

# Insect allergy in children

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## Purpose of review

Some aspects of insect sting allergy are unique in children. This review will identify and update the published data that exist pertaining specifically to insect allergy in children.

## Recent findings

Children have a different pattern of insect sting allergy than adults. Honeybee allergy is more common in children. Severe systemic reactions are less common than in adults but the risk of recurrence can persist for decades. Systemic reactions are limited to mild 'cutaneous' reactions in over 60% of children (but only 15% of adults). Children with mild systemic reactions rarely get worse. Children with moderate or severe systemic reactions still had a 30% chance of a similar reaction even 20 years later. The long-term immune tolerance induced by venom immunotherapy is greater in children than adults. Children who had received venom immunotherapy for 3–5 years were still immune 10–20 years later.

## Summary

Children with insect sting allergy are tested and treated in much the same way as adults. Children with mild systemic reactions do not require testing or immunotherapy. Children with moderate to severe systemic reactions are at risk for decades and should receive venom immunotherapy, which gives very long-lasting protection.

## Keywords

anaphylaxis, children, Hymenoptera, insect sting, pediatric, venom immunotherapy

## Introduction

In children, as in adults, stings can cause local or generalized allergic reactions. Large local reactions represent late-phase IgE-mediated allergic inflammation that increases over 24–48 h to a size often exceeding five inches (12.7 cm), and resolves in 5–10 days. Systemic (generalized) reactions may include any of the signs and symptoms of anaphylaxis. Other, unusual patterns of reaction have been reported which are not IgE mediated. The diagnosis and management of insect sting allergy has been reviewed in detail elsewhere [1<sup>•</sup>,2,3<sup>••</sup>,4<sup>••</sup>,5]. The purpose of this review is to identify and update the published data that exist pertaining specifically to children.

## Epidemiology and natural history

Insect sting allergy can occur at any age, often following a number of uneventful stings, but occurs more frequently when there is frequent exposure. Unlike allergies in general, insect sting allergy was more common in boys than in girls (as it is in adults) [6–8]. Although clearly familial in a few cases, this condition is not statistically more likely in those with a family history of sting reactions, and there is only a weak correlation with other allergic conditions [9].

Early studies described the medical records of a population of Boy Scouts attending a summer camp, of whom 0.8% had a history of allergic reactions to stings [10,11]. In another study, only 0.34% of 1175 schoolchildren had a history of systemic reaction to stings [7]. In a random sample of adults, 3% reported systemic allergic reactions [9]. The frequency of large local reactions is uncertain, but is estimated at 10% in adults. There are at least 50 fatal sting reactions each year in the United States and it is believed that many other sting fatalities are unrecognized [12–14]. The majority of deaths occurred in those over 45 years old, but insect sting fatalities have occurred in children, and are generally due to airway obstruction [12,13,15].

There are few studies describing the prevalence of positive venom skin tests or radio-allergosorbent test (RAST) responses in a pediatric population. In the report by Novembre *et al.* [7], only 3.7% of 1175 children had positive venom skin tests, but they only performed puncture tests at 100 µg/ml concentration, without intradermal tests or RAST. Allergic sensitization to venom is common in adults: over 30% of adults stung in the previous 3 months showed venom-specific IgE by skin

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## Abbreviations

**RAST** radio-allergosorbent test  
**VIT** venom immunotherapy  
**WBE** whole body extract

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test or RAST, and over 20% of all adults tested positive [9]. This asymptomatic sensitization was often transient, disappearing in 30–50% after 3–5 years, but was associated with a 17% frequency of a systemic reaction to a subsequent sting [16]. Similar findings for the RAST were reported in a rural population of 277 subjects of whom 45 were children [17].

The natural history of insect sting allergy in children was of special interest very early on because of observations that children have a much higher frequency of isolated cutaneous reactions and a lower frequency of vascular symptoms and anaphylactic shock than adults [8,18]. Among 235 children evaluated for insect allergy, 123 had cutaneous systemic reactions (52% overall; or 68% of those with a history of systemic reaction), 59 had more severe systemic reactions (25% overall; or 32% of those with a history of systemic reaction), and 53 (23%) had large local reactions. In the Hymenoptera Venom Study (a registry of the American Academy of Allergy Asthma and Immunology that included almost 3000 cases of whom 32% were under age 17 years), the severity of the history in the children was mild in 44%, moderate in 44%, and severe in 12%. The respective observations (mild, moderate, severe) for the adults age 17–39 years were 31, 41 and 26%, and in adults over age 39 years were 29, 33 and 38% [6].

In untreated adults with a history of sting anaphylaxis and positive venom skin tests who underwent sting challenge, 60% had another systemic reaction, some of which were life-threatening [19]. In adults with a history of cutaneous systemic reactions, venom immunotherapy (VIT) has been recommended because of the concern that future reactions could be life-threatening. The uncertain prognosis in cutaneous systemic reactors affects the majority of pediatric cases, and led to the extended follow-up of children to determine their natural history. The initial observations after 4 years reported that in untreated children with a history of cutaneous systemic reactions, 9% of 196 field stings (in 18% of the patients) caused another systemic reaction, none of which were more severe than the historical reaction (hives only) [20]. Schuberth *et al.* [21] reported extended follow-up of an expanded cohort of 268 cases for up to 9 years during which 180 children had 491 field stings. There was no abnormal reaction in 65% of the stings, large local reaction in 25%, cutaneous systemic (hives) in 9% and a moderate systemic reaction in two stings (0.4%). Among the 180 patients, five (2.8%) had systemic reactions that were more severe than the historical reaction: three (1.7%) had more severe cutaneous systemic reactions and two (1.1%) had a moderate reaction with respiratory symptoms. This was a dramatically lower risk than the adult population described by Hunt *et al.* [19], and led to the recommendation not to treat (or even test) children

with a history of cutaneous systemic reaction to a sting [2,3<sup>••</sup>,4<sup>••</sup>,22,23]. A later study of 113 children, mostly with large local and cutaneous systemic reactions, found that 13% had a systemic reaction to a subsequent sting [24]. A second sting challenge 2–6 weeks later caused systemic reactions in 17% of the children. The natural history of large local reactions has been observed in small numbers of patients, with consistent rates of systemic reaction in the range of 4–7% [25–27].

The data from those studies gave a new perspective to the puzzle of why whole body extracts (WBEs) were believed to have been clinically efficacious when in fact, they are no better than placebo. Many of the subjects described in the reports of WBEs had been children, or patients with large local reactions, both of whom are now known to have only 5–10% chance of a systemic reaction to a sting. Patients who were thought to have benefited from WBE treatment had actually benefited simply from the natural history of the disease and the inaccuracy of diagnosis with WBE [28].

The situation in children who have had more serious systemic reactions is not as well studied as in adults. Reisman [29] reported on the natural history in 220 patients. Among the 112 who had a history of systemic reaction at age 16 years or less, subsequent stings caused systemic reaction in 40%, compared with 73% in the adults. In the total group (all ages), there was no decline in the reaction rate with time over more than 10 years, but there was considerable variability in the occurrence of systemic reactions with different stings in the same patient. Settiple and Chafee [30] followed 119 patients of whom half were under age 12 years, and reported that field stings caused systemic reactions that were the same or worse than the historical reaction in 55%, and milder than the original in 5% (total 60% reaction rate). There are no clear data on whether any differences might exist in different age groups of children, especially under age 5 years. Published studies include mostly children aged 5–15 years, with a mean age of 9 years.

Although the chance of a sting reaction in ‘high-risk’ patients falls from about 50% initially to 35% after 3–5 years, and perhaps 20% risk after 10–15 years, the risk can persist for decades even with no intervening stings [29,31]. The expected decline in risk with time did not seem to occur in one study [29]. Although the same principles apply in children, the actual long-term risk of reaction in children has not been as well studied. We recently reported our survey in which we performed a 10–20-year follow-up on the 1033 children who had been evaluated for insect allergy at our center between 1978 and 1985 [25]. These subjects had a history of large local, mild cutaneous systemic, or anaphylactic systemic reaction to stings, and included those who had received a

course of VIT and others who remained untreated. We were able to contact 50% of the subjects, and over 40% had been stung during the observation period of 1987–1999. Our data confirm that the large local reactors have a 5–10% chance of a systemic reaction to a later sting (7% in our study). The outcome in children with cutaneous systemic reactions was quite similar to that reported in part of this population after the first 4 years, or 9 years, of observation by Valentine and Schuberth respectively. We observed 13% of such children to have a systemic reaction when stung 10–20 years after their original reaction. Compared with the previous reports, we did find that a somewhat higher proportion of these children progressed to a “moderate” reaction, involving some mild respiratory symptoms in addition to the cutaneous signs and symptoms. We estimate, after adjustment for selection and reporting bias, that there is about a 3% chance of the systemic reaction becoming worse with subsequent stings in such children. Notably, there has not been a single child in our cohort of 352 children with a history of mild systemic reactions who reported a severe grade of reaction to a subsequent sting. Our results are still consistent with the clinical recommendation that such children do not require VIT.

Our study also included children with a history of moderate or severe systemic reactions to stings. Most of these subjects (71%) had received VIT, so there are limited data on the long-term outcome in untreated cases. Nevertheless, the frequency of systemic reaction to stings 10–20 years after the original reaction was significantly higher in the untreated (32%) than in either the treated (5%) subjects with a history of moderate or severe reactions, or the untreated children with a history of cutaneous systemic reaction (13%). Furthermore, in children who had a history of anaphylaxis, many of the reactions that occurred during the observation period were severe. These results are the first to demonstrate that even though most children ‘outgrow’ insect sting allergy, a substantial number remain at risk for life-threatening reactions even after 10–20 years. This provides a clear rationale to recommend a course of VIT to such children.

## Diagnosis

The standard method of testing is the same in children as in adults, and the results are generally similar with regard to the strength and number of sensitivities detected. In adults, it has become apparent that a surprising number who have a clear history of systemic reaction to a sting are found to have negative venom skin tests, some of whom will still have a systemic reaction to a subsequent sting (almost all of whom have positive venom RAST) [32]. It is not clear to what extent this might occur in children. Skin tests were positive in 87% of the 235 children evaluated for insect sting allergy by Schuberth *et al.* [8], but in another study [33], the skin tests were positive

in only 76% of almost 3000 patients (one third were less than 17 years old) with a history of systemic reaction to stings. The degree of skin test sensitivity does not correlate reliably with the degree of clinical sting reaction in adults or children [8,34]. The strongest skin tests often occur in patients who have had only large local reactions and have a very low risk of anaphylaxis, whereas some patients who have had severe anaphylaxis show only weak skin test results. Schuberth *et al.* [8] also showed that honeybee venom sensitivity was more common in children than in the adults evaluated at the same center.

As in adults, the skin test technique is preferred over the RAST for optimal diagnostic sensitivity. About 10% of insect allergic patients who have negative venom skin tests will show positive results in the RAST. These tests are therefore complementary and some patients will need both tests to make a diagnosis. In one study, there was no correlation between the venom-IgE antibody level and the venom skin test response [8]. The mean venom-IgE level in children before starting VIT (31 ng/ml) was higher than that of adults (10 ng/ml) [35].

Diagnostic evaluation for fire ant allergy is limited by the availability of only whole-body extracts and not the venoms for testing and treatment. In children, the venom was clearly superior for diagnosis, since whole body extract had a 26% frequency of false-negative results [36]. A venom RAST is available in some laboratories.

## Venom immunotherapy

VIT may be recommended to prevent systemic reactions to insect stings in all individuals with a history of a past systemic reaction to a sting and positive venom skin tests. The relative need for treatment varies with the severity of the previous reaction. Although VIT has been established as being effective in children, there are no controlled studies of VIT in children [37]. Schuberth and Valentine and colleagues [18,20] showed that VIT was effective for children with mild (cutaneous) systemic reactions. Reisman *et al.* [38] compared the outcome of field stings in patients who did and did not receive VIT. Of the 127 untreated patients surveyed, 34 were under age 16 years. In the 48 treated patients who were stung (the number of children is not indicated), the two systemic reactions occurred in adults. In 15 untreated children who were stung, six (40%) had systemic reactions.

There are a few special considerations in children, relating mostly to the indications for treatment. The first is the recommendation, discussed above, that children who have a history of only cutaneous systemic reactions do not require VIT. Some have thought this to suggest that even children with more severe reactions are likely to outgrow the sensitivity, but our data show otherwise [25].

The recommended treatment regimen is the same in children as in adults, and safety has been at least as good or better [2,4<sup>••</sup>,39,40]. Rush regimens for initial VIT have been reported to be safe in children [41]. The recommended maintenance dose is 100 µg of each venom. In adults, lower doses (50 µg) often give incomplete protection, resulting in systemic reactions to stings in 15–20% of patients. The mean venom-specific IgG antibody response is greater in children than in adults, but the clinical efficacy of lower doses has not been tested [35,42]. The safety and efficacy of VIT is especially unreported for children under age 5 years, but some children have been treated successfully even at age 2–3 years.

Fire ant immunotherapy is often indicated in children because they have a very high exposure rate in endemic areas, and can have anaphylactic reactions [5]. The natural history of fire ant allergy in children has not been well studied and the efficacy of the available whole body extracts is supported by uncontrolled studies in adults [43,44].

Maintenance VIT is usually administered every 4 weeks for at least a year, and then may be given at lengthening intervals of every 6–8 weeks over several years in most cases. Although repeat skin tests or RASTs have been suggested every 2–3 years to determine when there has been a significant decline in venom-IgE, the low frequency of negative results makes the value of repeated testing questionable especially in children. Venom-specific IgE antibody levels rise in the first months of therapy, return to baseline after 12 months and then decline steadily during maintenance treatment (even after therapy is stopped and even after a sting). Skin tests generally remain unchanged in the first 3–5 years, but show a significant decline after 4–7 years [39,45–47].

The recommended duration of VIT is 3–5 years [2,4<sup>••</sup>]. Some adults require prolonged treatment because of high risk factors including near-fatal previous reaction, systemic reaction during VIT (to an injection or a sting), or honeybee venom allergy [31,48,49]. These caveats have not been confirmed in children but caution is generally recommended in such cases. In adults, the clinical and immunologic outcome was better with treatment of at least 5 years than with 3 years [49,50]. The relapse rate after stopping VIT in children is in the range of 5–10%, with most reactions being mild [21,46,51,52]. In our long-term study of the outcome in insect allergic children, there was a very low relapse rate after 10–20 years in patients who had received 3–5 years of treatment (mean 3.5 years), an outcome that was significantly better than that observed in our adult population [25].

## Conclusion

Children have a different pattern of insect sting allergy than adults. Honeybee allergy is more common in chil-

dren. Severe systemic reactions are less common than in adults but the risk of recurrence can persist for decades. Children with cutaneous systemic reactions have a benign prognosis and do not require VIT. Children with moderate or severe systemic reactions should receive VIT with the same dose and regimen as that used in adults, although it would seem practical to consider reduced doses in very young children (3–6-year-olds). The long-term immune tolerance induced by VIT is greater in children than adults.

## 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

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 306).

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