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INSECT STING HYPERSENSITIVITY

As spring and summer approach and people look to spend more time engaged in outdoor activities, it is timely that we discuss insect sting hypersensitivity. Patients with previous allergic reactions to insect stings are especially nervous. Most importantly, patients with mast cell disorder are at risk of future life-threatening reactions from insect stings. It is critical that clinicians are able to provide information about available treatment options. This review will discuss the approach to the diagnosis and treatment of insect sting hypersensitivity.

ADVERSE REACTION TO STING INSECTS

There are fundamentally two types of IgE-mediated reactions to insect stings. The first type is the large local reaction (LLR) which is defined by swelling contiguous to the site of the sting. This swelling increases in size over the following 24 to 48 hour period and resolves 3 to 10 days later.[1] There is no universal definition of a LLR, however, the swelling can be larger than 10 cm in diameter around the sting site and can affect the entire extremity. This local reaction may lead to lymphangitis, often confused with cellulitis. It can be differentiated from cellulitis by its early onset (after 1-2 days) and also by the absence of fever or other markers of infections, such as an increase in WBC or neutrophilia. The risk of a systemic reaction in patients who experience a large local reaction is less than 10%.[1] In general, a LLR is not dangerous but may lead to significant impact to local tissue from local swelling. The exception to this is an unfortunate sting occurring accidentally in the oropharynx. A 30-year-old female who had a sting in her upper palate after drinking from a soda can where an insect was hidden ended up in the emergency room two hours later with significant swelling of the oropharynx with airway compromise from progressive swelling that extended to the oropharyngeal region.

Systemic reactions (SR) are characterized by any signs and symptoms distant from the initial sting site. These reactions can be further divided into cutaneous (CSR) and anaphylactic reactions. CSR usually present with generalized pruritus, flushing, urticaria and angioedema. These are commonly seen in children but uncommon in the adult population. Anaphylaxis involves different systems including the skin (urticaria, angioedema, flushing, and pruritis), gastrointestinal system (difficult or painful swallowing, nausea, vomiting, diarrhea, and abdominal cramps), respiratory system (bronchospasm, coughing, respiratory distress, upper and lower obstruction), cardiovascular system (hypotension) and sometimes neurological symptoms (loss of consciousness, etc.). The cardiovascular and respiratory symptoms constitute both a serious and potentially life threatening event for the patient. The onset of SR is usually seen within 20 minutes in 75% of patients and within 40 minutes in 87% of insect sting anaphylaxis. Laryngeal edema and circulatory failure are the most common causes of death from an insect sting anaphylaxis reaction and half of the fatal reactions occur in people with no prior history of systemic reaction to a stinging insect.[1,2]

CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE[1]

Recommendation Rating Scale

Category of Evidence

- Ia Evidence from meta-analysis of randomized controlled trials
- Ib Evidence from at least one randomized controlled trial
- IIa Evidence from at least one controlled study without randomization
- IIb Evidence from at least one other type of quasi-experimental study
- III Evidence from non-experimental descriptive studies, such as comparative studies
- IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of Recommendation

- A Directly based on category I evidence
- B Directly based on category II evidence or extrapolated recommendation from category I evidence
- C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
- LB Laboratory Based
- NR Not rated

NATURAL HISTORY

The importance of defining the type of allergic reaction is paramount in insect sting reactions. The history of the reaction will allow for a proper diagnosis and clear approach to patient counselling about their risk of future reactions.

There are people in the community who have asymptomatic sensitization and their risk of future SR is low (estimated at 5-15%). Unfortunately, there is no diagnostic test that can predict future reactions in this population other than baseline serum tryptase. It should be noted that high serum tryptase levels have prognostic implications, with higher risk for SR to stinging insects in future and failure to respond to venom immunotherapy (VIT).[1] As a result, it is not recommended to perform any investigation in those patients without a history of reaction.[3]

Patients with a history of LLR have a risk of systemic reaction of approximately 4-15% if re-stung and some of these reactions can be severe.[4]

In patients with a history of SRs, the risk of future anaphylaxis to stings is 40-60%. The severity of the reaction will depend on the severity of the previous reaction. Among those who have had a severe reaction, the risk of having a future severe reaction is increased.[5] Among patients with a history of CSR, there is an approximate 10% risk of future SR and a 3% chance of a more severe reaction.[5]

The risk of future SR is associated with elevated tryptase levels, use of antihypertensive medications (i.e. ACE inhibitors), increased age, beekeeper occupation, and multiple stings or sequential stings (within weeks or months of each other). One other issue that clinicians may encounter in clinical practice is the degree of sensitivity (skin test or specific serum IgE) which correlates with the frequency of reaction rather than severity. This is important as many patients believe that the larger the skin test size, the greater the likelihood of a more severe reaction.[3]

PREVENTION OF INSECT STING REACTION/ALLERGIC REACTION

There are effective measures that have been recommended for patients with a history of SR (**recommendation: D evidence**):

1. Measures to avoid insect stings[2]
   a. Minimize preparing, grilling or eating outdoors
   b. Minimize flowering plants
   c. Minimize drinking from straws, cans or bottles when outdoors
   d. Remove fallen fruits near lounging areas
   e. Cover trashcans
   f. Watch for nests in bushes or in the ground when mowing
   g. Avoid walking barefoot (**recommendation: D evidence**)

2. Discuss the need to have access to an epinephrine autoinjector with education on its indication and its use (**strong recommendation: C evidence**)

3. Referral for evaluation by an allergist/immunologist for diagnosis and long-term therapy. (**strong evidence: D evidence**)

One of the important discussions to have with patients is the use of an epinephrine autoinjector. When counselling patients, it is important to focus on why and when the autoinjector should be available. Although this is prudent in high-risk patients for future reactions, there is also a burden to the patient such as inconvenience, cost and fear of use that accompany the epinephrine prescription.[6] From anecdotal experience, patients with a history of insect sting anaphylaxis who are undergoing VIT have a better quality of life in comparison to those who carry an epinephrine autoinjector. For patients with a history of large local reactions or CSR, the risk of a systemic/anaphylactic reaction is low, and it is important to discuss their low risk of anaphylaxis with them so that they can make an informed decision about whether carrying an epinephrine autoinjector is needed for personal security.

WHO NEEDS VENOM IMMUNOTHERAPY?

One of the only types of anaphylaxis for which VIT has been proven highly effective is insect sting anaphylaxis. The indication for VIT is a history of insect sting anaphylaxis plus evidence of an allergy by way of either positive intradermal venom test or the presence of venom-specific IgE. Clinicians are reminded that positive intradermal testing does not predict severity of future sting reactions. The consulting allergist is often asked to investigate patients who have family members with serious or fatal reactions to stings. There is no current evidence of increased risk of insect sting allergy (ISA) in first degree family members of these patients. Moreover, testing family members without history of insect stings may lead to increased anxiety and negative impact on their quality of life. For patients with CSR and LLRs, venom immunotherapy is not indicated as the risk of a more severe anaphylactic reaction remains low. However, among those with frequent exposures and reactions leading to poorer quality of life, VIT may result in a decrease in local swelling yielding benefit for the affected patient.

Among those patients who have a remote history of severe SR, the relative risk of these patients does not decline over time. In children who did not receive VIT, systemic reactions can occur within 20 years if re-stung.[7] This important point suggests that a re-assessment of venom allergy status is needed with the possibility of VIT.

The detection of specific IgE antibodies in serum is less sensitive than skin testing. However, in situations where venom skin testing is not an option i.e., severe atopic dermatitis or due to chronic concurrent medication usage (antihistamines), serum specific IgE-testing may be the only way of assessing allergy status. Ultimately, the patient's clinical history remains the basis for guiding and informing the best treatment practice. Alternatively, there are many factors that may lead to a person having a negative skin test despite a positive history. These factors include systemic diseases such as mastocytosis. Mastocytosis presents with severe systemic allergic reactions and increased serum tryptase levels. Patients with mastocytosis have demonstrated an increased risk of future severe anaphylactic reactions, including during desensitization to VIT injection. As a result, these patients are at risk of treatment failure, and/or increased relapse rate if VIT is stopped. Mastocytosis may present in up to 2% of patients with insect sting anaphylaxis.[1] Clinicians should consider measuring serum tryptase levels in patients who have had a severe life-threatening reaction, hypotension as well as those with a negative allergy skin test (positive history).[1]

VENOM IMMUNOTHERAPY AND EPINEPHRINE AUTOINJECTOR

VIT significantly reduces the risk of future SR by greater than 95% among those individuals sensitized. After diagnostic confirmation of ISA, VIT should be recommended. VIT to the honeybee, yellow jacket, hornet, and wasp is an extremely effective approach for those patients with SR to a sting. It reduces the risk of subsequent sting anaphylaxis from 60%

in the untreated population to less than 5% in treated patients.[1] These patients should naturally be informed of the goal of the treatment which is to prevent a severe anaphylactic reaction. Secondary goals of reduction of anxiety around insect sting reactions is also achieved.[1] These patients should continue to have an epinephrine autoinjector available.

Among individuals who have a low risk of systemic anaphylactic reaction, such as those with a LLR or CSR where the risk of anaphylaxis remains less than 5% with re-stings, the clinical conundrum centers on whether these patients need VIT. Sometimes this decision can be confusing for patients in whom venom immunotherapy is not recommended but to whom access to an epinephrine autoinjector is provided. Prescribing an epinephrine autoinjector can cause impairment in the patient's quality of life[7] and this situation may be better addressed with discussion using a shared decision making model which involves both the patient and their family.

The current recommendation for the duration of the VIT is 3-5 years (**strong recommendation; B evidence**). However, there are risk factors that may necessitate the need for VIT to be considered lifelong therapy such as in those patients with a severe reaction before VIT (severe respiratory distress, hypotension, or syncope, etc.), systemic reaction during the VIT, honeybee allergy and increased serum tryptase level (**strong recommendation; C evidence**).[1]

Allergic reactions to insect stings can be life-threatening and negatively impact the lives of those individuals affected. It is crucial that we remember the importance of shared decision making with patients and their families and offer VIT in those individuals found to be at high risk of systemic allergic reactions. VIT is an effective treatment to reduce the future risk of having a severe life-threatening anaphylactic reaction. Helping patients venture outside their homes is an important quality of life improvement that allergists can offer to their patients. Insect sting hypersensitivity causes a great deal of anxiety and helping patients overcome it can be tremendously rewarding.

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