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INSECT STING ANAPHYLAXIS

David B.K. Golden, M.D
Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Blvd., Baltimore, MD 21224

Abstract

Anaphylaxis to insect stings has occurred in 3% of adults and can be fatal even on the first reaction. Large local reactions are more frequent but rarely dangerous. The chance of a systemic reaction to a sting is low (5–10%) in large local reactors and in children with mild (cutaneous) systemic reactions, and varies between 25% and 70% in adults depending on the severity previous sting reactions. Venom skin tests are most accurate for diagnosis but the RAST is an important complementary test. The degree of sensitivity on skin test or RAST does not reliably predict the severity of a sting reaction. Venom sensitization can be detected in 25% of adults, so the history is most important. Venom immunotherapy is 75–98% effective in preventing sting anaphylaxis. Most patients can discontinue treatment after 5 years, with very low residual risk of a severe sting reaction.

Keywords

anaphylaxis; venom; insect sting; Hymenoptera; immunotherapy

Stinging insects of the order Hymenoptera can cause systemic allergic reactions including anaphylaxis, but such reactions are rare with biting insects. This review will describe the clinical patterns and treatment of sting reactions, which how they may resemble or differ from other causes of anaphylaxis.

CLINICAL FEATURES

Transient pain, itching and swelling are normal responses to stings, but allergic reactions can cause more severe local reactions or generalized systemic reactions. Large local sting reactions cause delayed and prolonged local inflammation increasing over 24 to 48 hours and resolving in 3 to 10 days. These reactions resemble “late phase reactions” which are IgE dependent. Most patients with large local reactions patients have detectable venom-specific IgE.(1)

Systemic (generalized) reactions may cause any one or more of the signs and symptoms of anaphylaxis. Although the definition of anaphylaxis would seem to exclude reactions involving only cutaneous manifestations (urticaria, angioedema, pruritus, flush), these are included in this review because they must be considered in diagnosis and treatment of insect allergy as potential precursors of more severe anaphylactic reactions.(2) There are also reports of chronic urticaria and cold urticaria developing after insect stings, usually without any immediate hypersensitivity reaction, and with uncertain risk of anaphylaxis to a future sting.(3) Unusual patterns of reaction have also been reported including nephropathy, central and peripheral

Corresponding Author: David B.K. Golden, M.D., Telephone: (410) 931-0404, Fax: (410) 931-0405, Email dgolden1@jhmi.edu

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neurologic syndromes, idiopathic thrombocytopenic purpura, and rhabdomyolysis, but most of these are not IgE related.(4,5)

Systemic (generalized) allergic sting reactions result in cutaneous, vascular or respiratory symptoms and signs, either singly or in any combination, with possible involvement of other less common target tissues. Cardiac anaphylaxis can also cause bradycardia, arrhythmias, angina or myocardial infarction. Abdominal cramps are not uncommon, and "spontaneous abortion" can occur as a result of sting anaphylaxis. There may be a greater chance of systemic reaction if there are multiple stings at one time, or if there are repeated stings in the same summer. In contrast to food anaphylaxis, the slower the onset of the sting reaction, the less likely it is to be life-threatening.(6,7)

Whether anaphylaxis differs clinically between children and adults is unclear for most causes, but is known for insect sting allergy. Cutaneous symptoms are most common overall, affecting 80%; they are the sole manifestation in 15% of adults but in more than 60% of affected children. (8) Almost 50% of reactions in both children and adults included respiratory complaints. Symptoms and signs of hypotension were uncommon in children but occurred in over 60% of adults, with half experiencing loss of consciousness (rare in children).(7,9) The clinical presentation can be vague and uncertain both during the reaction and in the history. To aid proper diagnosis and treatment, objective documentation should be made whenever possible, including description of cutaneous findings, vital signs, pulse oximetry and air flow measurements.

Treatment of insect sting anaphylaxis is no different from other causes of anaphylaxis.(10, 11) Biphasic and protracted anaphylaxis have been reported with insect stings, so medical observation should extend for 3 to 6 hours depending on severity. Some individuals are resistant to epinephrine, especially those on beta-blocker medication. Nevertheless, the risk of stopping beta-blockers in patients with cardiac disease may exceed the risk of continuing the drugs. (12) Patients discharged from emergency care of anaphylaxis should receive instruction about the need for an epinephrine kit, an allergy consultation and preventative treatment, and should understand that using the kit is not a substitute for emergency medical attention.(13)

ETIOLOGY

Stinging insects of the order Hymenoptera are the main cause of insect-related anaphylaxis. There are 3 families of Hymenoptera with clinical importance: the bees (honeybees, bumblebees), vespids (yellow jackets, hornets, wasps), and stinging ants (genus Solenopsis and others). Exposure to these insects is affected by environmental and ecological factors. The africanized honeybee ("killer bee") is an aggressive hybrid resulting from an experiment intended to enhance honey production. The danger from the africanized honeybee stems from the numbers of stings because of swarm-and-attack behavior. Their venom is actually no different than that of other honeybees. Imported fire ants arrived almost 100 years ago in Mobile, Alabama, and have rapidly become an increasing public health hazard in the south and southeast parts of the United States.(14,15) There have been increasing reports of anaphylaxis due to other species of stinging ants in Asia and Australia.(16)

The immunochemical characteristics and immunogenetic relationships of the Hymenoptera venoms have been thoroughly studied.(17,18) Venoms contain multiple protein allergens, most having enzymatic activity. Honeybee venom is immunochemically distinct from the other Hymenoptera, but vespid venoms have a high degree of cross reactivity with each other and contain essentially the same allergens. Skin tests are positive to all 3 of the common vespid skin test preparations (yellow jacket, yellow hornet, white-faced hornet) in most vespid allergic patients. Polistes wasps are not as closely related to the other vespids, and only 50% of yellow jacket allergic patients have positive tests to wasp venom. Fire ant venoms are different in that

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they contain very little protein, in a suspension of alkaloid toxins that causes the characteristic vesicular eruption. The proteins in fire ant venoms are antigenically unique except for one that shows limited cross reactivity with a vespid allergen. The diagnostic and therapeutic materials currently supplied by commercial laboratories are fire ant whole body extracts which, unlike the other insect whole body extracts, do show reasonable allergenic activity for diagnostic skin testing and for preventative immunotherapy.(19)

EPIDEMIOLOGY/NATURAL HISTORY

Knowledge of the epidemiology and natural history of Hymenoptera venom sensitivity is crucial in clinical decision-making. It was the lack of this information that prolonged the mistaken conclusion that whole body extract therapy was effective in the prevention of anaphylaxis.(20) The studies of whole body extract were not placebo controlled, and included children, large local reactors, mild systemic reactors, and individuals who had negative venom skin tests, all of whom are now known to have very low risk of anaphylaxis to stings.

Insect sting allergy can occur at any age, often following a number of uneventful stings, and is more common than previously thought. Systemic allergic reactions are reported by up to 3% of adults, and almost 1% of children have a medical history of severe sting reactions.(21,22) The frequency of large local reactions is uncertain, but is estimated at 10% in adults. At least 50 fatal sting reactions occur each year in the United States.(6) Half of all fatal reactions occur with no history of previous sting reactions. Many sting fatalities may be unrecognized. It is possible to document in some postmortem blood samples, the presence of both venom-specific IgE antibodies as well as elevated serum tryptase suggesting a possible fatal sting reaction in some cases of unexplained sudden death.(23,24) However the presence of IgE antibodies to Hymenoptera venom is not, in itself, unusual. Over 30% of adults stung in the previous 3 months showed venom-specific IgE by skin test or RAST, and over 20% of all adults tested positive to yellow jacket or honeybee venom, even though most had no history of allergic sting reactions.(21) Venom sensitivity in asymptomatic adults is often transient, disappearing more rapidly than it does in patients with a history of anaphylaxis. Of the subjects with initial positive skin tests, 30–60% became negative after 3–6 years. Those who remained positive showed a 17% frequency of a systemic reaction to a sting.(25)

Systemic reactions can become progressively more severe with each sting in some cases, but this seems to be the exception rather than the rule. In prospective sting challenge studies, less than 1% of the patients had reactions more severe than their past reactions.(26,27) In two retrospective surveys, there were a larger number of subjects who described worsening of the reaction with subsequent stings.(7,28) Allergic reactions to stings usually follow a predictable and individual pattern in each patient. Anaphylactic reactions to stings can occur even decades apart, with or without intervening stings.

DIAGNOSIS

History

The history is paramount in diagnosis and must be elicited with insight and attention to detail. Patients usually fail to admit sting reactions without specific inquiry, often do not seek medical attention, and believe the reaction was a chance occurrence which could not happen again. (21) The history should include all previous stings, the time course of the reactions, and all associated symptoms and treatments. The reaction to any given sting can be variable, even in sting allergic individuals. Even without intervening stings, sensitization can persist for decades and result in subsequent anaphylactic reactions to stings. If intervening stings have occurred without systemic reaction there could be less risk of subsequent severe reaction, but the

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possibility of future anaphylaxis cannot be excluded when diagnostic tests reveal venom-specific IgE antibodies.(26)

The significance of the sting reaction can be over- or under-estimated. Symptoms are sometimes exaggerated by fear, panic, exercise, heat, alcohol or underlying cardio-respiratory disease. For this reason, objective documentation of the physical findings during the reaction should be sought (measurements of blood pressure or reduced air flow, observed urticaria). The throat or chest discomfort, dyspnea, lightheadedness, nausea and other constitutional symptoms can be due to anxiety/panic disorder or simple fear. Insect sting challenge studies have often elicited subjective symptoms that mimic anaphylaxis, but with no objective evidence of reaction.

Diagnostic Tests

Diagnostic tests are indicated in patients who have had systemic reactions to stings.(11,29) If the risk of future anaphylaxis is judged to be low (less than 10%), diagnostic testing (and venom immunotherapy) is not required. This is the case in patients with only large local reactions to stings, and in children who had only cutaneous systemic reactions. There are also patients who request venom testing due to fear of the reactions experienced by family members or others. Testing is not advised in such cases because of the frequent occurrence of positive venom tests in individuals who have been previously stung without abnormal reaction.

Unfortunately, skin tests are not a useful screening test and are not recommended in those with no history of systemic allergic reaction to a sting. A screening test for insect allergy would be desirable in order to prevent the morbidity and mortality of the initial anaphylactic episode. In fact, half of all fatal reactions occur without prior reactions to stings. Venom immunotherapy is indicated only in patients who have a history of previous systemic reaction because venom skin tests can be positive in many adults who have had previous stings and will have no reaction to a future sting. It should not be possible to have positive tests for venom-specific IgE antibodies in individuals who have never been stung. Although such cases have been described, we found that all those who could be traced through family members were found to have had stings in early childhood that they cannot recall.(21) Other possible explanations include cross-reactivity with plant allergens (airborne or food-related) or with carbohydrate determinants.(30,31)

The preferred diagnostic method is venom skin testing because of its high degree of sensitivity and proven safety.(32) In vitro methods can be useful but are not as sensitive and can therefore yield false-negative results. The standard method of skin testing is with the intradermal technique using the five Hymenoptera venom protein extracts (or whole body extracts of imported fire ants). For Hymenoptera venom testing, intradermal tests are performed with venom concentrations in the range of 0.001 to 1.0 μg/ml to find the minimum concentration giving a positive result. Puncture tests at ≤1 μg/ml concentration may be used initially for patients with a history of very severe reactions. Sensitization may have occurred to multiple venoms even when there has only been a reaction to a single insect. Therefore, skin testing should be performed with a complete set of 5 Hymenoptera venoms, a negative diluent (HSA-saline) control, and a positive histamine control.

Skin test results are clearly positive in 65–85% of patients with a convincing history. Negative skin tests in a history-positive patient can be due to loss of sensitivity after a remote sting reaction. Negative skin tests after recent sting anaphylaxis can occur during the refractory period of “anergy” for several weeks after a sting reaction, and should therefore be repeated after 1 to 6 months.(33) Venom skin tests also show unexplained variability over time such that tests can be negative on one occasion and positive on another.(34) It may be best to perform venom skin tests on 2 separate occasions before making final therapeutic selection of venoms.

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Some cases of sting anaphylaxis appear to be non-IgE mediated and may be related to sub-clinical mastocytosis or simply “toxic” mast cell mediator release. The venom causing the strongest skin test reaction is usually the insect that caused the most recent sting. Most importantly, the degree of skin test sensitivity does not correlate reliably with the degree of sting reaction. 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 abrupt and near-fatal anaphylactic shock show only weak skin test (or RAST) sensitivity. In fact, about 25% of patients presenting for systemic allergic reactions to stings are skin test positive only at the 1.0 μg/ml concentration. Once again, it is the history that is most predictive.

The detection of allergen-specific IgE antibodies in serum (typically by RAST), is less sensitive than skin testing, but is useful when skin tests cannot be done (patients with a severe skin condition or unavoidable medications than suppress skin tests).(32,35) Another use of the RAST is to resolve the discordance when skin tests are negative in a patient with a history of severe reaction to a sting. It is not clear whether there is any difference in prognostic value of skin tests and RAST. Patients with negative skin tests and positive RAST have been reported to have systemic reactions to subsequent stings, although the frequency may be lower than patients with positive venom skin tests.(26)

Other diagnostic techniques are of limited value. Some investigators have suggested that sting challenge is the most specific diagnostic test, but others find this unethical and impractical.(27,36,37) Furthermore, a single negative challenge sting does not preclude anaphylaxis to a subsequent sting.(26,38)

PREVENTION

Precautions

Individuals susceptible to allergic reactions to stings should avoid related exposures, particularly outdoor foods and drinks that attract or harbor stinging insects. However, excessive fear impairs quality of life and can be considered among the indications for venom immunotherapy.(39) When to carry or use an epinephrine injector depends on the clinical setting. Although having an emergency injector is reassuring to some individuals, it is frightening to others and conveys a concern about possible dangerous reactions to stings.(40) Many experts suggest that an injector is not necessary when the chance of a systemic reaction is only 5–10% such as in large local reactors, children with cutaneous systemic reactions, and patients on venom immunotherapy. On the other hand, some feel that even a 2% chance of anaphylaxis warrants carrying epinephrine, even if it doesn’t warrant venom immunotherapy. Most insect allergic patients can be advised to keep an epinephrine injector at the ready when stung, but may not need to use it if the reaction does not occur or remains limited to mild symptoms. Some patients have had rapid onset of severe reactions and (until immunized) should potentially use epinephrine immediately after being stung.

Venom Immunotherapy

Treatment for prevention of anaphylactic reactions is not always available: immunotherapy is currently possible only for Hymenoptera venom. Therapy with whole insect body extracts was proved to be no better than placebo whereas venom immunotherapy was 95% effective.(41, 42) The indications for venom immunotherapy require a history of previous systemic allergic reaction to a sting and a positive diagnostic test for venom-specific IgE. Those with a recent history of anaphylaxis and a positive skin test have a 30% to 70% chance of systemic reaction to a subsequent sting.(27,41,43) A low risk (<10%) has been found in children and adults with a history of large local reactions, and in children with systemic reactions limited to cutaneous signs and symptoms (with no respiratory or circulatory manifestations).(44–47) Venom

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immunotherapy is not required in these low-risk cases, but some patients will still request treatment because of their fear of reaction and the impact on their quality of life. Children with moderate or severe systemic reactions have up to 30% chance of reaction to a sting even decades later.(44) Unfortunately, there is no test that predicts which patients will progress to more severe reactions. Even intervening stings without reaction do not eliminate the risk of anaphylaxis to a later sting.

Initial venom immunotherapy can follow any of several recommended schedules. The common "modified rush" regimen is more rapid than "traditional" regimens, achieving the 100 mcg maintenance dose with eight weekly injections, instead of taking 4 to 6 months.(48) With these regimens, adverse reactions are no more common than in traditional regimens of inhalant allergen therapy, and both regimens are equally effective. Even 1–3 day rush regimens are not associated with a higher frequency of adverse reactions to venom injections.(49–51) Treatment is usually recommended with each of the venoms giving a positive skin test. Therapy is 98% effective in completely preventing systemic allergic reactions to stings when treatment includes mixed vespid venoms (300 mcg total dose), but complete protection is achieved in only 75% to 85% of patients utilizing 100 mcg of any single venom (eg honeybee, yellow jacket or Polistes wasp). Fire ant immunotherapy using whole body extracts has been reported to be reasonably safe and effective, and should be employed in cases of significant systemic reaction, although there have been no controlled trials.(52) Fire ant venoms are not available for diagnosis or treatment, but there has been a very successful controlled trial of Jack Jumper ant venom immunotherapy in Australia.(53)

Adverse reactions to venom immunotherapy occur no more frequently than with inhalant allergen immunotherapy.(54,55) Systemic symptoms occur in 10–15% of patients during the initial weeks of treatment, regardless of the regimen used. Most reactions are mild, and fewer than half require epinephrine injection. Virtually all patients can achieve the full dose even after initial systemic reactions. In the unusual case of recurrent systemic reactions to injections, therapy may be streamlined to a single venom and given in divided doses, 30 minutes apart. Large local reactions to injections are common, occurring in up to 50% of patients. Unlike standard inhalant immunotherapy, the uniform target dose in venom immunotherapy may make it necessary to advance the dose in the face of large local reactions, beyond what might otherwise be considered the "maximum tolerated dose".

Immunologic mechanisms of venom immunotherapy have been gradually elucidated, but remain sketchy. Venom-IgE rises initially with treatment, then declines steadily over time toward very low levels after 5–10 years. Venom-IgG levels generally increase with treatment, and have been correlated with clinical protection.(56) Lymphocyte subsets and cytokine responses show a moderation of Th2 responses with increased IL-10 initially and increased osteopontin more slowly during treatment.(57–59)

Maintenance doses of venom immunotherapy are administered every 4 weeks for at least a year. Most experts agree that the maintenance interval then may be gradually increased to every 6 to 8 weeks over several years. Venom skin tests or RASTs are repeated periodically, usually every 2–3 years, to determine when there has been a significant decline in venom-IgE.(11) Skin tests generally remain unchanged in the first 2–3 years, but show a significant decline after 4–6 years. Less than 20% of patients are skin test negative after 5 years, but 50–60% become negative after 7–10 years (although most remain positive by RAST).(60,61)

The duration of venom immunotherapy is indefinite according to the recommendation in the product package insert. Initial efforts to stop treatment when the RAST became negative were successful, but only a few patients become RAST-negative within 5 years of treatment.(62–65) Extended study of a large number of adults has shown that when venom immunotherapy

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is stopped after five years, the chance of a systemic reaction will remain 10 percent for each sting even more than 10 years after stopping treatment and even if skin tests become negative.(61,66) When sting reactions occur after stopping venom immunotherapy, most are quite mild and almost always are less severe than the pre-treatment reaction. A higher frequency of relapse occurs in patients who had very severe (near-fatal) sting reactions before therapy, those who had a systemic reaction during therapy (to a sting or a venom injection), those with honeybee allergy, and those who had less than five years of therapy.(61,67–69) Patients with any of these four high-risk characteristics may need to be treated indefinitely, but there are no data on the outcome after more than 15 years of treatment. Some patients will prefer to continue venom treatment for security and improved quality of life. Children who have had 3 to 5 years of venom immunotherapy have a very low chance of systemic reaction even 10 to 20 years after stopping treatment.(44)

CONCLUSION

Anaphylaxis to insect stings has occurred in 3% of adults and can be fatal even on the first reaction. Large local reactions are more frequent but rarely dangerous. The chance of a systemic reaction to a sting is low (5–10%) in large local reactors and in children with mild (cutaneous) systemic reactions, and varies between 25% and 70% in adults depending on the severity previous sting reactions. Venom skin tests are most accurate for diagnosis but the RAST is an important complementary test. The degree of sensitivity on skin test or RAST does not reliably predict the severity of a sting reaction. Venom sensitization can be detected in 25% of adults, so the history is most important. Venom immunotherapy is 75–98% effective in preventing sting anaphylaxis. Most patients can discontinue treatment after 5 years, with very low residual risk of a severe sting reaction.

Anaphylaxis to insect stings is unique in some ways, especially its mode of antigen exposure, its well-described natural history, its milder relatives (large local and cutaneous reactions) and its remarkable response to immunotherapy. Familiarity with these features permits better recognition and prevention of insect sting anaphylaxis. There is a need for improved accuracy in diagnostic tests for insect sting allergy, which may be achieved with dialyzed venoms, recombinant venoms allergens, basophil activation tests, or other in vitro procedures.

There remains a need to determine the best predictive factors that distinguish those who would react to stings from those who are sensitized but do not have anaphylaxis. Such a test would identify those individuals who are at risk before their first reaction occurs, those who are immunized but have incomplete protection, and those who will have increased risk of reaction if they discontinue venom immunotherapy. We could then target our therapy to those most likely to benefit and spare those who are sensitized but are not really in danger. Such insight may come from studying large local reactors (who are highly sensitized but have the lowest risk of anaphylaxis), untreated patients who do not react to a challenge sting, and patients who relapse after stopping venom immunotherapy.

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References

1. Green A, Reisman R, Arbesman C. Clinical and immunologic studies of patients with large local reactions following insect stings. J Allergy Clin Immunol 1980;66:186–9. [PubMed: 7410742]
2. Sampson H, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National

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Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7. [PubMed: 16461139]

3. Hogendijk S, Hauser C. Wasp sting-associated cold urticaria. Allergy 1997;52:1145–6. [PubMed: 9404573]
4. Light WC, Reisman RE, Shimizu M, et al. Unusual reactions following insect stings. J Allergy Clin Immunol 1977;59:391. [PubMed: 140188]
5. Reisman RE, Livingston A. Late-onset allergic reactions, including serum sickness, after insect stings. J Allergy Clin Immunol 1989;84:331. [PubMed: 2778239]
6. Barnard JH. Studies of 400 Hymenoptera sting deaths in the United States. J Allergy Clin Immunol 1973;52:259–64. [PubMed: 4746790]
7. Lockey RF, Turkeltaub PC, Baird-Warren IA, Olive CA, Olive ES, Peppe BC, et al. The Hymenoptera venom study. I. 1979-1982:demographic and history-sting data. J Allergy Clin Immunol 1988;82:370–81. [PubMed: 3170986]
8. Schuberth KC, Lichtenstein LM, Kagey-Sobotka A, Szklo M, Kwiterovich KA, Valentine MD. An epidemiologic study of insect allergy in children. I. Characteristics of the disease. J Pediatr 1982;100:546–51. [PubMed: 7062201]
9. American Academy of Allergy Insect Allergy Committee. Insect sting allergy, cooperative study. JAMA 1965;193:115–20. [PubMed: 14304353]
10. Lieberman P, Kemp SF, Oppenheimer J, Lang DM, Bernstein IL, Nicklas RA, et al. The diagnosis and management of anaphylaxis: An updated practice parameter. J Allergy Clin Immunol 2005;115:S483–523. [PubMed: 15753926]
11. Moffitt JE, Golden DBK, Reisman RE, Lee R, Nicklas R, Freeman T, et al. Stinging insect hypersensitivity: A practice parameter update. J Allergy Clin Immunol 2004;114:869–86. [PubMed: 15480329]
12. Tenbrook J, et al. Should beta-blockers be given to patients with heart disease and peanut-induced anaphylaxis? A decision analysis J Allergy Clin Immunol 2004;113:977–82.
13. Clark S, Long AA, Gaeta TJ, Camargo CC. Multicenter study of emergency department visits for insect sting allergies. J Allergy Clin Immunol 2005;116:643–9. [PubMed: 16159637]
14. Kemp SF, deShazo RD, Moffitt JE, et al. Expanding habitat of the imported fire ant: a public health concern. J Allergy Clin Immunol 2000;105:683–91. [PubMed: 10756216]
15. Tracy JM, Demain JG, Quinn JM, et al. The natural history of exposure to the imported fire ant. J Allergy Clin Immunol 1995;95:824–8. [PubMed: 7722162]
16. Shek LP, Ngiam NS, Lee BW. Ant allergy in Asia and Australia. Curr Opin Allergy Clin Immunol 2004;4:325–8. [PubMed: 15238800]
17. Hoffman, DR. Hymenoptera venoms: composition, standardization, stability. In: Levine, MI.; Lockey, RF., editors. Monograph on Insect Allergy. 4. Milwaukee: American Academy of Allergy Asthma and Immunology; 2004. p. 37-53.
18. King TP, Spangfort MD. Structure and biology of stinging insect venom allergens. Int Arch Allergy Immunol 2000;123:99–106. [PubMed: 11060481]
19. 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. [PubMed: 1987866]
20. Golden DB. Insect sting allergy and venom immunotherapy: A model and a mystery. J Allergy Clin Immunol 2005;115:439–47. [PubMed: 15753884]
21. Golden DBK, Marsh DG, Kagey-Sobotka A, Addison BI, Freidhoff L, Szklo M, et al. Epidemiology of insect venom sensitivity. JAMA 1989;262:240–4. [PubMed: 2739018]
22. Settipane GA, Newstead GJ, Boyd GK. Frequency of Hymenoptera allergy in an atopic and normal population. J Allergy 1972;50:146–50.
23. Hoffman DR. Fatal reactions to Hymenoptera stings. Allergy Asthma Proc 2003;24:123–7. [PubMed: 12776446]
24. Schwartz HJ, Sutheimer C, Gauerke B, Zora JA, Yunginger JW. Venom-specific IgE antibodies in postmortem sera from victims of sudden unexpected death. J Allergy Clin Immunol 1984;73:189.

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25. Golden DBK, Marsh DG, Freidhoff LR, Kwiterovich KA, Addison B, Kagey-Sobotka A, et al. Natural history of Hymenoptera venom sensitivity in adults. J Allergy Clin Immunol 1997;100:760–6. [PubMed: 9438483]
26. Golden DBK, Breisch NL, Hamilton RG, Guralnick MW, Greene A, Craig TO, et al. Clinical and entomological factors influence the outcome of sting challenge studies. J Allergy Clin Immunol 2006;117:670–5. [PubMed: 16522469]
27. vanderLinden PG, Hack CE, Struyvenberg A, vanderZwan 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;94:151–9. [PubMed: 8064067]
28. Golden DBK, Langlois J, Valentine MD. Treatment failures with whole body extract therapy of insect sting allergy. JAMA 1981;246:2460–63. [PubMed: 7299969]
29. Bilo BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JNG. EAACI. Diagnosis of Hymenoptera venom allergy. Allergy 2005;60:1339–49. [PubMed: 16197464]
30. Aalberse RC, Koshte V, Clemens JGJ. Immunoglobulin E antibodies that crossreact with vegetable foods, pollen, and Hymenoptera venom. J Allergy Clin Immunol 1981;68:356–64. [PubMed: 7298999]
31. Hemmer W, Frocke M, Kolarich K, Wilson IBH, Altmann F, Wohrl S, et al. Antibody binding to venom carbohydrates is a frequent cause for double positivity to honeybee and yellow jacket venom in patients with stinging insect allergy. J Allergy Clin Immunol 2001;108:1045–52. [PubMed: 11742287]
32. Hamilton RG. Diagnostic methods for insect sting allergy. Curr Opin Allergy Clin Immunol 2004;4:297–306. [PubMed: 15238796]
33. Goldberg A, Confino-Cohen R. Timing of venom skin tests and IgE determinations after insect sting anaphylaxis. J Allergy Clin Immunol 1997;100:183–4.
34. Graif Y, Confino-Cohen R, Goldberg A. Reproducibility of skin testing and serum venom-specific IgE in Hymenoptera venom allergy. Ann Allergy 2006;96:24–9.
35. Hamilton RG. Responsibility for quality IgE antibody results rests ultimately with the referring physician. Ann Allergy Asthma Immunol 2001;86:353–4. [PubMed: 11345276]
36. Reisman RE. Intentional diagnostic insect sting challenges: A medical and ethical issue. J Allergy Clin Immunol 1993;91:1100. [PubMed: 8491944]
37. Rueff F, Przybilla B, Muller U, Mosbech H. The sting challenge test in Hymenoptera venom allergy. Allergy 1996;51:216–25. [PubMed: 8792917]
38. Franken HH, Dubois AEJ, Minkema HJ, vanderHeide S, deMonchy JGR. Lack of reproducibility of a single negative sting challenge response in the assessment of anaphylactic risk in patients with suspected yellow jacket hypersensitivity. J Allergy Clin Immunol 1994;93:431–6. [PubMed: 8120270]
39. Oude-Elberink JNG, deMonchy JGR, Golden DBK, Brouwer JLP, Guyatt GH, Dubois AEJ. Quality of life in yellow jacket allergic patients I. Development and validation of a health-related quality of life questionnaire in yellow jacket allergic patients. J Allergy Clin Immunol 2002;109:162–7. [PubMed: 11799384]
40. Oude-Elberink JNG, deMonchy JGR, vanderHeide S, Guyatt GH, Dubois AEJ. Venom immunotherapy improves health-related quality of life in yellow jacket allergic patients. J Allergy Clin Immunol 2002;110:174–82. [PubMed: 12110838]
41. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. N Engl J Med 1978;299:157–61. [PubMed: 78446]
42. Muller U, Thurnheer U, Patrizzi R, Spiess J, Hoigne R. Immunotherapy in bee sting hypersensitivity: Bee venom versus wholebody extract. Allergy 1979;34:369–78. [PubMed: 546252]
43. Reisman RE. Natural history of insect sting allergy: Relationship of severity of symptoms of initial sting anaphylaxis to resting reactions. J Allergy Clin Immunol 1992;90:335–9. [PubMed: 1345753]
44. Golden DBK, 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;351:668–74. [PubMed: 15306668]

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45. Graft DF, Schuberth KC, Kagey-Sobotka A, Kwiterovich KA, Niv Y, Lichtenstein LM, et al. A Prospective study of the natural history of large local reactions following Hymenoptera stings in children. J Pediatr 1984;104:664–8. [PubMed: 6716215]
46. Mauriello PM, Barde SH, Georgitis JW, Reisman RE. Natural history of large local reactions from stinging insects. J Allergy Clin Immunol 1984;74:494–8. [PubMed: 6491095]
47. Valentine MD, Schuberth KC, Kagey-Sobotka A, Graft DF, Kwiterovich KA, Szklo M, et al. The value of immunotherapy with venom in children with allergy to insect stings. N Engl J Med 1990;323:1601–3. [PubMed: 2098016]
48. Golden DBK, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of Hymenoptera venom immunotherapy. Ann Intern Med 1980;92:620–4. [PubMed: 7387002]
49. Bernstein JA, Kagan SL, Bernstein DI, Bernstein IL. Rapid venom immunotherapy is safe for routine use in the treatment of patients with Hymenoptera anaphylaxis. Ann Allergy 1994;73:423–8. [PubMed: 7978535]
50. Birnbaum J, Charpin D, Vervloet D. Rapid Hymenoptera venom immunotherapy: comparative safety of three protocols. Clin Exp Allergy 1993;23:226–30. [PubMed: 8472191]
51. Tankersley MS, Walker RL, Butler WK, Hagan LL, Napoli DC, Freeman TM. Safety and efficacy of an imported fire ant rush immunotherapy protocol with and without prophylactic treatment. J Allergy Clin Immunol 2002;109:556–62. [PubMed: 11898006]
52. Freeman TM, Hyghlander R, Ortiz A, Martin ME. Imported fire ant immunotherapy: effectiveness of whole body extracts. J Allergy Clin Immunol 1992;90:210–5. [PubMed: 1500625]
53. Brown SG, Wiese MD, Blackman KE, Heddle RJ. Ant venom immunotherapy: a double-blind placebo-controlled crossover trial. Lancet 2003;361:1001–6. [PubMed: 12660058]
54. Lockey RF, Turkeltaub PC, Olive ES, Hubbard JM, Baird-Warren IA, Bukantz SC. The Hymenoptera venom study III: Safety of venom immunotherapy. J Allergy Clin Immunol 1990;86:775–80. [PubMed: 2229842]
55. Mosbech H, Muller U. Side effects of insect venom immunotherapy: results from an EAACI study. Allergy 2000;55:1005–10. [PubMed: 11097308]
56. Golden DBK, Lawrence ID, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Clinical correlation of the venom-specific IgG antibody level during maintenance venom immunotherapy. J Allergy Clin Immunol 1992;90:386–93. [PubMed: 1527321]
57. Akdis CA, Blesken T, Akdis M, et al. Role of interleukin 10 in specific immunotherapy. J Clin Invest 1998;102:98–106. [PubMed: 9649562]
58. Konno S, Golden DBK, Schroeder J, Hamilton RG, Lichtenstein LM, Huang SK. Level of osteopontin is increased after bee venom immunotherapy. J Allergy Clin Immunol 2005;115:1317–8. [PubMed: 15940155]
59. Larche M, Akdis C, Valenta R. Immunological mechanisms of allergen-specific immunotherapy. Nat Rev Immunol 2006;6:761–71. [PubMed: 16998509]
60. Golden DBK, Kwiterovich KA, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Discontinuing venom immunotherapy: Outcome after five years. J Allergy Clin Immunol 1996;97:579–87. [PubMed: 8621842]
61. Golden DBK, Kwiterovich KA, Addison BA, Kagey-Sobotka A, Lichtenstein LM. Discontinuing venom immunotherapy: Extended observations. J Allergy Clin Immunol 1998;101:298–305. [PubMed: 9525443]
62. Muller U, Berchtold E, Helbling A. Honeybee venom allergy: results of a sting challenge 1 year after stopping venom immunotherapy in 86 patients. J Allergy Clin Immunol 1991;87:702–9. [PubMed: 2005323]
63. Randolph CC, Reisman RE. Evaluation of decline in serum venom-specific IgE as a criterion for stopping venom immunotherapy. J Allergy Clin Immunol 1986;77:823–7. [PubMed: 3711549]
64. Reisman RE, Lantner R. Further observations of stopping venom immunotherapy: comparison of patients stopped because of a fall in serum venom-specific IgE to insignificant levels with patients stopped prematurely by self-choice. J Allergy Clin Immunol 1989;83:1049. [PubMed: 2732405]
65. Urbanek R, Forster J, Kuhn W. Discontinuation of bee venom immunotherapy in children and adolescents. J Pediatr 1985;107:367–71. [PubMed: 4032132]

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66. Golden DBK, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. J Allergy Clin Immunol 2000;105:385–90. [PubMed: 10669863]

67. Lerch E, Muller U. Long-term protection after stopping venom immunotherapy. J Allergy Clin Immunol 1998;101:606–12. [PubMed: 9600496]

68. Muller U, Helbling A, Berchtold E. Immunotherapy with honeybee venom and yellow jacket venom is different regarding efficacy and safety. J Allergy Clin Immunol 1992;89:529–35. [PubMed: 1740583]

69. Reisman RE. Duration of venom immunotherapy: Relationship to the severity of symptoms of initial insect sting anaphylaxis. J Allergy Clin Immunol 1993;92:831–6. [PubMed: 8258617]