significantly reduces the chance of sting anaphylaxis.[124,132,133] Honeybee venom allergy correlated with higher risk of systemic reaction than vespid venom allergy. There was also a correlation of severe anaphylaxis to a sting with the use of antihypertensive medications (β-blockers and ACEIs). This has been reported in relation to immunotherapy and anaphylaxis in general. Patients with mastocytosis who are taking these antihypertensive medications should consult their physicians about the possibility of changing to an alternative medication (if it is safe and effective). Fatal anaphylaxis has been reported in patients with mastocytosis who discontinued VIT.[134,135]

When to discontinue VIT remains controversial. However, the historical recommendation of 3- to 5-year VIT may not be optimal for venom allergic patients with mastocytosis. Patients with mastocytosis have lower probability of long-term protection and consequently a greater risk for recurrent severe, even fatal anaphylaxis if they discontinue VIT.[134,135] In a thorough review, Bonadonna et al[136] recommend VIT for life in patients with mastocytosis and venom allergy. Because the efficacy of VIT is less than optimal in patients with mastocytosis, they should continue to carry 2 epinephrine injectors.[124]

Because there appears to be a high correlation with mastocytosis when the basal tryptase level exceeds 11.4 ng/mL, this diagnosis should be entertained (and basal serum tryptase measured) in patients with severe anaphylaxis from Hymenoptera, especially when there was hypotension (and/or the absence of urticaria). The frequency of elevated basal serum tryptase level is 25% in patients with Mueller grade IV sting anaphylaxis but is approximately 5% in patients who had mild-to-moderate systemic reactions to stings (grade I, II, III) in whom the clinical significance is less clear.[24] Some experts suggest that the evaluation of all patients with a history of a systemic reaction to Hymenoptera should include measurement of the basal serum tryptase.[80,136] If clonal mast cell disease is suspected, initial evaluation for venom-specific IgE should begin using in vitro methods, with skin testing in those individuals who test negative using in vitro methods. If the serum tryptase is elevated (>11.4 ng/mL) bone marrow biopsy should be considered. Mastocytosis can occur with normal serum tryptase.[129] There is a cost and burden associated with abnormal results of basal tryptase (eg, bone marrow biopsy, consultation with other specialists, anxiety associated with an abnormal test result). However, an abnormal result is associated with more chance of severe anaphylaxis to stings, greater chance of systemic reactions during VIT (to a sting or venom injection), and increased chance of sting anaphylaxis after stopping VIT. The potential benefits and risks of ordering the test should be considered with each patient.

Summary Statement 11: Consider testing patients with mastocytosis for insect venom sensitivity and identify other high risk factors for severe anaphylaxis to stings (including medications). (Recommendation; D evidence) Discuss with the patient the benefits and risks for testing and for VIT.

Individuals with known mastocytosis may warrant being tested for Hymenoptera venom sensitivity because insect stings are the most common cause of anaphylaxis in such patients. In patients with mastocytosis, sting anaphylaxis is more likely to occur and more likely to be life-threatening, and the risk can be significantly reduced with VIT. The frequency of sting anaphylaxis in patients with mastocytosis and positive skin or serum test results for venom IgE is not known. The positive predictive value of venom-IgE tests in asymptomatic, healthy individuals is poor. Nevertheless, it is the opinion of this work group that, when test results are positive for venom IgE in patients with mastocytosis, the clinician should discuss with the patient the potential benefits and risks of VIT. The presence of other high-risk factors (Table 1) would be likely to further increase the risk of severe anaphylaxis to a sting and would add to the strength of recommendation for VIT. It is not known whether children with mast cell disorders (particularly those with urticaria pigmentosa) have the same risks as adults.

It seems likely that dysregulation of other mediators of anaphylaxis will be found to correlate with the frequency or severity of reactions to stings. It has already been confirmed that levels of platelet-activating factor (PAF) and PAF-acetylhydrolase correlate with the severity of sting anaphylaxis and with fatal anaphylaxis.[137,138]

Management of Venom/Insect Allergy

Treatment of Acute Sting Reactions

Summary Statement 12: Advise the patient to treat acute systemic reactions to insect stings like any anaphylactic reaction, with timely

12a. epinephrine injection (Strong Recommendation; A evidence),
12b. supportive therapy (Strong Recommendation; A evidence), and
12c. transport to an emergency department. (Strong Recommendation; C evidence)

Epinephrine is the drug of choice for the treatment of anaphylaxis.[139,140] The recommended dose is 0.01 mg/kg, up to 0.3 mg in children, and 0.3 to 0.5 mg in adults, depending on the severity of the reaction. Intramuscular injection in the anterolateral thigh will achieve a more rapid and higher plasma concentration than subcutaneous or intramuscular injection in the arm.[141,142] Delayed use of epinephrine might be ineffective.[143] Reports of fatal and near-fatal anaphylaxis reveal that fatal outcome is associated with delay or lack of administration of epinephrine.[144–146] Patients allergic to insect venom should carry epinephrine at an appropriate dosage for administration in case of a sting. Patients and caregivers of children who have experienced a systemic reaction to an insect sting should be taught how to administer epinephrine and under what circumstances to do so. They should be instructed to follow the package inset for managing the device, including protecting it from excess heat. There is no contraindication to the use of epinephrine in a life-threatening situation, such as anaphylaxis. Repeat dosing might be required for persistent or recurrent symptoms, so more than 1 unit should be prescribed, particularly for those with severe reactions or those who live or spend time in locations distant from medical attention. Patients who also have cardiovascular disease should be given epinephrine for use in the event of an allergic reaction, despite concern about epinephrine's cardiac effects, because the risk of a life-threatening anaphylactic reaction is judged to exceed the risk of administering epinephrine in such patients (even in those using a â-blocker medication). Antihistamines and corticosteroids should not be considered substitutes for epinephrine. In patients who have a relatively low risk of anaphylaxis from a sting, the need to carry injectable epinephrine can be determined by the patient and physician after discussion of the relative risk of reaction in addition to the cost and burden of having to carry epinephrine. Patients with a low risk of reaction include those with a history of only large local reactions to stings or of strictly cutaneous systemic reactions, those receiving maintenance VIT, and those who have discontinued VIT after more than 5 years of treatment. Factors associated with a higher risk include a history of extreme or near-fatal reactions to stings, systemic reactions during VIT (to an injection or a sting), a history of anaphylaxis to a honeybee sting, increased basal tryptase levels, underlying medical conditions or concomitant medications, or frequent unavoidable exposure to stinging insects.

Summary Statement 13: Treat large local reactions symptomatically, with antihistamines, cold compresses, and analgesics as needed. In severe cases a short course of oral corticosteroids may be useful. Antibiotics are usually not necessary. (Recommendation; D evidence)