

Clinical reactivity to insect stings

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Purpose of review

Allergy to insect stings remains a hazard worldwide and is the object of updated guidelines on management. This paper reviews the various clinical responses that may occur following an insect sting.

Recent findings

Although the general population is at slight risk, certain groups are more susceptible, including occasionally stung adult male agricultural workers, hobby honey beekeepers and family members of beekeepers. Individuals with systemic mastocytosis are especially reactive to stings. The body of evidence attesting to the marked beneficial effect that 3–5 years of venom immunotherapy has on the natural history of hymenoptera hypersensitivity is especially evident in children. Case reports indicate other consequences of hymenoptera sting, and these are discussed.

Summary

Hypersensitivity to insect stings is common and may be life threatening. Although most occur away from medical facilities, their diagnosis and management are important to a wide spectrum of health care professionals. Most reactions to stings are nonallergic manifestations of the venom's toxic effects, and present as erythema, pain and swelling about the sting site. Fire ants bite with their mandibles and pivot their head, inflicting multiple stings that usually result in a sterile pseudopustule at the site. Hypersensitivity responses to venom range from large local reactions (a late-phase response) to life-threatening anaphylaxis. Venom-specific immunotherapy is highly effective in the modification of subsequent reactions to hymenoptera stings, as is whole body extract for fire ant stings.

Keywords

clinical manifestations, hymenoptera, hypersensitivity

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Abbreviation

VIT venom-specific immunotherapy

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Introduction

Allergy to insect stings is prevalent throughout the world. Most insect stings are associated with toxic local reactions of various sizes, being characterized by pain, swelling and redness at the site, and usually last 1–2 days, resolving with simple treatment measures. Large local reactions, which affect 10–15% of adults [1^{••}], are considered to be late-phase manifestations of IgE-mediated hypersensitivity, may involve a whole extremity, and may last up to a week. More serious systemic reactions occur in 0.4–0.8% of children and 3% of adults [1^{••}].

The insects of the order Hymenoptera, which include ants, bees, hornets, wasps and yellow jackets, have a stinging apparatus at the tail end of their abdominal segment and are capable of delivering between 100 ng (fire ants) [2,3] and 50 μ g (bees and vespids) [4] of venom. Venoms have various peptide and protein components, some of which are capable of inducing toxic or vasoactive responses. Although tolerance to multiple stings is variable, in most situations 1500 stings would be required to deliver a lethal dose of venom for a nonallergic adult who weighs 70 kg [5]. That 40–50 deaths per year in the USA are attributed to hymenoptera stings [6] demonstrates the potential severity of hypersensitivity reactions occurring in persons with venom-specific IgE antibodies, developed either directly through previous stings or indirectly such as with exposure to honeybee debris in the beekeeping environment [7].

Following a systemic reaction to an apparent sting, the diagnosis of stinging insect hypersensitivity should be confirmed (through appropriate skin tests and/or in-vitro assays) and followed up by venom-specific immunotherapy in order to prevent future severe systemic reactions to subsequent stings [1^{••},8[•]].

This review focuses on the clinical reactions elicited by stings from this group of insects. The Joint Council of Allergy, Asthma and Immunology recently published a comprehensive updated practice parameter on the diagnosis and management of stinging insect allergy [1^{••}].

Stinging insects

The insects of the order Hymenoptera responsible for clinical reactions include insects from the families of *Vespidae* (hornets, wasps and yellow jackets), *Apidae* (bees) and *Formicidae* (fire ants – *Solenopsis* spp.).

Yellow jackets are ground-dwelling urbanized insects and can be encountered during yard work, gardening, or farming. They are aggressive if their nests are disturbed, and their frequent association with food and drinks in outdoor settings, especially in the late summer, are sources of stings in the mouth, oropharynx, or oesophagus. Acute swelling with resulting airway compromise can occur even in nonallergic persons. Most hornets build large papier mâché nests that are several feet in diameter and are usually found in trees or shrubs. Hornets are also aggressive in the vicinity of their nests and, like yellow jackets, they are known to follow and sting individuals over distances. Wasps build honeycomb nests, some out of mud, that are several inches or more in diameter. The nests can be found in shrubs, under the eaves of houses or barns, and occasionally in pipes on playgrounds or under patio furniture. They tend to be much less aggressive than the other vespids. Most members of the vespid family are attracted to sweet food, and consequently they are found around garbage cans, leftover food, or at outdoor events where food and soft drinks are served.

Domestic honeybees are found in commercial hives and on flowers. Wild honeybee nests can be found in tree hollows, old logs, or in buildings. Hives may contain thousands of bees. Honeybees are usually docile but may be aggressive around their hives, especially during cool damp weather. Africanized honeybees, which are especially aggressive, are hybrids resulting from interbreeding of domestic honeybees and African honeybees. Accidentally introduced in South America, their territory has expanded northward, and they can be found in several of the southern states of the USA [1[•],9]. Occasionally, Africanized queen bees have mistakenly been brought into the northern USA and Canada by the beekeeping industry, but they are intolerant of the winter there. They are far more aggressive than domestic/wild honeybees, and their hives are frequently in proximity to human habitation. Africanized honeybees are more likely to attack in swarms and, unlike non-Africanized bees, they may pursue and sting over long distances. Their venom is antigenically similar to domestic honeybee venom, presenting no special allergic risk, the main threat being their antagonistic nature and increased attack rate. Honeybees usually leave a barbed stinger with an attached venom sac in the skin, which continues to pump venom even after detachment from the insect's body. Bumblebees, another member of the *Apidae* family, are slow-moving and nonaggressive, rarely sting, and are responsible for relatively few hypersensitivity reactions, despite their common use as pollinators of vegetables in commercial green houses [10].

The fire ant, which can be red or black in colour, nests in mounds that are several inches high and can extend

from 1 to 2 feet in diameter. They are endemic to the southeastern and southcentral USA, but they have also expanded northward into Virginia and westward into California, facilitated by urbanization [11,12]. Recent reports of building invasion with sting attacks inside occupied dwellings, including health care facilities, heighten public health concerns about these insects [13]. Multiple fire ant mounds, some quite large, are generally found a few feet apart and often in areas not denuded of vegetation. In sandy areas, their nests are flat and obscure. Fire ants are very aggressive, particularly if their nests are disturbed, and often inflict multiple stings. One or more sterile pseudopustules, which develop over the ensuing 24 h, are characteristic of fire ant stings [14], but their absence does not exclude fire ants as the cause.

Locale is important in determining the most likely insect causing the sting. Yellow jackets are the most common causes of allergic reactions because they frequent urban settings. *Polistes* wasps are especially common in the Gulf Coast states of the USA and in the Mediterranean countries of Europe [15]. Sensitization to fire ant venom is the most prevalent stinging insect problem in the southeast USA because of the abundance of these insects and their high attack rate [16,17].

Other Hymenoptera insects have caused allergic sting reactions. Some of these include the sweat bee as well as several types of ants, including *Rhytidoponera* (green-head ant) and *Myrmecia* (jumper and bull ants) [18[•]] in Australia, and *Pogonomyrmex* (harvester ant) in the USA [19].

At-risk populations

Systemic reactions to hymenoptera venom occur throughout the general population (3%) in both urban and rural settings. Adult males are stung more frequently and thus are at higher risk for reactions [20]. Beekeepers who are repeatedly stung on multiple occasions are reported to be at virtually no risk for developing systemic reactions to honeybees, whereas occasionally stung family members and hobby beekeepers have been reported to have an incidence rate of systemic reactivity of approximately 20% [7]. A recent epidemiologic study of the natural history of hymenoptera sensitivity in Spain [21] revealed that adult male agricultural workers were at greater risk for having systemic reactions or large local reactions, especially if they experience more than five stings in a 4-year period, providing further evidence that incidental but higher sting rates contribute to risk.

Systemic mastocytosis is over-represented in the Hymenoptera-allergic population, and it is associated with an increased risk for more severe reactions following field stings or sting challenges, increased side effects of venom

immunotherapy as well as reduced efficacy of venom-specific immunotherapy (VIT), and treatment failures [22]. In addition, however, these individuals may lack sensitization to venoms by skin test or radioallergosorbent test; thus, the diagnosis of mastocytosis must be considered in patients with a history of systemic reactivity to hymenoptera sting and without evidence of venom-specific IgE.

Clinical reactions to insect stings

In evaluating patients and their responses to insect stings, it is useful to determine whether reactions are local or systemic. These are discussed separately below.

Local reactions

Most insect stings cause transient localized reactions, requiring only symptomatic treatment. These reactions are not IgE mediated and future allergic reactions are unlikely. However, when a sting occurs in the oropharynx or oesophagus due to accidental ingestion of a stinging insect, even in a nonallergic person the resulting local reaction may lead to asphyxia secondary to swelling. Fire ant stings are painful and typically cause a sterile pseudopustule 24 h after the sting, the pain from which frequently persists up to 72 h. The material in the vesicle is necrotic, and it should be left intact to prevent secondary infection [1**].

Large local reactions

Some local reactions can expand from the site of the sting and consist of extensive erythematous swelling surrounding the sting site, and may involve the entire limb. These often continue to enlarge over 48 h before resolving slowly over a few days, and such reactions are usually painful and/or pruritic. These represent late-phase reactivity induced by IgE-mediated hypersensitivity [15,23] but they are not a significant risk factor (<10%) for future systemic reactions.

Systemic reactions

Systemic reactions may be mild, manifesting as a generalized cutaneous response with urticaria and/or angio-oedema. Anaphylaxis, a heightened level of systemic reactivity involving other organ systems, may occur and is life threatening. As in all allergic responses, anaphylaxis results from immunologically induced mast cell or basophil mediator release after exposure to the specific venom antigen in previously sensitized persons [24]. An anaphylactic response classically develops minutes after a sting, and is usually featured as a single episode responding rapidly to treatment. Variants occur, such as late-onset, protracted and biphasic anaphylaxis [25]. Biphasic reactivity has been well documented in the setting of insect sting hypersensitivity [26] and must not be overlooked in post-treatment observation strategies.

Systemic reactions to insect stings typically have a rapid onset. In a recent study [18*], 45% of all reactions (including local ones) began within 5 min after a sting, and notably 81% of anaphylactic reactions with respiratory and/or cardiovascular symptoms or changes in consciousness began within 10 min of the sting.

Symptoms of anaphylaxis can affect most organ systems. The most commonly affected are cutaneous (urticaria, erythema, angio-oedema), respiratory (dyspnoea, wheeze, decreased oxygen saturation), gastrointestinal (abdominal pain, nausea, vomiting) and cardiovascular (hypotension, tachycardia, syncope), often anteceded by a sense of impending doom (angor) [24].

Severe toxic reactions, sometimes indistinguishable from allergic reactions, may develop after multiple simultaneous stings. These responses are due to venom components that directly release mediators, many of which are produced during the course of allergic reactions. The number of stings required to elicit such responses varies among individuals, but the vast majority of reports occur in patients enduring more than 50 stings. Such events have been observed following Africanized honeybee attacks, leading to severe complications such as acute renal failure [27,28].

A recent review from Australia [18*] reported on findings in the evaluation of anaphylactic reactions in response to insect stings. Contrary to existing views, it was noted that stings on the head or neck are not more likely to lead to life-threatening reactions, and lesser reactions did not necessarily lead to greater reactions from future stings. In concert with current understanding, those investigators reported that the spectrum of clinical symptoms and signs are typical of anaphylaxis from other sources; that pre-existing asthma was a risk factor for severe asthmatic responses; that anaphylaxis is usually species specific; that persons who are multiply stung simultaneously may have true anaphylaxis and just not a 'toxic' response; and that anaphylaxis from other sources is not a risk factor for hypersensitivity reactions (outside the setting of systemic mastocytosis) to insect stings.

Other, much rarer complications of insect stings include the following [29–41]: serum sickness, vasculitis, neuritis, myasthenia gravis, cerebral infarction, Guillain–Barré syndrome, encephalitis, Reye-like syndrome, intravascular coagulation, optic neuropathy, hand–foot syndrome, acquired cold urticaria, oculopalatal syndrome, rhabdomyolysis, myocardial infarction and cardiac arrhythmia.

Natural history of stinging insect allergy

The natural history of allergy to insect stings is greatly dependent on the nature of the initial reaction. Both local and systemic reactions are discussed below.

Local reactions

Large local reactions usually recur in similar form with future stings but are not a significant risk factor ($<10\%$) for anaphylaxis to subsequent stings [42]. Because the risk is quite low, VIT is generally not indicated in this population [1^{••}].

In the setting of fire ant stings, as mentioned above the pseudopustule formed in response to the sting contains necrotic tissue and is not caused by infection at the site of the sting. The vesicle should be left intact, but if opened then it should be cleansed with soap and water to prevent secondary infection. In the absence of infection, these lesions are not treated with antibiotics [43].

Systemic reactions

Without medical intervention, individuals who have had an allergic reaction from an insect sting are at risk for further life-threatening allergic reactions if they are re-stung. VIT has been shown to reduce significantly the risk for subsequent systemic reactions [1^{••},8[•],44,45]. Specific venom extracts of honeybee, yellow jacket, white-faced hornet, yellow hornet and wasp venom are available for skin testing and immunotherapy.

Adults with a history of systemic reactivity, even those with only cutaneous manifestations, who have demonstrable specific IgE antibodies (either via a positive skin and/or in-vitro test response), are at risk for subsequent life-threatening reactions if they are re-stung. VIT is indicated in these patients. Approximately 30–60% of patients with a history of anaphylaxis from an insect sting and venom-specific IgE antibodies will experience a systemic reaction when re-stung [1^{••},8[•]].

Although children have been thought to ‘outgrow’ their allergy to insect stings, there are few reports documenting the natural history of this reaction. Recently, Golden *et al.* [46^{••}] studied the outcome of allergic reactions to insect stings in childhood 10–20 years afterward in patients who had and had not received VIT. A total of 512 patients responded to the survey, with a mean follow-up period of 18 years, a mean duration of VIT of 3.5 years in treated patients, and a sting incidence of 43%. Systemic reactions occurred less frequently in patients who had received VIT (3%) than in untreated patients (17%). It was concluded that VIT in children leads to a significantly lower risk for systemic reaction to stings, even 10–20 years after treatment is stopped, and that this prolonged benefit is greater than that seen in adults.

Those aged 16 years of age and younger who have experienced isolated cutaneous reactions without systemic manifestations after an insect sting from a wasp, hornet, or yellow jacket have been shown in studies to be at only slightly increased risk for systemic reactivity

($\leq 10\%$) on subsequent sting as compared with the general population [47,48]. For this reason, VIT is generally only offered to children who have experienced a generalized reaction beyond cutaneous symptoms.

Less is known about the natural history of fire ant venom hypersensitivity and the efficacy of immunotherapy, but fire ant whole-body extract has been shown to contain relevant venom allergens [1^{••},49,50]. Accumulating evidence in the absence of a double-blinded controlled study supports the contention that immunotherapy with fire ant whole-body vaccine is protective [51,52]. Immunotherapy for patients with fire ant hypersensitivity using whole-body vaccine should be initiated in those with a history of a systemic reaction to a fire ant sting who have a positive skin-test response to whole-body extract or in-vitro assay [1^{••},8[•]].

Persons with insect sting allergy who are taking β -adrenergic blocking agents are generally thought to be at greater risk for more serious anaphylaxis in response to a sting [25,53] or VIT [54], although this was challenged by a recent study [55]. Currently, patients who have stinging insect hypersensitivity should not be prescribed β -adrenergic blocking agents unless absolutely necessary. If a patient with stinging insect hypersensitivity cannot discontinue β -adrenergic blocking therapy, then the decision to administer immunotherapy should be made on an individual basis after analysis of potential risks and benefits. There are some reports that taking angiotensin-converting enzyme inhibitors may also increase the risk for anaphylaxis [56,57].

VIT is extremely effective in reducing the risk for a subsequent systemic reaction from an insect sting to less than 5%, and those who do experience reactions have milder symptoms. Details on the dosage schedule, maintenance dosage and duration of VIT are beyond the scope of this review but are covered in detail elsewhere [1^{••},8[•]].

Anaphylactic reactions following insect stings can have an impact on patients’ quality of life. A recent study [58] confirmed that, in addition to conferring protection in the event of future stings, VIT, with information about the risks and benefits of the treatment, improves health-related quality of life.

Conclusion

The clinical response of a person stung by an insect can vary from small local reactions mediated by toxins to larger local reactions that may involve late-phase responses from IgE-mediated sensitivity, to generalized manifestations indicating systemic reactivity, which may be life-threatening. The most common sources are yellow jackets and other vespids (wasps and hornets), fire ants and honeybees. Only persons with systemic allergic

reactions are candidates for VIT, and in children VIT is recommended only in those with more than cutaneous manifestations. Persons at particular risk for adverse reactivity to insect stings are adults who are occasionally stung, such as male agricultural workers, hobby beekeepers and family members of those involved in the beekeeping industry. Toxic reactions that occur after multiple simultaneous stings may be clinically indistinguishable from allergic reactions.

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 Moffitt JE, Golden DBK, Reisman RE, *et al.* Stinging insect hypersensitivity: a practice parameter update. *J Allergy Clin Immunol* 2004; 114:869–886.
- This is an updated practice parameter on the diagnosis and management of stinging insect allergy. It is a comprehensive and up-to-date review.
- 2 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.
- 3 Hoffman DR, Jacobson RS. Allergens in Hymenoptera venom. XII. How much protein in a sting? *Ann Allergy* 1984; 52:276–278.
- 4 Guralnick MW, Benton AW. Entomological aspects of insect sting allergy. In: Levin MI, Lockey RF, editors. Monograph on insect allergy, 4th ed. Milwaukee: American Academy of Allergy, Asthma and Immunology; 2003. pp. 11–26.
- 5 Goddard J. Physician's guide to arthropods of medical importance. 4th ed. Boca Raton, FL: CRC Press; 2003.
- 6 Barnard JH. Studies of 400 Hymenoptera sting deaths in the United States. *J Allergy Clin Immunol* 1973; 52:259–264.
- 7 Day JH, Buckeridge DL, Welsh AC. Risk assessment in determining systemic reactivity to honeybee stings in sting-threatened individuals. *J Allergy Clin Immunol* 1994; 93:691–705.
- 8 Freeman T. Hypersensitivity to Hymenoptera stings. *N Engl J Med* 2004; 351:1978–1984.
- This is another recent and thorough review of the area of stinging insect allergy.
- 9 McKenna WR. Africanized honeybees. In: Levin MI, Lockey RF, editors. Monograph on insect allergy, 4th ed. Milwaukee: American Academy of Allergy, Asthma and Immunology; 2003. pp. 27–36.
- 10 Hamilton RG. Diagnosis of Hymenoptera venom sensitivity. *Curr Opin Allergy Immunol* 2002; 2:347–351.
- 11 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.
- 12 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.
- 13 deShazo RD, Williams DF, Moak ES. Fire ant attacks on residents in health care facilities: a report of two cases. *Ann Intern Med* 1999; 131:424–429.
- 14 Ellis AK, Day JH. Allergy to insect bites and stings. *Allergy* 1996; 9:18–22.
- 15 Golden DBK. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol* 2005; 115:439–437.
- 16 Tracy JM, Demain JG, Quinn JM, *et al.* The natural history of exposure to the imported fire ant. *J Allergy Clin Immunol* 1995; 95:824–828.
- 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.
- 18 Solley GO. Stinging and biting insect allergy: an Australian experience. *Ann Allergy Asthma Immunol* 2004; 93:532–537.
- This is a very interesting chart review of over 17 years of clinic data involving over 1700 patients referred for possible insect sting allergy.
- 19 Yates AB, Moffitt JE, deShazo RD. Anaphylaxis to arthropod bites and stings. *Immunol Allergy Clin North Am* 2001; 21:635–651.
- 20 Leveau P. Risk factors for allergy to hymenoptera stings. *Allerg Immunol (Paris)* 1993; 25:220, 224–226.
- 21 Fernandez J, Soriano V, Mayorga L, Mayor M. Natural history of Hymenoptera venom allergy in Eastern Spain. *Clin Exp Allergy* 2005; 35:179–185.
- 22 Dubois AE. Mastocytosis and Hymenoptera allergy. *Curr Opin Allergy Clin Immunol* 2004; 4:291–295.
- 23 Golden D. Insect allergy. In: Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER, editors. Middleton's allergy: principles and practice, 4th ed., vol. 2. Philadelphia, PA: Mosby; 2003. pp. 1475–1486.
- 24 Ellis AK, Day JH. Diagnosis and management of anaphylaxis. *CMAJ* 2003; 169:307–312.
- 25 Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986; 78:76–83.
- 26 Ellis AK, Day JH. A prospective evaluation of 103 patients with biphasic anaphylaxis [abstract 935]. *J Allergy Clin Immunol* 2004; 113:S259.
- 27 Gabriel DP, Rodrigues AG Jr, Barsante RC, *et al.* Severe acute renal failure after massive attack of Africanized bees [letter]. *Nephrol Dial Transplant* 2004; 19:2680.
- 28 Daher Ede F, da Silva Junior GB, Bezerra GP, *et al.* Acute renal failure after massive honeybee stings. *Rev Inst Med Trop Sao Paulo* 2003; 45:45–50.
- 29 Reisman R, Livingston A. Late onset allergic reactions including serum sickness after insect stings. *J Allergy Clin Immunol* 1989; 84:331–337.
- 30 Moffitt JE. Allergic reactions to insect stings and bites. *South Med J* 2003; 96:1073–1079.
- 31 Chen DM, Lee PT, Chou KJ, *et al.* Descending aortic thrombosis and cerebral infarction after massive wasp stings. *Am J Med* 2004; 116:567–569.
- 32 Boz C, Velioglu S, Ozmenoglu M. Acute disseminated encephalomyelitis after bee sting. *Neurol Sci* 2003; 23:313–315.
- 33 Likittanasombut P, Witoonpanich R, Viranuvatti K. Encephalomyelorradiculopathy associated with wasp sting. *J Neurol Neurosurg Psychiatry* 2003; 74:134–135.
- 34 Gawlik R, Rymarczyk B, Rogala B. A rare case of intravascular coagulation after honey bee sting. *J Investig Allergol Clin Immunol* 2004; 14:250–252.
- 35 Sheth HG, Sullivan TJ. Optic neuropathy and orbital inflammatory mass after wasp stings. *J R Soc Med* 2004; 97:436–437.
- 36 Carr ME. Hand–foot syndrome in a patient with multiple fire ant stings. *South Med J* 2004; 97:707–709.
- 37 Kalogeromitros D, Gregoriou S, Papaioannou D, *et al.* Acquired primary cold contact urticaria after Hymenoptera sting. *Clin Exp Dermatol* 2004; 29:93–95.
- 38 Panagariya A, Sharma B, Garg A. Oculopalatal syndrome with ataxia following hymenoptera sting. *J Assoc Physicians India* 2003; 51:1007–1008.
- 39 Lin CC, Chang MY, Lin JL. Hornet sting induced systemic allergic reaction and large local reaction with bulle formation and rhabdomyolysis. *J Toxicol Clin Toxicol* 2003; 41:1009–1011.
- 40 Kim YO, Yoon SA, Kim KJ, *et al.* Severe rhabdomyolysis and acute renal failure due to multiple wasp stings. *Nephrol Dial Transplant* 2003; 18:1235.
- 41 Fisher BA, Antonios TF. Atrial flutter following a wasp sting. *J Postgrad Med* 2003; 49:254–255.
- 42 Mauriello PM, Barde SH, Georgitis JW, *et al.* Natural history of large local reactions from stinging insects. *J Allergy Clin Immunol* 1984; 74:494–498.
- 43 DeShazo R, Butcher B, Banks W. Reactions to stings of the imported fire ant. *N Engl J Med* 1990; 323:462–466.
- 44 Reisman R. Insect stings. *N Engl J Med* 1994; 331:523–527.
- 45 Valentine M, Schuberth K, Kagey-Sobotka A. The value of immunotherapy with venom in children with allergy to insect stings. *N Engl J Med* 1990; 323:1601–1603.
- 46 Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM.
- Outcomes of allergy to insect stings in children, with and without venom immunotherapy. *N Engl J Med* 2004; 351:668–674.
- This is an excellent prospective evaluation confirming not only that VIT is protective in children with a history of systemic reactivity to insect stings but also that children do not 'outgrow' hymenoptera allergy, as was previously thought.
- 47 Schultze-Werninghaus C, Wahn U, Niggemann B. Evaluation of the risk of anaphylactic reactions by wasp venom-extract challenges in children. *Pediatr Allergy Immunol* 1999; 10:133–137.
- 48 Reisman RE. Stinging insect allergy. *Med Clin North Am* 1992; 76:883–894.
- 49 Freeman TM, Hylander R, Ortiz A, Martin M. Imported fire ant immunotherapy: effectiveness of whole body extracts. *J Allergy Clin Immunol* 1992; 90:210–215.
- 50 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.

- 51 Freeman TM, Hylander R, Ortiz A, Martin M. Imported fire ant immunotherapy: effectiveness of whole body extracts. *J Allergy Clin Immunol* 1992; 90:210–215.
- 52 Stafford C. Hypersensitivity to fire ant venom. *Ann Allergy* 1996; 77:87–99.
- 53 Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. *J Allergy Clin Immunol* 1988; 81:1–5.
- 54 Hepner M, Ownby D, Anderson J. Risk of severe reactions in patients taking beta blocker drugs receiving allergen immunotherapy injections. *J Allergy Clin Immunol* 1990; 86:407–411.
- 55 Alam MM, Alvarez del Real G, Hsieh FH. Cardiopulmonary resuscitation (CPR) in patients with acute anaphylaxis taking beta-blockers [abstract]. *J Allergy Clin Immunol* 2005; 115 (Suppl 2):160.
- 56 Simon P, Potier J, Thebaud HE. Risk factors for acute hypersensitivity reactions in hemodialysis. *Nephrologie* 1996; 17:163–170.
- 57 Hermann K, Ring J. The renin-angiotensin in patients with repeated anaphylactic reactions during Hymenoptera venom hyposensitization and sting challenge. *Int Arch Allergy Immunol* 1997; 112:251–256.
- 58 Oude Elberink JN, Dubois AE. Quality of life in insect venom allergic patients. *Curr Opin Allergy Clin Immunol* 2003; 3:287–293.