

EDITORIAL



Immunotherapy in Allergy to Insect Stings in Children

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The earliest reported death from an allergic reaction to a stinging insect was that of King Menes of Egypt, who died in 2641 B.C., purportedly as the result of a wasp or hornet sting.¹ Currently, there are at least 40 fatal stings per year in the United States,² and it is likely that many others go unrecognized.³

Stinging insects are found in the Hymenoptera order, and three particular families, the Apidae, the Vespidae, and the Formicidae, are of greatest importance in allergy. The Apidae family includes honeybees and bumblebees, the Vespidae family yellowjackets, yellow hornets, white-faced hornets, and paper wasps, and the Formicidae family fire ants. Whereas yellowjackets are prominent in the northern United States, the major culprits in the Southwest are wasps, and in the Southeast imported fire ants.

Reactions to insect stings vary from a minimal, "normal" reaction to a life-threatening anaphylactic reaction.⁴ Typically, insect stings cause local pain and erythema that resolve within a few hours after the sting. Analgesics and cold compresses are the only treatment necessary for these reactions.

Some people may have more pronounced local reactions. These large local reactions are limited to the area contiguous to the site of the sting; they may become very large, even affecting an entire limb. They develop over a period of 12 to 24 hours, and they are thought to represent a late-phase IgE-dependent reaction.³

Generalized allergic reactions to insect stings develop in approximately 1 person in 30 to 300 people.^{5,6} Although the clinical manifestations of IgE-mediated systemic reactions vary from person to person, the most common symptoms are dermal in nature and include generalized urticaria, flushing, and angioedema.⁴ In the less common, but

more severe, anaphylactic reactions, upper-airway edema and circulatory collapse can result in death.

Venom immunotherapy has been shown to be an effective and safe treatment for preventing sting-induced anaphylaxis in persons with a history of systemic reactions to insect stings.^{7,8} However, although venom immunotherapy is effective, there are disadvantages associated with it, such as cost, inconvenience, the occurrence of local and systemic reactions, and the need for prolonged treatment.⁹ Thus, before initiating venom immunotherapy, it is important to determine which patients with Hymenoptera sensitivity should be considered for treatment.

In 1983, Schuberth and colleagues¹⁰ showed that children with reactions to insect stings that were limited to the skin generally had a benign course. Subsequent stings in two groups of children, those who received venom immunotherapy and those who did not, resulted in reactions that were milder than the original reaction. This finding was confirmed by the same group in a report published in the *Journal* in 1990.¹¹ In this study, 242 children, each with a history of a systemic dermal reaction to an insect sting and a positive response in a skin test to one or more of five Hymenoptera venoms, were evaluated. In 36 of 68 children who received venom immunotherapy, 84 stings resulted in 1 systemic reaction (1.2 percent of stings), whereas in 86 untreated children, 196 stings resulted in 18 systemic reactions (9.2 percent of stings). Although the number of reactions to an insect sting was significantly greater in the untreated group ($P < 0.001$), 16 of the 18 reactions were milder than the original reaction and 2 were similar in severity to the original reaction. The authors concluded that, since there was no progression to a more severe reaction, venom im-

munotherapy is not necessary for children in whom the Hymenoptera reactions consist of dermal reactions only.

Unlike sting-induced dermal reactions, sting-induced anaphylactic reactions can result in death. An important question is whether anaphylaxis is likely to be repeated in patients who previously had such a reaction. Reisman¹² sought to answer this question by following 220 patients who had sting-induced systemic reactions and had subsequent stings in the absence of venom immunotherapy. The patients were grouped according to the severity of the original reaction. Of those who had had severe symptoms when they were first stung, such as upper-airway obstruction, severe respiratory distress, loss of consciousness, or hypotension, shock, or both, 46 percent had severe systemic reactions when stung again. Thus, the chance of a second severe reaction was about 50-50 in this group. The author concluded from these results that the severity of a reaction to a second insect sting is related to the severity of the reaction to the initial sting. However, it is unclear from these data whether this conclusion can be applied to children. In the Reisman study,¹² the majority of the patients (70 percent) whose original reactions were severe were older than 16 years of age.

In this issue of the *Journal*, Golden and colleagues¹³ expand their follow-up of children who had allergic reactions to insect stings. They studied the long-term outcome of venom immunotherapy in children by comparing two groups of patients, those who had received venom immunotherapy and those who had not. Their data consisted of follow-up interviews with 512 patients who had been enrolled between 1978 and 1987 in their established cohort of 1033 children with a diagnosis of allergy to insect stings. The responses were stratified according to the severity of the original reaction and whether or not the patients had received venom immunotherapy.

Of the 512 patients evaluated, 43 percent received subsequent stings between 1987 and 1999. The rate of stings was similar in the treated and untreated groups and among patients whose original reaction had been a limited cutaneous systemic allergic reaction and those whose original reaction had been a moderate-to-severe systemic allergic reaction. The rate of systemic reactions after a subsequent sting was significantly greater among untreated patients (17 percent) than among treated patients (3 per-

cent). When patients whose original reaction was systemic were surveyed, 32 percent of those with an initial moderate-to-severe systemic reaction who had not received venom immunotherapy had a systemic reaction after a subsequent sting. This rate of reaction was significantly greater than the rate (13 percent) noted among patients whose original reaction had been cutaneous. Thus, as Reisman¹² previously demonstrated for adults, Golden and colleagues¹³ now show that a large percentage of children who have moderate-to-severe systemic allergic reactions to insect stings are likely to have similar systemic reactions if they receive subsequent stings.

A critical observation is that even many years after venom immunotherapy had been stopped, it still appeared to exert an effect, as shown by a marked reduction in the rate of systemic reactions among children who had previously had moderate-to-severe systemic allergic reactions. In addition, like adults, the few children who had been treated and who had subsequent systemic reactions had more severe original reactions. Thus, the findings support not only the use of venom immunotherapy in children who have a moderate-to-severe systemic allergic reaction to insect stings, but also the consideration of prolonged therapy for children with especially severe systemic allergic reactions to insect stings, which is similar to the recommendations for adults.

As the authors point out, there has been a misconception perpetrated by both parents and physicians — the common belief that children typically outgrow insect-sting allergy. For this reason, it has been thought that venom immunotherapy may not be warranted in children, since, with advancing age, reactions to insect stings would be less severe. Golden and colleagues now set the record straight. Indeed, for most children who have systemic allergic reactions to insect stings — that is, those with dermatologic manifestations only — venom immunotherapy is not warranted. However, for the small percentage of children who have more severe sting-induced systemic allergic reactions, there is a high likelihood that they will have similar severe reactions if they receive subsequent stings. It is to be hoped that now, with hard data provided, physicians will be able to move beyond misconceptions and support the use of venom immunotherapy for the children most at risk.

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