What's Eating You? Bees, Part 2: Venom Immunotherapy and Mastocytosis

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Bee stings are common in the United States. In part 1 of this series, we reviewed the characteristics of bumblebees, honeybees, and Africanized honeybees; the types and pathophysiology of sting reactions; and the medical management and prevention of bee stings. In this article, we review the concepts and practice of venom immunotherapy. We further discuss the diagnosis of systemic mastocytosis, initially presenting as anaphylaxis, and the efficacy of immunotherapy in patients with mastocytosis.

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A systemic bee sting reaction can affect individuals of any age, and it is difficult to predict who might be most at risk. Large local reactions occur in 10% to 15% of adults, whereas systemic reactions possibly leading to anaphylaxis occur in only 0.5% to 3.0% of adults and 0.4% to 0.8% of children.[1-3] After an individual has been stung and the reaction has been evaluated, the risk for a future systemic response can be better predicted. Age of occurrence and extent of the first reaction are the best predictors of how a future sting reaction will manifest, though variations in severity do occur.[4-6] Although adults with large local reactions might demonstrate venom-specific immunoglobulin E (IgE) antibodies, there is little likelihood (5%–10%)[3,7-9] of progression to an anaphylactic reaction in subsequent stings. The risk for future systemic reactions is 10% to 20% for individuals who have experienced mild systemic reactions[9] and for most children,[10] whereas the risk can be as high as 60% for individuals who have had severe anaphylactic reactions.[9,11] Indeed, repeat episodes of anaphylaxis are more common in adults than children.[3]

The amount of time between stings can be a mitigating factor. The risk for hypersensitivity to bee stings decreases as the time between stings increases, resulting in spontaneous resolution.[1,6,12] The risk for a hypersensitivity reaction decreases from more than 50% to 35% three to 5 years after an initial sting. The risk is further reduced to 25% after 10 years.[6,8,12] For some, however, the risk remains high, even without a recent sting.[12]

Predicting who might be at risk for anaphylaxis from bee stings, other than someone who had already experienced a severe systemic reaction, is difficult.[13] Even a history of atopy appears to convey minimal increased risk,[7] except perhaps in beekeepers, who have frequent exposure to bees.[14] Thus, systemic allergic reactions warrant referral to an allergist and consideration of immunotherapy after the immediate sting has been controlled.

Immunotherapy

The purpose of immunotherapy is to increase a sensitive patient's tolerance to venom exposure in a subsequent sting. Theoretically, it stimulates an increase in venom-specific immunoglobulin G titers while decreasing venom-specific IgE antibodies.[13,15] The relationship between the levels of antibodies and the efficacy of immunotherapy, however, is variable. It has been shown that immunotherapy prompts a shift in type 2 helper T cells (T_H2) to type 1 helper T cells (T_H1) in cytokines, in particular interleukin 10, though this is an incomplete explanation of the

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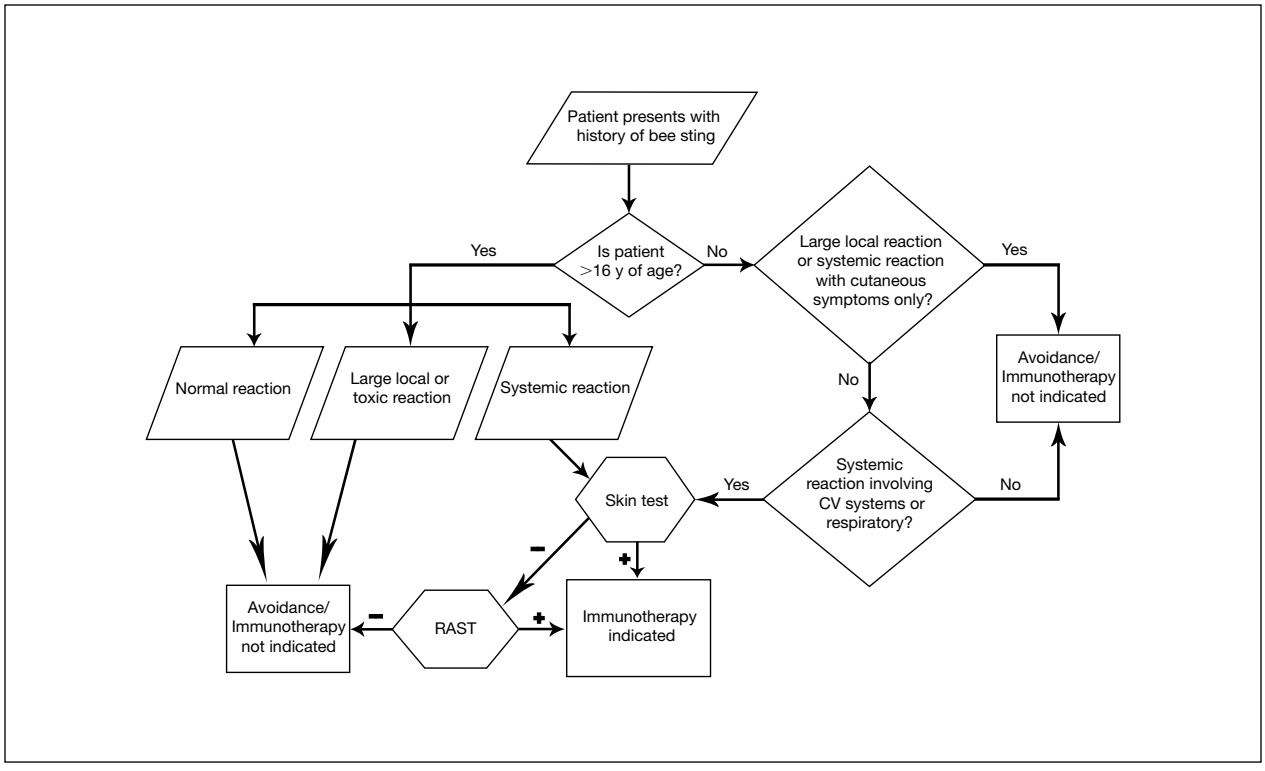

Figure 1. Patient selection for venom immunotherapy. CV indicates cardiovascular; RAST, radioallergosorbent test.

mechanism of protection.[16,17] At the very least, immunotherapy reduces the release of mediators and suppresses the late-phase inflammatory response.[16]

Figure 1 provides an algorithm for patient selection for venom immunotherapy. The primary goal of immunotherapy is preventing life-threatening reactions.[2] Based on the natural history of insect sting allergies and the relatively low (≤20%) risk for a future anaphylactic reaction,[4] not everyone who reacts to bee stings will require immunotherapy. In the absence of a generalized reaction, immunotherapy is not recommended or required[18] because a positive skin test without a systemic reaction occurs in 15% to 25% of the general population.[1,4,6] Immunotherapy is not indicated when a patient demonstrates venom-specific IgE antibodies but does not have a sting history consistent with an allergic reaction.[12,18] Immunotherapy also has not proved necessary for children who have had only cutaneous symptoms without cardiovascular or respiratory complaints because their risk for progressing to a more severe systemic reaction is low (5%–10%).[10] In general, immunotherapy only is indicated for adults or children who have experienced an anaphylactic reaction, or adults with generalized cutaneous reactions who have demonstrated venom-specific IgE antibodies with a positive skin test or radioallergosorbent test (RAST).[2,3,18,19] Adults and children who have exhibited systemic reactions, especially reactions that developed quickly and/or involved cardiovascular or respiratory symptoms, have a very high risk of future anaphylaxis and are prime candidates for immunotherapy. In some cases, a person with a past systemic reaction will have a negative skin test or RAST. Although it is not clear why a negative skin test or RAST occurs, these individuals should not receive immunotherapy.[2,15] It has been proposed, however, that because immunotherapy has provided some protection for individuals who have only suffered large local reactions, it also might be considered in individuals, such as beekeepers, who are at continued risk for being stung.[5,20]

The primary risk of venom immunotherapy is an allergic response after injection—from mild site reactions to full anaphylaxis—occurring in 3% to 12% of patients.[2,11] Therefore, injections should be given in a setting where anaphylaxis can be recognized and promptly treated.[2,15] Individuals who experience systemic reactions during immunotherapy might take longer to reach the maintenance dose and, therefore, are less likely to achieve venom protection.[21] Premedication with antihistamines has been shown to reduce a delay in protection without reducing the efficacy of the therapy.[22] The relative contraindications for immunotherapy include conditions that would

prevent or hinder the effects of epinephrine in treating anaphylaxis, such as taking beta-blockers, angiotensin-converting enzyme inhibitors, tricyclic antidepressants, or monoamine oxidase inhibitors, or having severely uncontrolled asthma or cardiovascular conditions.[2,18]

The intradermal skin test is the most sensitive test for venom-specific IgE antibodies.[2,4] This test usually is performed no earlier than 3 or 4 weeks after the inciting sting to lessen the possibility of a false-negative test resulting from an anergic refractory period.[3,20,23] After initially gathering a history of sting reactions, the allergist will conduct an intradermal skin test with very dilute quantities of venom, gradually increasing to 1.0 μg/mL. A positive reaction, indicating circulating IgE specific to the venom, results in the development of a wheal and flare within 15 minutes that is 5 mm larger than the wheal of a negative control.[15] When skin testing is impractical (eg, extensive skin disease) or the skin test is negative in the face of a past systemic reaction, then an in vitro test (RAST), although not as sensitive, is acceptable for diagnosis.[11,23,24]

When a positive skin test or RAST has been obtained and the results correlate with the sting history, then an immunotherapy schedule is selected. Initially, dosages of very dilute (1000- or 10,000-fold dilution of maintenance dose) venom are injected, with gradual increases in dosage twice weekly for 14 weeks or once weekly for 28 weeks.[18] When the maintenance dose (100 μg, twice the amount of venom in a single honeybee sting)[2,4,15] is reached, the interval between injections gradually increases to once every 4 to 8 weeks.[2]

Maintenance therapy generally is continued for at least 3 to 5 years, but the duration should be individualized for each patient.[18,23] At present, neither loss of skin test reactivity nor RAST sensitivity are used as criteria for discontinuing immunotherapy.[2,7] After completing the treatment regimen, approximately 2% to 4% of patients will experience an anaphylactic reaction.[11,25] There is an overall 4% to 15% risk for future reaction[26] and a 17% cumulative frequency 10 years after treatment is ended[27]; however, most systemic reactions following immunotherapy are milder than those without immunotherapy.[3,4] Individuals who initially suffered a severe anaphylactic reaction are at greatest risk for subsequent reactions and may choose to continue allergen immunotherapy indefinitely.[20] Thus, it is still necessary for an allergic individual to carry an epinephrine auto-injector and be instructed on its use because immunotherapy does not always provide persistent immunity.[5]

Systemic Mastocytosis and Anaphylaxis

Of all the conditions that are included in the differential diagnosis for anaphylaxis,[19] perhaps the condition of greatest interest to dermatologists is systemic mastocytosis. In some patients without cutaneous signs of mastocytosis, anaphylaxis (which may or may not be IgE mediated)[28] might be the first clinical indication of this condition.[29] Hymenoptera stings, in particular, cause mast cell degranulation, which in turn causes histamine release. This process occurs in patients with mastocytosis at an overwhelming rate and results in an anaphylactoid reaction.

To differentiate individuals with systemic mastocytosis from individuals with strictly systemic anaphylaxis, it is diagnostically useful to determine serum levels of alpha-tryptase (secreted constitutively) and beta-tryptase (secreted during mast cell degranulation), with a B12 monoclonal antibody capture assay (measures alpha-tryptase and beta-tryptase) and a G5 monoclonal antibody capture assay (measures only beta-tryptase)[30] in the immediate management phase. In the absence of anaphylaxis, a patient with mastocytosis secretes a high basal rate of alpha-tryptase,[30] whereas levels of secreted beta-tryptase correlate well with the clinical severity of anaphylaxis in victims with or without mastocytosis.[29,31,32] In an acute setting, a ratio of alpha-tryptase and beta-tryptase to beta-tryptase of 20 or more is indicative of mastocytosis, whereas a ratio of 10 or less indicates a primary anaphylactic event (a normal ratio is approximately 13.5).[30,32] These measurements ideally should be drawn between 1 and 1.5 hours after the onset of anaphylaxis, when serum tryptase levels peak. Levels generally remain elevated for up to 6 hours postreaction.[31,33] In the event of death, elevated serum tryptase levels are not specific to anaphylaxis and should not be considered the primary cause of death.[34]

A patient with a confirmed diagnosis of mastocytosis is especially susceptible to severe systemic sting reactions. Therefore, after the immediate life-threatening event concludes, any patient with an elevated tryptase ratio consistent with mastocytosis should undergo a thorough workup. Initially, the patient should be inspected for cutaneous signs of mastocytosis because approximately 80% of patients will have skin findings.[35] The most common findings are urticaria pigmentosa (Figure 2), though telangiectasia macularis eruptiva perstans or mastocytomas may be present. These lesions may be few and subtle or even absent. Faint macules or nodules will have a positive Darier sign (urticaria with surrounding erythema induced by rubbing).[36] A biopsy should be performed on any suspicious lesion for histologic confirmation of

Figure 2. Urticaria pigmentosa. Photograph © Bernard Cohen, MD; Dermatlas (http://www.dermatlas.org).

mastocytosis.[37] Under the microscope, the biopsy may demonstrate large mononuclear cells (15 or more) with basophilic cytoplasm densely aggregated in the papillary dermis, confirmed preferably with tryptase immunohistochemistry or stained with Giemsa or toluidine blue.[35] A lack of skin lesions, however, does not exclude mastocytosis.[36] The gold standard for diagnosis is a bone marrow biopsy demonstrating confirmed mast cell infiltrates.[35,38] Without skin findings or a positive bone marrow histology, 3 of the following minor diagnostic indicators are necessary: atypical mast cell morphology (eg, spindle cells); elevated serum basal tryptase levels (>20 ng/mL); bone marrow with CD2, CD25, and CD35 expression; and a positive codon 816 c-*kit* mutation in an extracutaneous location (eg, peripheral blood, visceral organ, bone marrow).[35]

Systemic mastocytosis and/or an elevated basal tryptase level is a significant risk factor for a severe or fatal anaphylactic reaction to a bee sting because patients are more prone to immediate systemic reactions.[29,32,37,39] Patients with confirmed mastocytosis and a history of a systemic sting reaction might have a negative skin test and RAST.[28] Nonetheless, venom immunotherapy should be strongly considered in patients with mastocytosis because immunotherapy has been shown to reduce the severity of reactions on subsequent stings, albeit with less efficacy than in an individual without mastocytosis.[32,38,40] Because efficacy might require maintenance doses of venom immunotherapy, several investigators recommend that immunotherapy be continued indefinitely.[29,32] The patient also should be thoroughly counseled on the necessity of carrying an epinephrine autoinjector[38] and on other preventive measures.

Comment

In summary, long-term venom immunotherapy should be strongly considered for individuals who have suffered life-threatening reactions to bee stings. Other candidates are those with known systemic mastocytosis and those who come into frequent contact with bees and have suffered large local reactions. Systemic mastocytosis itself may initially present as anaphylaxis, so this should always be included in the differential diagnosis in patients with severe reactions to bee stings.

REFERENCES

1. Golden DB, Marsh DG, Kagey-Sobotka A, et al. Epidemiology of insect venom sensitivity. *JAMA*. 1989;262:240-244.
2. Portnoy JM, Moffitt JE, Golden DB, et al. Stinging insect hypersensitivity: a practice parameter. *J Allergy Clin Immunol*. 1999;103:963-980.
3. Yates AB, Moffitt JE, de Shazo RD. Anaphylaxis to arthropod bites and stings: consensus and controversies. *Immunol Allergy Clin North Am*. 2001;21:635-651.
4. Golden DBK. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol*. 2005;115:439-447.
5. Hamilton RG. Diagnosis of Hymenoptera venom sensitivity. *Curr Opin Allergy Clin Immunol*. 2002;2:347-351.
6. Reisman RE. Natural history of insect sting allergy: relationship of severity of symptoms of initial sting anaphylaxis to re-sting reactions. *J Allergy Clin Immunol*. 1992;90:335-339.
7. Antonicelli L, Bilo MB, Bonifazi F. Epidemiology of Hymenoptera allergy. *Curr Opin Allergy Clin Immunol*. 2002;2:341-346.
8. Mauriello PM, Barde SH, Georgitis JW, et al. Natural history of large local reactions from stinging insects. *J Allergy Clin Immunol*. 1984;74:494-498.
9. Golden DBK. Insect allergy. In: Adkinson NF, Yunginger JW, Busse WW, et al, eds. *Middleton's Allergy: Principles and Practice*. 6th ed. St. Louis, Mo: Mosby; 2003:1475-1486.
10. Valentine MD, Schuberth KC, Kagey-Sobotka A, et al. The value of immunotherapy with venom in children with allergy to insect stings. *N Engl J Med*. 1990;323:1601-1603.
11. Reisman RE. Insect stings. *N Engl J Med*. 1994;331:523-527.
12. Golden DB, Marsh DG, Friedhoff LR, et al. Natural history of Hymenoptera venom sensitivity in adults. *J Allergy Clin Immunol*. 1997;100:760-766.
13. Parker JL, Santrach PJ, Dahlberg MJE, et al. Evaluation of Hymenoptera sting sensitivity with deliberate sting challenges: inadequacy of present diagnostic methods. *J Allergy Clin Immunol*. 1982;69:200-207.
14. Annila IT, Karjalainen ES, Annila PA, et al. Bee and wasp sting reactions in current beekeepers. *Ann Allergy Asthma Immunol*. 1996;77:423-427.
15. Li JT, Yunginger JW. Management of insect sting hypersensitivity. *Mayo Clin Proc*. 1992;67:188-194.

16. Akdis CA, Blaser K. Immunologic mechanisms of specific immunotherapy. *Allergy*. 1999;54(suppl):31-32.
17. McHugh SM, Deighton J, Stewart AG, et al. Bee venom immunotherapy induces a shift in cytokine responses from a TH-2 to a TH-1 dominant pattern: comparison of rush and conventional immunotherapy. *Clin Exp Allergy*. 1995;25:828-838.
18. Joint Task Force on Practice Parameters. Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol*. 2003;90(1 suppl 1):1-40.
19. Joint Task Force on Practice Parameters. The diagnosis and management of anaphylaxis. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. *J Allergy Clin Immunol*. 1998;101 (6 pt 2):S465-S528.
20. Moffitt JE. Allergic reactions to insect stings. *South Med J*. 2003;96:1073-1079.
21. Bousquet J, Menardo JL, Velasquez G, et al. Systemic reactions during maintenance immunotherapy with honey bee venom. *Ann Allergy*. 1988;61:63-68.
22. Brockow K, Kiehn M, Riethmuller C, et al. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol*.1997;100:458-463.
23. Valentine MD, Golden DBK. Diagnosis of insect allergy. In: Levine MI, Lockey RF, eds. *Monograph on Insect Allergy*. 2nd ed. Pittsburgh, Pa: Dave Lambert Associates; 1986:37-41.
24. Golden DB. Stinging insect allergy. *Am Fam Physician*. 2003;67:2541-2546.
25. Reisman RE, Livingston A. Venom immunotherapy: 10 years of experience with administration of single venoms and 50 micrograms maintenance doses. *J Allergy Clin Immunol*. 1992;89:1189-1195.
26. Reisman RE. Duration of venom immunotherapy: relationship to the severity of symptoms of initial insect sting anaphylaxis. *J Allergy Clin Immunol*. 1993;92: 831-836.
27. Golden DBK. Discontinuing venom immunotherapy. *Curr Opin Allergy Clin Immunol*. 2001;1: 353-356.
28. Fricker M, Helbling A. Schwarz L, et al. Hymenoptera sting anaphylaxis and urticaria pigmentosa: clinical findings and results of venom immunotherapy in ten patients. *J Allergy Clin Immunol*. 1997;100:11-15.
29. Muller UR. New developments in the diagnosis and treatment of hymenoptera venom allergy. *Int Arch Allergy Immunol*. 2001;124:447-453.
30. Schwartz LB, Irani AM. Serum tryptase and the laboratory diagnosis of systemic mastocytosis. *Hematol Oncol Clin North Am*. 2000;14:641-657.
31. Schwartz LB, Yunginger JW, Miller J, et al. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest*. 1989;83:1551-1555.
32. Haeberli G, Bronnimann M, Hunziker T, et al. Elevated basal serum tryptase and hymenoptera venom allergy relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. *Clin Exp Allergy*. 2003;33:1216-1220.
33. LaRoche D, Vergnaud M, Sillard B, et al. Biochemical markers of anaphylactoid reactions to drugs. comparison of plasma histamine and tryptase. *Anesthesiology*. 1991;75:945-949.
34. Randall D, Butts J, Halsey J. Elevated postmortem tryptase in the absence of anaphylaxis. *J Forensic Sci*. 1995;40: 208-211.
35. Akin C, Metcalf DD. Systemic mastocytosis. *Ann Rev Med*. 2004;55:419-432.
36. Odom RB, James WD, Berger TG. Mastocytosis (urticaria pigmentosa). In: James WD, Berger T, Elston D, eds. *Andrews' Diseases of the Skin: Clinical Dermatology*. 9th ed. Philadelphia, Pa: WB Saunders Co; 2000: 778-782.
37. Ludolph-Hauser D, Rueff F, Fries C, et al. Constitutively raised serum concentrations of mast-cell tryptase and severe anaphylactic reactions to Hymenoptera stings. *Lancet*. 2001;357:361-362.
38. Dubois AE. Mastocytosis and Hymenoptera allergy. *Curr Opin Allergy Clin Immunol*. 2004;4:291-295.
39. Krishna MT, Fearby S, Annila I, et al. Hymenoptera stings and serum tryptase. *Lancet*. 2001;357:1527-1528.
40. Engler RJ, Davis WS. Rush Hymenoptera venom immunotherapy: successful treatment in a patient with systemic mast cell disease. *J Allergy Clin Immunol*. 1994;94: 556-559.