

exists between the antigens in fire ant venom and the antigens in venoms of other Hymenoptera.^{52,53}

The Clinical Spectrum of Venom Allergy

Summary Statement 1: Evaluate patients with a history of a systemic reaction to an insect sting for the presence of venom-specific IgE. If venom IgE is present these patients are at increased risk for subsequent sting anaphylaxis, which can be prevented by VIT. (Strong Recommendation; A Evidence)

Summary Statement 2: Evaluate the patient for details of the history of any reactions to insect stings. (Strong Recommendation; B evidence)

Categories of Adverse Sting Reactions

Most insect stings are associated with normal transient local reactions characterized by pain, swelling, and redness, which usually last from a few hours to a few days and generally resolve with simple treatment measures. Adverse reactions to stings may be allergic or nonallergic, with local or systemic manifestations. Some local reactions are IgE mediated, with intense and prolonged local induration and swelling (large local reactions, see below). Systemic allergic reactions can run the full spectrum of signs and symptoms of anaphylaxis, from the mildest (generalized erythema, pruritus, and hives), through mild anaphylaxis, to the most severe anaphylaxis (hypotensive shock or respiratory obstruction and arrest). Cardiac anaphylaxis can cause myocardial ischemia (Kounis syndrome) or arrhythmias.^{35,54} Unusual reactions have been reported, including neuropathies, seizures, renal failure (with rhabdomyolysis), serum sickness, and hemorrhagic episodes, including metrorrhagia.⁵⁵ These reactions are mostly toxic in nature and delayed in onset, but the mechanism of many of the unusual reactions is not known.

Definitions of Specific Venom Allergy Conditions

Insect stings can trigger a range of immune and clinical responses. It is common for venom-specific IgE antibodies to be induced by an insect sting, although this is more often transient than persistent. Stings also induce production of IgG antibodies.

Large local reactions (LLRs) are abnormally large localized reactions contiguous with the Hymenoptera sting site. Although occasionally rapid in onset, the swelling usually increases 6 to 12 hours after the sting, progresses in 24 to 48 hours, and subsides after 3 to 10 days. There is no universal definition of a LLR, but the induration is often larger than 10 cm in diameter and can involve an entire extremity (crossing joint lines). These reactions represent late-phase IgE-associated inflammatory responses to venom allergens. They do not represent cellulitis even though lymphangitic streaks may be present. They are generally not dangerous but can occasionally cause a compartment syndrome in some anatomically constrained places and could cause airway compromise if the sting occurs in the oropharynx (eg, after drinking from a straw or canned beverage).^{31,56}

Systemic reactions (SRs) are typically IgE mediated and may present with a variety of symptoms, involving multiple organ systems.⁵⁷ Cutaneous symptoms may include pruritus, flushing, urticaria, and angioedema. Respiratory symptoms may include stridor, wheezing, and dyspnea. Gastrointestinal symptoms can include abdominal cramping, nausea, vomiting, and diarrhea. Cardiovascular symptoms and signs are usually related to hypotension and may include lightheadedness, syncope, or cardiovascular shock. Cardiac anaphylaxis can cause arrhythmias or the symptoms and signs of acute coronary insufficiency or myocardial infarction. This is attributable to the high concentration of mast cells near the coronary arteries and cardiac conduction fibers.³⁵ Kounis syndrome or allergic angina is the occurrence of the symptoms and signs of angina coincident with an acute allergic reaction and has been

reported after Hymenoptera sting.⁵⁴ Systemic reactions to stings must be differentiated from toxic reactions or anxiety reactions (often subjective symptoms with no objective signs). The pattern and timing of symptoms, the presence of objective signs, and the response to treatment may help clarify the nature of the reaction. Measurement of serum tryptase early in the reaction may provide evidence of anaphylaxis if levels are elevated or significantly increased from basal level.^{58,59}

Serum sickness–like reactions to stings have occurred and may be associated with the presence of venom-specific IgE, but the mechanism of the reactions and the risk of anaphylaxis are unknown.⁶⁰ Cold urticaria and cold-induced anaphylaxis have been reported after insect stings, generally without anaphylaxis.^{61,62}

Prevalence, Natural History, and Prevention

Epidemiology of Venom Allergy

The prevalence of LLRs in the general population is approximately 10%, with estimates ranging from 2.4% to 26.4%, and higher among beekeepers (14%–43%).^{56,63} The results of skin testing and/or specific IgE testing are reported to be positive in up to 80% of individuals with LLRs.^{16,56}

The prevalence of SRs ranges from 0.5% to 3.3% in US reports and from 0.3% to 7.5% in European reports.⁶ The rates of SRs among children are lower, ranging from 0.15% to 0.8%.⁶³ Fatality from insect sting anaphylaxis accounts for 20% of all cases of any-cause fatal anaphylaxis, with an incidence of 0.03 to 0.48 fatalities per 1 million population.⁶³ In the United States, there are at least 40 deaths annually due to insect sting anaphylaxis, although this is believed to be underreported.^{5,64} Biphasic anaphylactic reactions are associated with the most severe events but may be less frequent in insect sting allergy than other causes of anaphylaxis.

Venom sensitization is common in the general population, estimated to be between 9.3% and 28.7%.⁶³ In the months after a sting, transient sensitization occurs in up to 40% of adults.⁷ This high frequency of asymptomatic sensitization gives the tests a very limited positive predictive value in the absence of a clinical history of allergic reaction to a sting. For this reason, venom testing cannot be used to screen asymptomatic children or adults.¹⁰ Atopy is associated with venom sensitization but not with allergic reactions to stings.

The frequency of insect stings in the general population depends largely on climate and risk of exposure. Between 56% and 94% of the adult population report being stung at least once.^{6,63,65} Attack rate is estimated at 10% per year for yellow jackets and up to 50% for IFAs in endemic areas.⁶⁶

Natural History and Factors Influencing the Occurrence of Allergic Reaction

The clinical history is paramount in predicting the chance of future allergic reactions to stings. Asymptomatic sensitization is associated with a relatively low risk of systemic reaction to future stings, estimated at 5% to 15%.^{9,10} When systemic reactions occur, they can range from the mildest to the most severe manifestations of anaphylaxis. Unfortunately, there is no test that can distinguish those who will react to future stings and those who will not, and no test other than basal serum tryptase that can predict how severe a reaction might be.

Patients with a history of LLRs have an approximately 7% chance of systemic reaction to a future sting (range, 4%–15%) in both adults and children. Like the other low-risk sensitized individuals, some of these reactions will be severe, and many will be relatively mild (eg, cutaneous).^{1–3,16,67}

The frequency of systemic reaction to a future sting in patients with a history of systemic reactions to stings is approximately 50% (range, 25%–75%).^{11–13,15} The chance of reaction is in the lower end