

Stinging insect hypersensitivity in children

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In the past two decades, many advances have been made in the treatment of patients with insect venom sensitivity. An effective treatment (venom immunotherapy) has been developed and indications for therapy refined. In the past year, reports concerning fatal toxic reactions to multiple stings, Africanized ("killer") bees, bumblebee venom allergy and treatment, and reactions to fire ant stings have been published. Papers have also appeared on the use of sting challenges in the diagnostic evaluation of insect sting allergy, laboratory investigations of the mechanism of action of venom immunotherapy, and the outcome of discontinuing venom treatment after 5 years in insect-allergic patients.

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Abbreviation

RAST radioallergosorbent test

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Allergic reactions to insect stings cause about 50 deaths each year in the United States [1]. Many clinicians believe that this figure is probably a low estimate because sudden deaths at poolside or on the golf course may be mistakenly ascribed to cardiac events. Schwartz [2•] reviewed the 1992 data on the 326 visits (1.4%) coded as allergic events from a total of 23,647 emergency room visits at a Cleveland suburban hospital. The major categories were insect sting reactions, drug reactions, and food reactions. Idiopathic reactions were next in frequency, followed by various miscellaneous reactions, including exercise and contact "allergy." He noted that only 27% of patients allergic to insect sting were given a prescription for self-injectable epinephrine, and only 12.5% were referred to an allergist. Antibiotics caused most of the drug reactions; seafood, peanuts, and other nuts were responsible for most of the food reactions. This paper provides a "snapshot" of the type and frequency of allergic episodes that cause people to seek care in a suburban emergency room.

Fatal toxic reaction to multiple stings

Although nearly all the deaths related to insect stings are caused by allergic reactions to one or two stings, a large number of stings may also cause fatal toxic reactions. Watemburg *et al.* [3•] reported a tragic case of the death of a 3-year-old boy who sustained more than 40 stings from a swarm of oriental hornets in Israel. The child vomited several times in the first 2 hours, had a seizure associated with fever (39°C) and hypoglycemia (32 mg/dL), and then suffered progressive neurologic deterioration, respiratory and renal failure, coagulopathy, and liver dysfunction.

Killer bees

Fatal toxic reactions usually occur in young children or the elderly. It has been estimated that the LD₅₀ (lethal dose for 50% of the population) equals 19 honeybee stings per kilogram of body weight (*ie*, 500 stings in a child, 1100 stings in an average-sized adult female, and 1400 stings in an average-sized adult male) [4]. Africanized (killer) bees are a growing health menace in Texas and Arizona, where reports of toxic reactions to a large number of stings (500 to 1000) are becoming increasingly common. Fatalities have occurred in South America, Central America, and the United States as the bees have migrated northward. Two reviews by Schumacher [5•] and Sherman [6] have been published recently. Schumacher [5•] describes severe toxic reactions characterized by shock and hypoxia. He discusses new approaches that are under investigation to reduce blood

levels of venom, including production of honeybee antivenom and hemodialysis. He suggests that honeybee-allergic individuals who wish to remain in endemic areas receive venom immunotherapy, possibly administered at higher doses, with increased frequency of doses, or for longer periods than usually recommended. Sherman [6] calls for authorities to expand public awareness, teach avoidance measures, remove troublesome hives, and develop sting treatment protocols for ambulance personnel and emergency departments.

Bumblebee sting allergy

Bumblebee stings are very rare because these insects are less plentiful and less aggressive than other Hymenoptera. The Dutch bioindustry has used bumblebees in greenhouses for the pollination of vegetable flowers such as tomatoes, however, and bumblebee stings and systemic reactions to them are becoming more common.

Hoffman [7] described the immunochemical and structural relationships between bumblebee and honeybee venom antigens using sera from allergic patients and hyperimmunized rabbits. They found a high degree of cross-reactivity between bumblebee and honeybee venoms. The authors proposed that this was largely related to a high level of structural similarity in the phospholipases, hyaluronidases, and acid phosphates. Bumblebee venom contained several proteins not found in honeybee venom, however. They concluded that a skin test with honeybee venom would detect almost all cases of bumblebee venom allergy, but a radioallergosorbent test (RAST) with bumblebee venom could detect some additional cases.

In 1993, Kochuyt *et al.* [8] reported on seven patients who had developed an occupational allergy to bumblebee stings at a farm that cultures bumblebees to pollinate tomato plants. Four of the seven patients demonstrated increasingly larger local reactions to stings before developing sting-induced anaphylaxis. Generalized pruritus or urticaria (or both) was present in all subjects; five had angioedema. Two patients had rhinoconjunctivitis and wheezing, and two others had laryngeal involvement. Honeybee-venom skin test results were positive in the five patients tested. Six of seven had a positive reaction to honeybee-venom RAST. The efficacy of honeybee-venom immunotherapy in this clinical situation was demonstrated when six of the patients tolerated accidental bumblebee stings without sequelae.

Recently, de Groot *et al.* [9•] described the use of bumblebee venom to treat a similar group of six patients. In two patients, there was evidence on RAST to suggest that honeybee-venom immunotherapy would not be expected to protect these individuals completely. For example, in one patient, RAST inhibition showed that

the major portion of the IgE response was directed to bumblebee-specific antigens; in the other patient, there was no response found to honeybee venom. Two patients tolerated in-hospital sting challenge after 1 year of bumblebee-venom therapy. Bumblebee venom is not available at this time for skin testing and immunotherapy in the United States. For now, skin testing and treatment with the highly cross-reactive honeybee venom will probably suffice.

Fire ant venom allergy

An extensive review of the subject of fire ant venom allergy was recently published by Hoffman [10•]. This paper discusses the history of the entry of *Solenopsis richteri* and then *Solenopsis invicta* into the southeastern United States, the biology of the imported fire ants, the outcome and epidemiology of fire ant stings, studies of the composition of venom and allergenic extracts, the diagnosis and treatment (including immunotherapy) of fire ant venom allergy, and the control of fire ants and prospects for the future.

Fire ants have spread across the southern United States, as far north as Richmond, Virginia, and westward through most of Texas. The fire ant stings by grasping the victim's skin with its mandible, injecting venom slowly through a stinger. Then it rotates slightly and stings again. The result is a semicircle of stings that develop into sterile pustules over the next 12 to 24 hours. Serious systemic allergic reactions and fatalities are becoming more common. The annual attack rates in these regions have been estimated to be 6% to 58% of the population. The venoms have been well characterized, and many of the relevant allergens have been sequenced. Whole-body extract remains the diagnostic and therapeutic material, however, because a commercial venom preparation is not now available and may never be available. Fortunately, unlike the situation found in flying Hymenoptera sensitivity, the whole-body extract has been demonstrated to be effective in preventing recurrent systemic reactions to stings. Attempts to control fire ant colonies have met with only limited success. Therefore, fire ant venom allergy remains a major medical problem in the southeastern United States, and experts are concerned that these ants may continue to expand their territory.

The allergy group at Lackland Air Force Base in San Antonio, Texas, reported on the natural history of exposure to the imported fire ant in their area [11]. Their study population consisted of 107 medical students who had spent minimal time in imported-fire-ant endemic areas. During a very short stay (3 weeks) in San Antonio, about half the subjects sustained a suspected fire ant sting. This high rate of sting exposure was associated with the development of positive fire-ant-extract skin test results in 13% of the group.

Diagnostic sting challenge

The treatment of insect sting allergy was revolutionized in the late 1970s by the development of honeybee, yellow jacket, hornet, and wasp venoms for skin testing and immunotherapy. The new therapy had a 97% success rate in preventing recurrent sting-induced anaphylaxis. Recently, Dutch investigators asserted that venom immunotherapy was overutilized in the care of sting-allergic patients [12]. They suggested that all patients with a history of sting-induced systemic reactions and positive venom skin test results be challenged with a deliberate skin test to determine the need for venom immunotherapy. They reported that in this group of subjects, only 25% of patients sensitive to yellow jackets and 52% of patients sensitive to honeybees react to a challenge sting by the relevant insect. Franken *et al.* [13], also from the Netherlands, soon published a paper in which they demonstrated that a significant proportion of insect-allergic patients did not react to the first sting challenge but did develop a systemic allergic reaction when a second sting was administered at a later date. Hauk *et al.* [14] reported similar results in children. A vigorous debate has continued on this subject. The critics contend that sting challenges are unethical, because a significant risk of reaction exists [15,16]. In fact, in patients with a history of sting-induced hypotension, the recurrent reaction rate is somewhat higher, and most of these challenge-induced reactions are again severe in nature. Lichtenstein [17] has called for further investigation of this subject.

Goldberg *et al.* [18] evaluated the use of an intentional sting to determine whether three sting-allergic individuals could join the Israeli military service. Two of the patients had a history of a honeybee sting reaction and positive venom skin test results, and they tolerated an intercurrent honeybee sting without a problem. The honeybee-venom skin test result remained positive, however. A challenge sting was tolerated without reaction, and they were allowed to enter military service. The need for such a challenge sting to resolve inconclusive situations is fortunately quite rare.

Hauk *et al.* [19•] conducted a study to answer the concern that anxiety about a diagnostic challenge sting could induce early release mediators (*eg*, epinephrine), which might diminish the severity of or ablate a sting-induced allergic reaction. Twenty-one children with histories of large local reactions ($n = 5$) or moderate ($n = 5$) or severe ($n = 11$) systemic reactions participated in the study. The first sting resulted in a systemic reaction in four subjects; a second sting in 18 children caused two systemic reactions. Epinephrine, norepinephrine, and dopamine levels were measured before each sting and 1 and 2 minutes after each sting. Basal catecholamine levels did not differ between patients who tolerated the challenge stings and those who reacted to them. The authors concluded that the clinical outcome of in-hospital challenge stings was

not influenced by early increases in plasma catecholamine levels that may have been produced by anticipation of the pending stressful experience.

Venom immunotherapy

Mechanism of action

Nineteen patients who had received honeybee venom immunotherapy for 12 to 52 months were challenged with a live honeybee sting by Eberlein-König *et al.* [20]. Of these, six demonstrated a systemic reaction, and the other 13 tolerated the sting without problem. Blood was sampled before the sting and 15, 60, and 180 minutes after the sting. Mean serum histamine and tryptase levels at 15 minutes after the sting were increased in the reactors but not in the nonreactors. Because some nonreactors developed significant elevations of serum histamine level, the authors suggest that other immunotherapy-induced regulatory mechanisms in addition to lowered mediator release may have protected patients from the development of symptoms.

Jutel *et al.* [21•] studied changes in T-cell cytokine secretion in a group of 10 insect-allergic patients who received rush honeybee-venom immunotherapy. Venom immunotherapy resulted in decreased interleukin-4 and interleukin-5 and increased interferon gamma secretion in cultures of peripheral blood mononuclear cells stimulated by phospholipase A (the major honeybee venom antigen) but not by the control antigen, tetanus toxoid. This shift toward a more T helper 1–like pattern may help to explain the mechanism of protection from insect stings that results from venom immunotherapy.

Nearly simultaneously, McHugh *et al.* [22] examined the secretion of interleukin-4 and interferon gamma in peripheral blood mononuclear cells from 13 honeybee-allergic patients, which was stimulated by honeybee venom or nonspecific antigen before and during conventional and rush honeybee-venom immunotherapy. Before therapy, the insect-allergic patients had T helper 2 (interleukin-4) responses to venom and T helper 1 (interferon gamma) responses to nonspecific antigen. After rush or conventional venom immunotherapy, venom caused less interleukin-4 secretion and increased interferon gamma secretion. These studies demonstrate a direct effect of immunotherapy on T cells. This change in pattern could induce an isotope switch from IgE to IgG. Our understanding of the mechanism by which immunotherapy produces clinical benefit continues to expand, but many questions remain.

Duration of venom immunotherapy

The study of Hymenoptera sensitivity has been a major research interest of the Johns Hopkins Asthma and Allergy Center for more than two decades. Golden *et al.* [23••] recently published a long-anticipated paper that summarized the results of how their patients fared after

stopping venom immunotherapy. Seventy-four patients who had completed at least 5 years of venom injections were accepted for study regardless of the severity of their initial sting reaction or the persistence of venom skin-test sensitivity. Intentional sting challenges were performed every 1 or 2 years and caused systemic symptoms in only eight of 270 stings (3%) in seven of 74 patients (10%). Venom skin tests and serum venom-specific IgE levels decreased progressively from the time of initial assessment; the challenge stings did not slow this decline. They concluded that venom immunotherapy may be safely discontinued after 5 years of maintenance therapy in virtually all patients. There have been previous reports concerning the stopping of venom treatment, but this paper is valuable because it describes the largest and longest-studied group.

References and recommended reading

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