

Insect Sting Anaphylaxis

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Stinging insects of the order Hymenoptera can cause systemic allergic reactions including anaphylaxis, but such reactions are rare with biting insects. This article describes the clinical patterns and treatment of sting reactions, including 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 who have large local reactions 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 here, 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 also have been reported, including nephropathy, central and

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peripheral 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 also can 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 include respiratory complaints. Symptoms and signs of hypotension are uncommon in children but occur 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 anaphylaxis 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 who have 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 three 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 they have 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 caused by other species of stinging ants in Asia and Australia [16].

The immunochemical characteristics and immunogenetic relationships of the Hymenoptera venoms have been studied thoroughly [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 three 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 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 for preventing 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 now are known to have very low risk of anaphylaxis to stings.

Insect sting allergy can occur at any age, often following numerous 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 and elevated serum tryptase, suggesting a possible fatal sting reaction in some cases of unexplained sudden death [23,24]. The presence of IgE antibodies to Hymenoptera venom is not, in itself, however, unusual. Over 30% of adults stung in the previous 3 months showed venom-specific IgE by skin test or radioallergosorbent test (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 who have a history of anaphylaxis. Of the subjects who had initial positive skin tests, 30% to 60% became negative after 3 to 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; they often do not seek medical attention, and believe the reaction was a chance occurrence that 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 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 underestimated. Symptoms sometimes are 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 caused by anxiety/panic disorder or simple

fear. Insect sting challenge studies often have 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 who have had only large local reactions to stings, and in children who have had only cutaneous systemic reactions. There are also patients who request venom testing because of 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 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, the author found that all those who could be traced through family members were found to have had stings in early childhood that they could not 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 therefore can 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 $\mu\text{g}/\text{mL}$ to find the minimum concentration giving a positive result. Puncture tests at no more than 1 $\mu\text{g}/\text{mL}$ 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 five Hymenoptera venoms, a negative diluent (human serum albumin-saline) control, and a positive histamine control.

Skin test results are clearly positive in 65% to 85% of patients who have a convincing history. Negative skin tests in a history-positive patient can be

caused by 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; therefore, they should 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 two separate occasions before making the final therapeutic selection of venoms. Some cases of sting anaphylaxis appear to be non-IgE-mediated and may be related to subclinical 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 $\mu\text{g}/\text{mL}$ 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 that suppress skin tests) [32,35]. Another use of the RAST is to resolve the discordance when skin tests are negative in a patient who has 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 who have negative skin tests and positive RAST have been reported to have systemic reactions to subsequent stings, although the frequency may be lower than in patients who have 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. Excessive fear impairs quality of life, however, 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% to 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 does not 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 who have a history of large local reactions, and in children who have systemic reactions limited to cutaneous signs and symptoms (with no respiratory or circulatory manifestations) [44–47]. Venom immunotherapy is not required in these low-risk cases, but some patients still will request treatment because of their fear of reaction and the impact on their quality of life. Children who have 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 µg 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- to 3-day rush regimens are not associated with a higher frequency of adverse reactions to venom injections [49–51]. Treatment usually is 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 µg total dose), but complete protection is achieved in only 75% to 85% of patients using 100 µg 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% to 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 gradually have been elucidated, but remain sketchy. Venom IgE rises initially with treatment, then declines steadily over time toward very low levels after 5 to 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 increased gradually to every 6 to 8 weeks over several years. Venom skin tests or RASTs are repeated periodically, usually every 2 to 3 years, to determine when there has been a significant decline in venom IgE [11]. Skin tests generally remain unchanged in the first 2 to 3 years, but show a significant decline after 4 to 6 years. Less than 20% of patients are skin test negative after 5 years, but 50% to 60% become negative after 7 to 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 is stopped after 5 years, the chance of a systemic reaction will remain 10% 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 pretreatment 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 5 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].

Summary

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% to 10%) in large local reactors and in children with mild (cutaneous) systemic reactions, and risk varies between 25% and 70% in adults depending on the severity of 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 predict the severity of a sting reaction reliably. Venom sensitization can be detected in 25% of adults, so the history is most important. Venom immunotherapy is 75% to 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. Therapy then could be targeted to those most likely to benefit, and those who are sensitized but are not really in danger could be spared. 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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