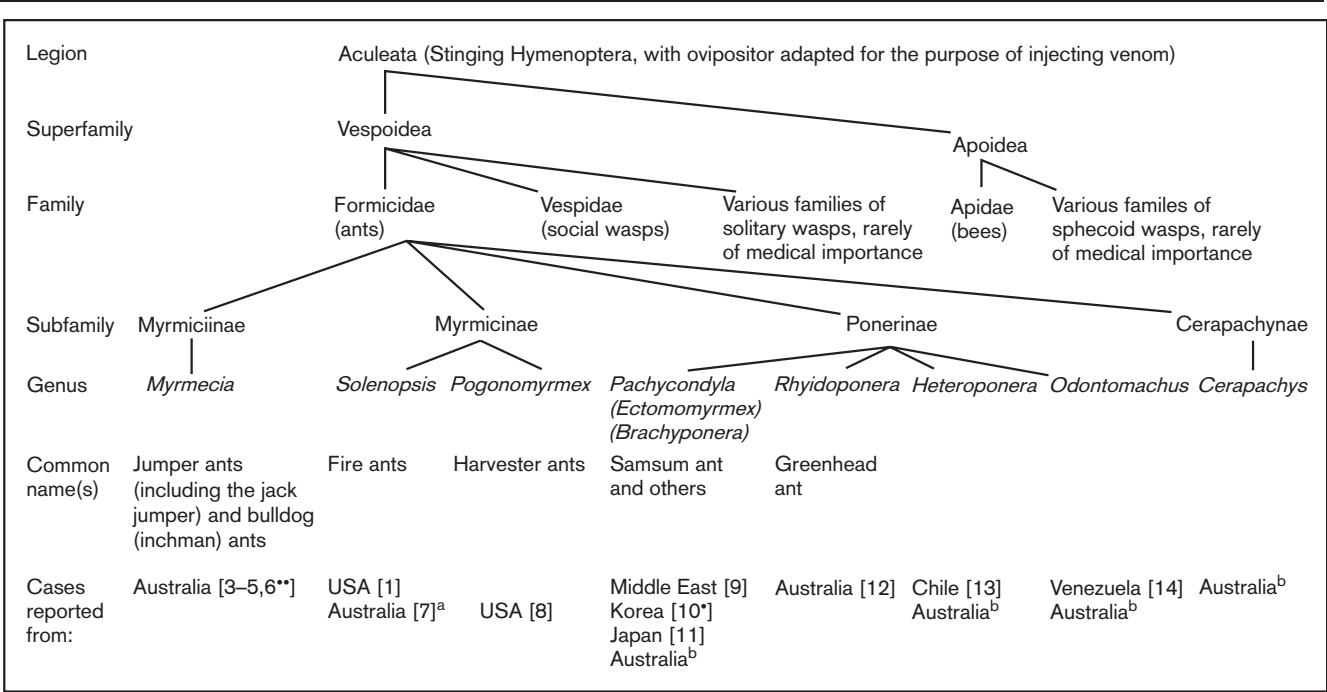
To our knowledge, a total of eight genera of ants have thus far been associated with ant venom allergy [1,3–5,6•,7–9,10•,11–14]. These are presented in Figure 1, according to a recently revised phylogenetic classification for the Aculeata [15]. We have not included biting ants that do not inject venom, such as *Formica* spp., because reactions occur to ant saliva infrequently and are almost universally mild. It should be noted that nomenclature changes could easily confuse the non-entomologist. For example, the genus *Pachycondyla* now includes ants previously classified under *Ectomomyrmex* and *Brachyponera*.

Despite the large number of ant species capable of causing anaphylaxis, notable public health problems appear to be limited to relatively few, namely *Solenopsis* spp. (IFA) in the United States [1], *Pachycondyla sennaarensis* (samsun ant) in the United Arab Emirates [9], *Pachycondyla chinensis* in Korea [10•], and the *Myrmecia pilosula* species complex, or jack jumper ant (JJA), in Australia [4,5,6•]. However, a reporting bias is likely. Anaphylaxis kills relatively few people; in less developed countries allergy treatment has a low priority and specialist allergy services may be absent or rudimentary.

What makes a species more dangerous than others?

IFAs typically form large colonies (up to 250 000 ants or more) and use pheromones to recruit large numbers of ants to attack. Up to 500 mounds per acre may be found in infested areas and invasion of human dwellings also

Figure 1. Phylogenetic relationships of stinging ants currently known or suspected of causing anaphylaxis in humans



^aOnly one case reported so far, with infestation confined to the Brisbane area. ^bReported without clinical details [7]. Correspondence with the authors revealed that specimens were sent in by doctors and patients for identification following 'allergic reactions' but no further details were recorded (Cas Vanderwoude, Fire Ant Control Centre, Queensland; personal communication).

occurs. The likelihood of human contact is therefore high [16,17*]. IFAs are small (2–6 mm) and deliver only 10–100 ng of protein per sting, containing four major allergens weighing 14 000–37 000 Daltons [18]. Typically, accidental exposures involve multiple stings by multiple ants.

In contrast, JJAs form small colonies (100–1000 ants) that often go unnoticed. Single ants venture long distances from their colonies. They are exceptionally aggressive, have highly developed vision, are attracted to movement (sometimes jumping from nearby bushes to attack), and thus frequently come into contact with humans. Twelve percent of the Tasmanian population is exposed to JJA stings every year, and stings are usually single [6**]. They are relatively large (10–12 mm) with powerful mandibles that enable a firm grasp whilst injecting venom with their abdominal stinger. On average, we have been able to obtain 30 µg venom protein per ant by venom sac dissection, and 10 µg by electrostimulation. The venom peptides have a relatively low molecular weight, the two main allergenic components weighing 5608 and 6067 Daltons [19]. Thus, unlike IFAs, JJAs deliver smaller numbers of stings but much larger amounts of venom and with a greater number of allergenic molecules per unit weight of venom protein. This, along with their efficient venom delivery mechanism, may contribute to the exceptionally high (70%) re-

sting reaction rate, for both accidental and diagnostic (in-hospital) stings [2**,6**].

Allergy prevalence is directly related to annual sting exposure rates, and increases significantly with advancing age [6**]. Presumably the cumulative risk of encountering a Th-2 type response increases with each successive exposure. Although some venoms may be inherently more allergenic, we do not understand the molecular characteristics that determine allergenicity. Some novel research suggests that the inherent ability to induce immunoglobulin E-independent histamine release may render some venom components more allergenic than others [20].

Population sting allergy prevalence

The prevalence of ant sting allergy has been reported at 2.1% for *Pachycondyla chinensis* in rural Korea [10*], and 2.4–3.0% for *Myrmecia* spp. (predominantly JJAs) in rural Victoria and the island of Tasmania, Australia [5,6**]. In each of these three studies, around half of those allergic had experienced severe reactions (respiratory or cardiovascular compromise). In Tasmania, the combined impact of bee, wasp and ant sting allergy is a 4.5% (95% CI 3.5–6.0%) prevalence of systemic insect allergy including all age groups and metropolitan as well as rural residents [6**]. To our knowledge, population prevalence data has yet to be reported for allergy to IFAs, but

immunoglobulin E specific for fire ant whole body extract has been found in 17% of adult blood donors in one infested area of Georgia, USA [17•].

Immunotherapy: efficacy and tolerability

The efficacy of venom immunotherapy (VIT) in preventing honeybee and vespid sting anaphylaxis is well accepted, although no properly randomized or double blinded studies have been performed, and failure rates of between 0 and 40% have been reported [21]. Thus, by current 'evidence-based medicine' standards, the proof for efficacy of VIT in general is suboptimal. Furthermore, there are significant differences between bee and vespid sting allergy in terms of VIT tolerability and efficacy [21,22], and the same may apply to ant sting allergy.

Jack jumper ant

Our recent double blind randomized, placebo-controlled trial demonstrated the feasibility and efficacy of ant VIT [2•]. We recruited highly JJA allergic, but otherwise healthy, adult volunteers who were positive to intradermal venom skin testing, and performed deliberate sting challenges after treatment according to an outpatient 'semi-rush' treatment program with either venom aiming for a maintenance dose of 100 µg or an otherwise identical product containing histamine instead of venom. In the placebo group, 21 out of 29 (72%) and one out of 35 (3%) in the VIT group reacted to sting challenge. In the placebo group 11 reactions were associated with hypotension or respiratory compromise. However, in the VIT group the single reaction consisted only of minor transient urticaria that quickly resolved without treatment. After crossover of 30 people from the placebo group to VIT, a similar efficacy was found, with again only one person experiencing a minor urticarial reaction.

Objective signs of a systemic hypersensitivity reaction to VIT were noted in 22 of 65 participants (34%). Although no participant withdrew from VIT during the trial, a small number have experienced ongoing difficulties due to recurrent hypersensitivity reactions or inconvenience of treatment. At this stage we expect that around 90% will elect to continue treatment (unpublished data), a figure that compares favourably with the overall percentage who continue with bee and wasp VIT [22].

Imported fire ant

Although known to be ineffective for bee, vespid and JJA sting allergy [23], WBEs continue to be used for treatment of IFA sting allergy. Although there is no conclusive evidence of efficacy of this approach, circumstantial evidence suggests that it may be effective [24]. It appears that IFA WBE can contain appreciable amounts of venom protein (perhaps 20 µg per maintenance dose) and simple quality control measures can be used to monitor allergen content [25]. However, some

concerns have been expressed about variability in venom content between commercial preparations [26], and treatment failures have been noted [27,28].

A placebo-controlled study of antihistamine and steroid premedication with a rush schedule for administering IFA WBE was recently published [29•]. The study was underpowered to identify potential benefit from premedication, because only three out of 58 patients (5%) had systemic reactions during treatment, which were all mild. This low rate of reactions during immunotherapy probably reflects the small amount of allergenic protein contained in IFA WBE. Nevertheless there was only one mild reaction to deliberate sting challenges, so it seems likely that the low dosage of allergen in the extract may protect from single or small numbers of stings, which contain very small amounts of venom protein.

Accidental IFA exposure frequently involves multiple ants stinging multiple times, thus achieving a significant antigenic load despite their small individual stings. In-hospital sting challenge procedures have used only one ant at a time, whose small amount of venom might have been depleted during the collection process, so their capacity to precipitate severe anaphylaxis, and thus adequately test treatment efficacy, remains unknown. Data based upon field stings from IFAs may lack this shortcoming [24], but has other serious limitations.

We also know that the natural history of insect allergy varies enormously between species, with prospective studies demonstrating re-sting reaction rates in allergic subjects of 70% for JJA stings [6•], 50% for bee stings and only 25% for yellow jacket stings [30,31]. The natural history of IFA sting allergy remains to be determined. Therefore, until a rigorously conducted placebo-controlled assessment is performed, the efficacy of IFA WBE immunotherapy remains subject to debate.

Other species

Immunotherapies for other species of ant have not been reported, although use of WBE for diagnosis of allergy to the venoms of both the samsum ant and *P. chinensis* have been described [9,32].

Immunotherapy: application

Now that the efficacy of ant VIT has been demonstrated, several further steps are required to make the treatment more widely available, 'fine tune' its clinical application, and monitor treatment utility and compliance with therapy in clinical practice outside the idealized trial setting.

Extracting and preparing ant venom extracts for human use

Early attempts at preparing JJA venom extracts for human use failed due to problems with venom extract

standardization combined with inadequate funding when government support for venom and antivenom research in Australia was reduced [33]. Our group initially used venom sac dissection to obtain a large batch of venom to test therapeutic efficacy. Simultaneously, we have overcome logistical problems to develop a field electrical stimulation method able to produce relatively large amounts of pure venom economically, and begun a detailed analysis of venom components and degradation products using mass spectrometry that will facilitate excellent standardization [19].

Unfortunately, a small market for the final product (south-eastern Australia only) has resulted in substantial funding problems. Wider availability of the treatment we have developed is by no means certain. This problem is likely to face other clinicians treating ant venom allergy, owing to the limited geographical distributions of many species, stringent (expensive) regulatory requirements and a profit-driven pharmaceutical system.

Identifying the causative insect

When a patient presents following sting anaphylaxis, identification of the causative insect to determine appropriate immunotherapy may present considerable challenges in a country such as Australia where seven genera of ant (including at least 89 distinct species

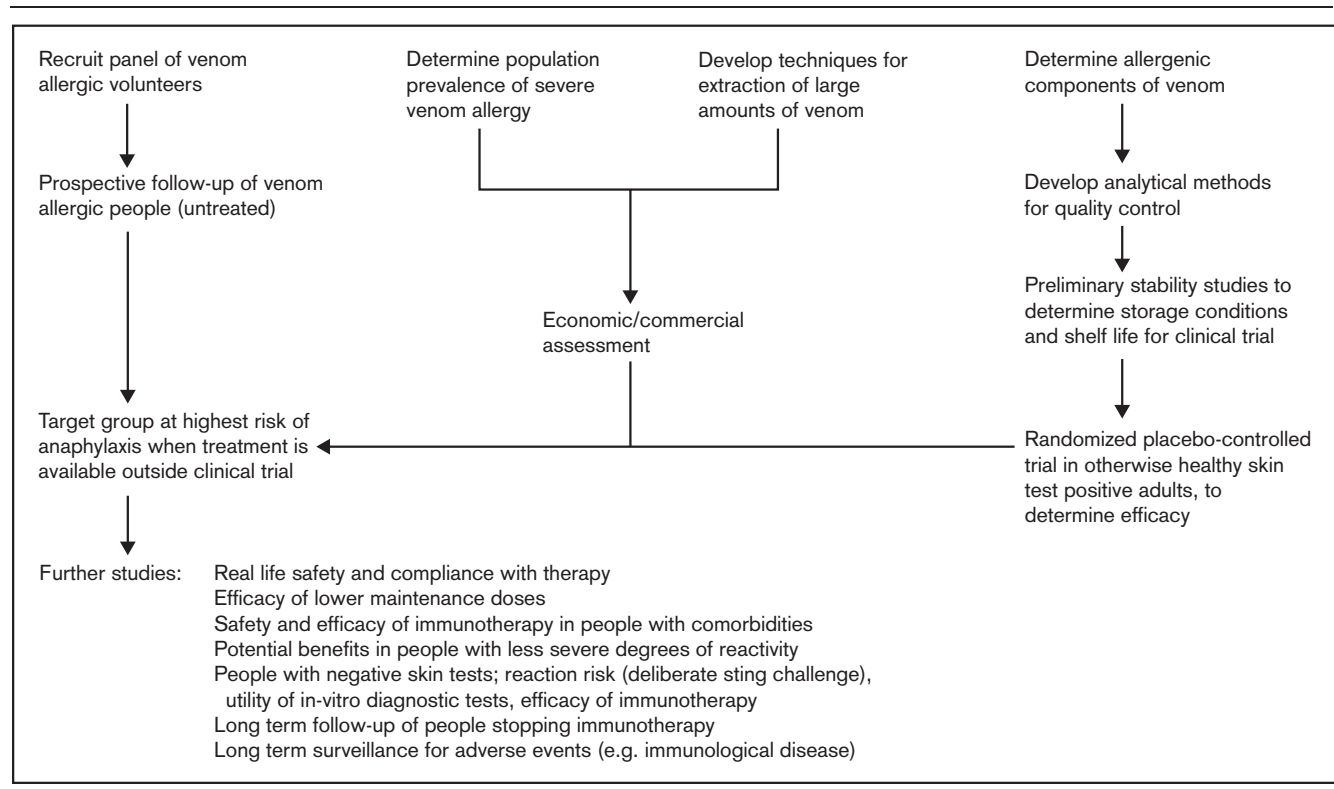
within the most important genus *Myrmecia* [34]), bees (honeybee, bumblebees and native sweat bees), paper wasps (native and introduced), native flower wasps, and the introduced yellow jacket (European wasp) may be responsible. Luckily, only a few species are both aggressive and sufficiently common in populated areas, resulting in the ability to narrow the possibilities down to a few depending on the geographical location.

Insect descriptions supplemented by serum venom-specific immunoglobulin E analysis in clinically uncertain cases enabled us to determine the causative insect in all patients participating in our Tasmanian epidemiological study, in which the main species were easily distinguished from one another [6••]. However we anticipate that the broader range of ant species with similar appearances on mainland Australia, as well as the recognized immunological cross-reactivity of some venom components between species [35], could create significant problems with diagnosis and selection of the appropriate venom extracts for immunotherapy.

Identifying those likely to benefit most from immunotherapy

Consistent with our knowledge of bee and wasp sting allergy, a prospective observational study of volunteers

Figure 2. Immunotherapy development process for *Myrmecia pilosula* (jack jumper ant) immunotherapy



over a 4-year period found the highest risk patients with JJA to be those over the age of 35 years with a history of severe reactions (i.e. with respiratory compromise or hypotension) [6•], a group that made up the majority of participants in our clinical trial [2•]. It remains to be determined to what extent those with milder degrees of allergy and those with negative skin tests (who were excluded from our trial) might benefit from VIT. No prospective studies for allergy to other ant species have been published.

It has long been recognised that approximately 90% of insect sting deaths occur in those aged over 30 years [36,37]. Some observations have also implicated co-existing disease and medications such as angiotensin-converting enzyme inhibitors and β -blockers as a factor in lethal bee and wasp sting reactions [38,39]. Of the small number of people dying recently from JJA stings in our region, all have had identifiable comorbidities and were aged 40 years or older [40]. Therefore, from the point of view of mortality reduction, focusing on people aged over 30 years would seem reasonable. However, the dramatic improvement in quality of life provided by VIT [41•] should not be denied to younger people who have experienced life-threatening reactions.

Conclusion

The risk to humans from a particular species of ant depends on a complex interaction between likelihood of human contact, insect aggression, efficiency of the venom delivery apparatus, and venom allergenicity. Ant VIT, at least in the setting of JJA sting allergy, is highly efficacious in preventing potentially lethal reactions in people with a history of severe reactions and who are intradermal skin test positive for venom-specific immunoglobulin E. Conversely, the efficacy of ant WBE immunotherapy remains to be proven. From a clinical perspective, we have identified a number of areas where further research might optimize our use of VIT (Fig. 2), but the biggest challenge faced in the provision of ant venom products is the lack of incentive for governments and pharmaceutical companies because of relatively small and unprofitable markets.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

- 1 Rhoades R. Stinging ants. *Curr Opin Allergy Clin Immunol* 2001; 1:343–348.
 - 2 Brown SGA, Wiese MD, Blackman KE, Heddle RJ. Ant venom immunotherapy: a double-blind, placebo-controlled, crossover trial. *Lancet* 2003; 361:1001–1006.
- This randomized double-blind, placebo-controlled crossover trial of VIT enrolled highly allergic but otherwise healthy adults and used a deliberate sting challenge to determine treatment efficacy.

- 3 Trinca JC. Insect allergy in Australia: results of a five-year survey. *Med J Aust* 1964; ii:659–663.
- 4 Clarke PS. The natural history of sensitivity to jack jumper ants (Hymenoptera formicidae *Myrmecia pilosula*) in Tasmania. *Med J Aust* 1986; 145:564–566.
- 5 Douglas R, Weiner J, Abrahamson M, O'Hehir R. Prevalence of severe ant venom allergy in southeastern Australia. *J Allergy Clin Immunol* 1998; 101:129–131.
- 6 Brown SGA, Franks RW, Baldo BA, Heddle RJ. Prevalence, severity, and natural history of jack jumper ant venom allergy in Tasmania. *J Allergy Clin Immunol* 2003; 111:187–192.
- This random population survey of 407 households, review of 264 emergency department presentations with sting anaphylaxis and follow-up of 388 allergic volunteers with JJA sting allergy over 4 years determines the prevalence of ant, honeybee and vespid sting allergy in a community and examines predictors of reaction severity.
- 7 Solley GO, Vanderwoude C, Knight GK. Anaphylaxis due to red imported fire ant sting. *Med J Aust* 2002; 176:521–523.
- 8 Pinnas JL, Strunk RC, Wang TM, Thompson HC. Harvester ant sensitivity: in vitro and in vivo studies using whole body extracts and venom. *J Allergy Clin Immunol* 1977; 59:10–16.
- 9 Dib G, Guerin B, Banks WA, Leynadier F. Systemic reactions to the Samsum ant: an IgE-mediated hypersensitivity. *J Allergy Clin Immunol* 1995; 96:465–472.
- 10 Cho YS, Lee YM, Lee CK, et al. Prevalence of *Pachycondyla chinensis* venom allergy in an ant-infested area in Korea. *J Allergy Clin Immunol* 2002; 110:54–57.
- This survey of 327 adult residents in an area of Korea infested with *P. chinensis* utilizes a combination of clinical history and serum venom-specific immunoglobulin E analysis to determine the prevalence of allergy to this ant.
- 11 Fukuzawa M, Arakura F, Yamazaki Y, et al. Urticaria and anaphylaxis due to sting by an ant (*Brachyponera chinensis*). *Acta Derm Venereol* 2002; 82:59.
- 12 Solley GO. Allergy to stinging and biting insects in Queensland. *Med J Aust* 1990; 153:650–654.
- 13 Ipinza J, Schenone H. *Heteroponera carinifrons*, an ant causing anaphylactic syndromes in Chile [in Spanish]. *Bol Chil Parasitol* 1972; 27:57–58.
- 14 Rodriguez-Acosta A, Reyes-Lugo M. Severe human urticaria produced by ant (*Odontomachus bauri*, Emery 1892) (Hymenoptera: Formicidae) venom. *Int J Dermatol* 2002; 41:801–803.
- 15 Brothers DJ. Phylogeny and evolution of wasps, ants and bees (Hymenoptera, Chrysidoidea, Vespoidea and Apoidea). *Zoologica Scripta* 1999; 28:233–249.
- 16 Kemp SF, deShazo RD, Moffitt JE, et al. Expanding habitat of the imported fire ant (*Solenopsis invicta*): a public health concern. *J Allergy Clin Immunol* 2000; 105:683–691.
- 17 Caplan EL, Ford JL, Young PF, Ownby DR. Fire ants represent an important risk for anaphylaxis among residents of an endemic region. *J Allergy Clin Immunol* 2003; 111:1274–1277.
- Despite the plethora of papers on IFA, none have determined the prevalence of allergy to this ant. Although this study did not examine clinical reaction severity, it looked at immunoglobulin E reactivity of a random sample of adult blood donors.
- 18 Hoffman DR, Dove DE, Jacobson RS. Allergens in Hymenoptera venom. XX. Isolation of four allergens from imported fire ant (*Solenopsis invicta*) venom. *J Allergy Clin Immunol* 1988; 82:818–827.
- 19 Davies NW, Wiese MD, Brown SGA. Composition and stability of Jack Jumper venom by ion trap mass spectrometry [abstract]. In: Proceedings and Abstracts of Australian and New Zealand Society for Mass Spectrometry, 19th Conference; 2–6 February 2003, Lorne. Published online by the Australian and New Zealand Society for Mass Spectrometry Inc. 2003. <http://www.latrobe.edu.au/anzsms/Conferences/ANZSMS19/ANZSMS19Abs/WeP/WeP-07.pdf>
- 20 Machado DC, Horton D, Harrop R, et al. Potential allergens stimulate the release of mediators of the allergic response from cells of mast cell lineage in the absence of sensitization with antigen-specific IgE. *Eur J Immunol* 1996; 26:2972–2980.
- 21 Muller U. Insect sting allergy: clinical picture, diagnosis and treatment. New York: Gustav Fischer Verlag; 1990.
- 22 Lockey RF, Turkeltaub PC, Olive ES, et al. The Hymenoptera venom study. III: Safety of venom immunotherapy. *J Allergy Clin Immunol* 1990; 86:775–780.
- 23 Weiner JM, Baldo BA, Donovan GR, Sutherland SK. Allergy to jumper ant (*Myrmecia pilosula*) stings in south-eastern Australia [abstract]. *Ann Allergy Asthma Immunol* 1995; 74:60.

- 24 Freeman TM, Hylander R, Ortiz A, Martin ME. Imported fire ant immunotherapy: effectiveness of whole body extracts. *J Allergy Clin Immunol* 1992; 90:210–215.
 - 25 Hoffman DR, Jacobson RS, Schmidt M, Smith AM. Allergens in Hymenoptera venoms. XXIII. Venom content of imported fire ant whole body extracts. *Ann Allergy* 1991; 66:29–31.
 - 26 Butcher BT, Reed MA. Evaluation of commercial imported fire ant extracts by crossed immunoelectrophoresis and radioallergosorbent test. *J Allergy Clin Immunol* 1988; 82:770–777.
 - 27 Rhoades RB, Stafford CT. Treatment failure with whole body extract immunotherapy to the imported fire ant [abstract]. *J Allergy Clin Immunol* 1991; 87:237.
 - 28 Paull BR, Coghlan BS. Fire ant allergy: Whole body extract treatment failures [abstract]. *J Allergy Clin Immunol* 1986; 77:141.
 - 29 Tankersley MS, Walker RL, Butler WK, *et al.* Safety and efficacy of an imported fire ant rush immunotherapy protocol with and without prophylactic treatment. *J Allergy Clin Immunol* 2002; 109:556–562.
- This study demonstrates the feasibility and safety of a rush immunotherapy schedule using treatment with WBE in people with IFA sting allergy. Although the ability of the sting challenge procedure to precipitate anaphylaxis and thus test efficacy is unknown, the results provide further data suggesting that IFA WBE is efficacious, at least in providing protection from single stings.
- 30 van der Linden PW, Hack CE, Struyvenberg A, van der Zwan JK. Insect-sting challenge in 324 subjects with a previous anaphylactic reaction: current criteria for insect-venom hypersensitivity do not predict the occurrence and the severity of anaphylaxis. *J Allergy Clin Immunol* 1994; 94:151–159.
 - 31 Blaauw PJ, Smithuis OL, Elbers AR. The value of an in-hospital insect sting challenge as a criterion for application or omission of venom immunotherapy. *J Allergy Clin Immunol* 1996; 98:39–47.
 - 32 Kim SS, Park HS, Kim HY, *et al.* Anaphylaxis caused by the new ant, *Pachycondyla chinensis*: demonstration of specific IgE and IgE-binding components. *J Allergy Clin Immunol* 2001; 107:1095–1099.
 - 33 Sutherland SK, Tibballs J. Australian animal toxins: the creatures, their toxins and care of the poisoned patient. 2nd ed. Melbourne: Oxford University Press; 2001.
 - 34 Ogata K, Taylor RW. Ants of the genus *Myrmecia* Fabricius a preliminary review and key to the named species (Hymenoptera: Formicidae: Myrmecinae). *J Natural History* 1991; 25:1623–1673.
 - 35 Street MD, Donovan GR, Baldo BA, Sutherland S. Immediate allergic reactions to *Myrmecia* ant stings: immunochemical analysis of *Myrmecia* venoms. *Clin Exp Allergy* 1994; 24:590–597.
 - 36 Parrish HM. Analysis of 460 fatalities from venomous animals in the United States. *Am J Med Sci* 1963; 245:129–141.
 - 37 Lecomte J, Leclercq M. Death due to Hymenoptera stings [in French]. *Bull Acad R Med Belg* 1973; 128:615–693.
 - 38 Mosbech H. Death caused by wasp and bee stings in Denmark 1960–1980. *Allergy* 1983; 38:195–200.
 - 39 Sasvary T, Muller U. Fatalities from insect stings in Switzerland 1978 to 1987 [in German]. *Schweiz Med Wochenschr* 1994; 124:1887–1894.
 - 40 Brown SGA, Wu QX, Kelsall GR, *et al.* Fatal anaphylaxis following jack jumper ant sting in southern Tasmania. *Med J Aust* 2001; 175:644–647.
 - 41 Oude Elberink JN, De Monchy JG, Van Der Heide S, *et al.* Venom immunotherapy improves health-related quality of life in patients allergic to yellow jacket venom. *J Allergy Clin Immunol* 2002; 110:174–182.
- Although VIT is highly efficacious in preventing anaphylaxis in allergic people, because of the very low death rate due to sting anaphylaxis it is unlikely that many deaths will be prevented by treatment. This study of vespid VIT demonstrates what is probably the most important benefit of immunotherapy, namely a substantial improvement in quality of life.