

Stinging Insect Allergy

DAVID B. K. GOLDEN, M.D., Johns Hopkins University School of Medicine, Baltimore, Maryland

Systemic allergic reactions to insect stings are estimated to occur in about 1 percent of children and 3 percent of adults. In children, these reactions usually are limited to cutaneous signs, with urticaria and angioedema; adults more commonly have airway obstruction or hypotension. Epinephrine is the treatment of choice for acute anaphylaxis, and self-injection devices should be prescribed to patients at risk for this allergic reaction. Stinging insect allergy can be confirmed by measurement of venom-specific IgE antibodies using venom skin tests or a radioallergosorbent test. Patients with previous large local reactions have a 5 to 10 percent risk of experiencing systemic reactions to future stings. Patients with previous systemic reactions have a variable risk of future reactions: the risk is as low as 10 to 15 percent in those with the mildest reactions and in some children, but as high as 70 percent in adults with the most severe recent reactions. Because of demonstrated efficacy (98 percent), venom immunotherapy is recommended for use in patients who are at risk for severe systemic reactions to future insect stings. Venom immunotherapy is administered every four to eight weeks for at least five years. Immunotherapy may be needed indefinitely in patients at higher risk for recurrence of anaphylaxis after treatment is stopped. (Am Fam Physician 2003;67:2541-6. Copyright© 2003 American Academy of Family Physicians.)

See page 2448 for definitions of strength-of-evidence levels.

Insect stings usually cause transient local inflammation and occasional toxic reactions. However, allergic hypersensitivity can result in more severe local reactions or generalized systemic reactions.¹ Large local reactions are usually late-phase IgE-mediated allergic reactions, with severe swelling (eight to 10 inches in diameter) developing over 24 to 48 hours and resolving in two to seven days. Systemic reactions also are IgE mediated and may cause one or more signs and symptoms of anaphylaxis, including generalized urticaria, angioedema, throat tightness, dyspnea, dizziness, and hypotensive shock. Compared with adults, children have a higher frequency of isolated cutaneous reactions to insect stings and a lower frequency of vascular symptoms and anaphylactic shock.²

Morbidity and mortality from insect sting anaphylaxis can be virtually eliminated by appropriate patient education about the risk of recurrent reactions and the use of preventive and protective measures. Family physicians have an important role in identifying patients who are at risk for severe, potentially life-threatening reactions to insect stings, providing initial education about prevention, and referring appropriate patients to an allergy

subspecialist. In addition, family physicians often are responsible for administering maintenance-dose injections to patients who are receiving venom immunotherapy. Hence, a knowledge of procedures, potential adverse effects, and long-term expectations for this treatment is important.

Etiology of Severe Reactions to Insect Stings

Only stinging insects of the Hymenoptera order cause anaphylaxis with any frequency, although cases of anaphylaxis subsequent to insect bites have been reported. The stinging insects that commonly cause severe allergic reactions include bees (honeybees, bumblebees), vespids (Vespidae family: yellow jackets, hornets, wasps), and fire ants (*Solenopsis* genus).

Honeybee venom is immunochemically distinct. In contrast, yellow jacket and hornet venoms have a high degree of cross-reactivity and contain essentially the same allergens.³ Wasps from the *Polistes* genus are less closely related to other vespids: only 50 percent of patients who are allergic to yellow jacket venom also are allergic to wasp venom.⁴

Fire ants have become a public health hazard in the southeastern and south-central

Compared with adults, children have a higher frequency of isolated cutaneous reactions to insect stings and a lower frequency of vascular symptoms and anaphylactic shock.

areas of the United States.⁵ Fire ant venoms contain only a small amount of protein in an unusual suspension of alkaloid toxins. These toxins cause the painful vesicles that are characteristic of fire ant stings. The allergenic proteins in fire ant venoms are unique, except for one protein that shows limited cross-reactivity with a vespid allergen.

Epidemiology and Natural History of Insect Sting Allergy

Insect sting allergy can occur in persons of any age, especially after multiple stings. Systemic reactions to insect stings are estimated to occur in 3 percent of adults; approximately 1 percent of children have a medical history of severe sting reactions.⁶ Large local reactions are more common than systemic reactions and are mediated by IgE in up to 85 percent of cases.^{7,8} IgE antibodies to Hymenoptera venom, measured by venom skin tests or a radioallergosorbent test (RAST), are present in 20 to 30 percent of normal adults who had an insect sting in the previous two to three years.⁶

At least 50 fatal reactions to insect stings are reported each year in the United States, and many sting fatalities may not be recognized.⁹ In a study¹⁰ of unexplained sudden deaths occurring during the sting season (May to October in the northern half of the United States, almost all year in the southern half), postmortem blood samples often were found to contain both venom-specific IgE antibodies and elevated serum tryptase, demonstrating the anaphylactic pathophysiology of the fatal episode. Almost one half of fatal reactions occur in persons with no history of allergic sting reactions.⁹

Patients with a history of systemic sting reactions and positive venom skin tests have been found, on average, to

have a 50 percent risk of experiencing another systemic reaction to a challenge sting (i.e., a high risk of anaphylaxis).¹¹ A risk range of 25 to 75 percent has been reported; factors influencing the degree of risk include the type of insect, the severity of the previous reaction, the age of the patient, the degree of sensitivity, and the number of years since the last reaction.¹² Some patients who do not react to a first sting challenge react to a subsequent sting.

Systemic reactions usually do not become progressively more severe with each sting. Often, the stinging insect allergy is self-limited. The risk of reaction declines from over 50 percent initially to 35 percent three to five years after the sting reaction, and to approximately 25 percent 10 years or more after the sting reaction.¹³ In some instances, the risk of anaphylaxis persists for decades, even with no intervening stings.

Children generally are considered to have a more benign course after insect stings, largely because they usually have only cutaneous systemic reactions.¹⁴ However, children with moderate or severe anaphylaxis have a high risk of future reaction, even 15 years after the sting-related anaphylactic reaction.¹⁵

The occurrence of systemic reactions to insect stings is not correlated with a family history of insect sting allergy, despite the clear familial pattern in a few cases.⁶

Acute Reaction and Treatment

Large local reactions to insect stings can be mistaken for cellulitis caused by inflammatory lymphangitis, but antibiotic therapy is not needed. Although an antihistamine may lessen the itching, oral corticosteroid therapy is most effective in reducing inflammation and swelling, especially when treatment is initiated within one to two hours after the sting.

Patients with anaphylaxis subsequent to an insect sting require full emergency medical attention and should be observed for three to six hours. The treatment of choice is epinephrine, with a 1:1,000 (1 mg per mL) aqueous solution administered intramuscularly or subcutaneously. Adults receive a 0.3-mL dose; children are given 0.01 mg per kg (maximum: 0.3 mL).¹⁶ [Evidence level C, consensus/expert guidelines] Guidelines suggest that the dose can be repeated every 10 to 15 minutes, up to two or three times, if absolutely needed; however, the risk of significant adverse effects (e.g., arrhythmias) increases with each dose.^{16,17} Cardiac monitoring is advised when doses are repeated.¹⁷ [Evidence level C, consensus/expert guidelines]

The Author

DAVID B. K. GOLDEN, M.D., is associate professor of medicine at Johns Hopkins University School of Medicine, Baltimore, director of allergy in the Department of Medicine at Sinai Hospital of Baltimore, and chief of the allergy division of internal medicine at Franklin Square Hospital, also in Baltimore. In addition, he is a founding member of a private allergy-clinical immunology group practice in Baltimore. Dr. Golden has career-long interests in insect sting allergy, venom immunotherapy, and anaphylaxis in general. He has published dozens of original research manuscripts as well as review articles and book chapters.

Address correspondence to David B. K. Golden, M.D., Johns Hopkins University, Asthma and Allergy Center, 5501 Hopkins Bayview Blvd., Baltimore, MD 21224. Reprints are not available from the author.

Intramuscular injection results in a better and more rapid response than subcutaneous injection.¹⁸

Some patients, especially those taking beta blockers, are resistant to epinephrine. Glucagon can be administered to these patients. Norepinephrine may be beneficial in some patients who respond poorly to epinephrine.^{16,17}

Anaphylaxis often is prolonged or recurrent. Patients should be observed for recurrence for three to six hours, depending on the severity of the reaction and the response to treatment. Prolonged anaphylaxis that does not clear with treatment may persist for 24 hours and requires extended observation and treatment.¹⁹

Before patients who have been treated for anaphylaxis are discharged from acute care, they must be instructed to obtain an epinephrine auto-injector (EpiPen, 0.3 mg; EpiPen Jr, 0.15 mg), an allergy consultation, and preventive treatment. Patients should understand that using the epinephrine self-injection device is not a substitute for emergency medical attention, and that delay in using the device increases the risk of fatal reaction to an insect sting. Information on identifying and, when possible, avoiding stinging insects should be provided (sample Web site: www.aaaai.org/patients/publicedmat/tips/stinginginsect.stm). Family physicians should repeat all pertinent information and instructions when the reaction is reviewed at a subsequent visit.

It is common to prescribe two or more self-injection kits so that epinephrine is available in different locations, and because a second injection may be required if emergency medical assistance is delayed. It is essential to teach patients how to use the epinephrine auto-injector correctly. Instruction and demonstration should be repeated annually.

Patients often do not seek medical attention for allergic reactions to insect stings and usually fail to report these reactions to their physician. Consequently, in taking a complete medical history, it is appropriate to ask specific questions about past anaphylactic reactions to insect stings.⁶

Diagnosis of Insect Sting Allergy

The diagnosis of insect sting allergy rests on the history, because positive test results can occur in persons who do not react to insect stings. Positive venom skin tests are used to confirm the presence of allergy in a patient who has reacted to an insect sting and to identify the specific insect(s) to which the patient is allergic.²⁰

For Hymenoptera venom, intradermal tests using venom concentrations ranging from 0.001 to 1.0 mcg per

mL are positive in 65 to 80 percent of patients with a history of systemic allergic reactions to insect stings. In patients with a history of such reactions, negative venom skin tests may occur during the three-week to six-week refractory period after a sting reaction or may represent loss of sensitivity after many years.

The level of sensitivity on a venom skin test or RAST is not an accurate predictor of the severity of subsequent sting reactions. In fact, the strongest reactions on skin tests often occur in patients who have had only large local reactions to insect stings and have a low risk of anaphylaxis, whereas weak sensitivity on skin tests (or RAST) may be demonstrated in some patients who have experienced abrupt, nearly fatal anaphylactic shock.²¹

Tests to detect allergen-specific IgE antibodies in serum (typically a RAST) are less sensitive than venom skin tests. However, the RAST technique is useful when venom skin testing cannot be performed because a patient has a severe skin condition or is taking a medication that would suppress the skin test. A RAST also can be used to resolve discordance when skin testing is negative in a patient with a history of severe allergic reaction to a sting.

Venom skin tests are not recommended in patients with no history of systemic allergic reactions to insect stings. A screening test for stinging insect allergy would be desirable to prevent morbidity and mortality from initial anaphylactic episodes. Studies have shown that one half of sting-related deaths occur with the first systemic reaction.⁹ At present, however, this first reaction cannot be prevented, because venom immunotherapy is indicated only in patients with previous systemic reactions. Unfortunately, venom skin tests are positive in a large number of adults who do not have a history of allergic sting reactions; most of these persons will not have allergic reactions to future insect stings.

Venom Immunotherapy

PATIENT SELECTION

When the history reveals a systemic reaction severe enough to justify venom immunotherapy, the patient should be referred to an allergist/immunologist for evaluation and testing. If skin tests are negative and the history is of a life-threatening reaction, serologic testing (RAST) also is done. When the history and venom testing both indicate insect sting allergy, venom immunotherapy is recommended and can be initiated by the allergy specialist.^{20,22} Some patients with positive venom tests are at low risk for severe reactions. Children with cutaneous systemic reac-

Venom skin tests and immunotherapy are indicated in patients with a history of systemic allergic reaction to an insect sting.

tions limited to generalized urticaria and angioedema (but no respiratory or vascular manifestations) are at low risk for anaphylaxis with a future sting and usually do not require venom immunotherapy.¹⁴

In some situations, venom immunotherapy may be considered in low-risk patients, such as children with cutaneous systemic reactions or patients of any age who have had large local reactions. Prophylaxis may be justified for reasons related to quality of life, so that these patients can participate in normal outdoor work or leisure activities without psychologic distress.

Progression from cutaneous reaction to life-threatening anaphylaxis has been reported in adults. Therefore, adults who have had cutaneous systemic reactions to insect stings are advised to undergo venom immunotherapy. Unfortunately, there is no test that predicts which low-risk patients (i.e., those with large local reactions or cutaneous systemic reactions) will have more severe reactions to future stings and therefore would benefit from venom immunotherapy.

INITIAL THERAPY

Because venom immunotherapy carries a risk of anaphylaxis, it should be performed only by a physician who is accustomed to treating this condition and in a clinic or office that is prepared to provide immediate treatment for severe anaphylaxis. Patients should be required to remain in the office for 30 minutes after an immunotherapy injection.

Initial venom immunotherapy can follow any of several recommended schedules to build up from relatively low initial doses to the full maintenance dose.²⁰ More rapid regimens are not associated with a higher frequency of adverse reactions. The recommended goal is a maintenance dose of 100 mcg for each venom to which the patient has a positive venom skin test. The same approach to dosing is recommended in children three years of age and older, although their immune response is double that of adults.

As a result of marked cross-reactivity, immunotherapy using yellow jacket venom alone can provide protection in patients with skin tests that are positive for both yellow

jacket and hornet venoms. However, treatment with any single venom in 100-mcg doses has been reported to give incomplete clinical protection in 15 to 20 percent of patients.^{23,24} Consequently, mixed vespid venoms (total dose: 300 mcg) are most commonly used, because they are 98 percent effective in preventing systemic allergic reactions to future stings. To achieve full protection with any single venom, some patients may need a higher than usual dose (e.g., 200 mcg).²⁴ Because a lower dose (e.g., 50 mcg) may not result in adequate immune response, fully effective maintenance therapy requires the use of a full dose in all patients.²³

Skin tests are positive for *Polistes* wasp venoms in at least 50 percent of vespid-allergic patients, and a separate injection of this venom usually is included. In these patients, the only way to eliminate the need for wasp venom immunotherapy is to confirm cross-reactivity of wasp and yellow jacket venoms with an invitro RAST inhibition technique. If RAST inhibition does not show specific wasp sensitivity, wasp venom immunotherapy could be eliminated; treatment with yellow jacket venom or a mixed vespid venom would be expected to protect these patients against systemic reactions to future wasp stings.⁴

Immunotherapy for patients with a history of anaphylactic reactions to fire ant stings also is available.

ADVERSE REACTIONS

Insect venom immunotherapy causes systemic reactions no more frequently than inhalant allergen immunotherapy.²⁵ Systemic symptoms occur in 10 to 15 percent of patients during the initial weeks of treatment, regardless of the regimen used.²⁶ Most of these systemic reactions are mild, and fewer than one half of the reactions require epinephrine injection.

In the unusual patient with recurrent systemic reactions to injections, therapy may be streamlined to a single venom, and the desired dose for the visit may be divided, with half doses given 30 minutes apart. If this approach results in successful treatment up to the level of the desired maintenance dose, consideration can be given to beginning treatment with other venoms to which the patient has demonstrated allergy.

Up to 50 percent of patients experience large local reactions to insect venom injections, especially in the dose range of 20 to 50 mcg.²⁶ Large areas of swelling from the injections (sometimes up to six inches in diameter) are not associated with an increased risk of systemic reactions to

subsequent injections. If the swelling can be tolerated, it should not limit the doses administered. Unlike the case in standard inhalant allergen immunotherapy, there is a uniform target dose in venom immunotherapy. Therefore, it may be necessary to proceed with the dosing schedule despite the occurrence of large local reactions.

Originally, there was considerable concern that premedication before immunotherapy would mask reactions and lead to problems later on. However, recent studies have shown that pretreatment with oral antihistamines significantly lowers the frequency of adverse reactions and does not interfere with the efficacy of treatment.^{27,28}

MAINTENANCE THERAPY AND MONITORING

Once patients are receiving the full venom dose(s) they require, maintenance venom immunotherapy is administered every four weeks for at least one year. Most experts agree that the maintenance interval then may be increased to every six to eight weeks over several years.

Guidelines suggest that venom skin tests or RASTs may be repeated every two to three years to determine when there has been a significant decline in venom IgE antibodies (even though these tests do not reliably indicate the occurrence or severity of future reactions to insect stings).^{20,29} [Evidence level C, consensus/expert guidelines] In patients with more severe allergic reactions, it may be more appropriate to repeat the tests after five years. Skin tests generally remain unchanged in the first two to three years of venom immunotherapy but show a significant decline in venom IgE antibodies after four to six years. Venom skin tests become negative after five years in fewer than 20 percent of patients who receive venom immunotherapy but are negative after seven to 10 years in 50 to 60 percent of patients.³⁰

Measurements of venom-specific IgG antibodies in serum correlate strongly with clinical protection. Tests for these IgG-blocking antibodies usually are not needed because of the almost guaranteed efficacy of venom immunotherapy; however, the tests can be useful to monitor efficacy when longer intervals are used for maintenance immunotherapy.

DURATION

Since 1979, when the U.S. Food and Drug Administration labeled Hymenoptera venom extract for use in venom immunotherapy, the standard recommendation (reflected in the package inserts from the two manufacturers of the

In most patients with insect sting allergy, venom immunotherapy can be discontinued after five years of maintenance therapy. Some high-risk patients should be treated indefinitely.

venom extract) has been for indefinite treatment. Current practice parameters reflect the research results reported over the past 20 years.²⁰

Patients who prematurely stop venom immunotherapy after one to two years are at moderately high risk for systemic allergic reactions to future insect stings.^{31,32} A study³³ of more than 100 children and adults found that when venom immunotherapy is stopped after five years, there is a 10 percent risk of systemic reaction to each future sting, even 10 years or more after treatment is discontinued and even if venom skin tests become negative. When sting reactions occur after venom immunotherapy has been stopped, they usually are quite mild or at least less severe than the original pretreatment reaction.

Patients who display a higher frequency of anaphylaxis recurrence after venom immunotherapy is stopped include those with honeybee allergy, those who had a systemic reaction during therapy (to a sting or a venom injection), those who received treatment for fewer than five years, and those who had severe (nearly fatal) sting reactions before therapy. Patients with any of these high-risk characteristics probably should receive venom immunotherapy indefinitely.

It has been reassuring to note that venom IgE antibody levels (as measured by skin tests or RAST) decline steadily with time as venom immunotherapy proceeds and continue to fall after treatment is stopped, with no sign of persistent increase, even after challenge stings. Immunologic evidence supports the hypothesis that cellular suppression is induced by high-dose immunotherapy, but only after four or five years.³⁴

The author indicates that he does not have any conflicts of interest. Sources of funding: Dr. Golden has served as a consultant to ALK-Abello, Inc., Dey Laboratories, and Greer Laboratories. He has research contracts with AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Merck and Company, Inc., Novartis Pharmaceuticals, Schering Corporation, and Wallace Laboratories, and is on the speakers bureau for ALK-Abello, Inc., AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals, Dey Laboratories, Pfizer Inc., GlaxoSmithKline, and Schering Corporation.

Insect Sting Allergy

REFERENCES

1. Yunginger JW. Insect allergy. In: Middleton E Jr, et al., eds. *Allergy: principles and practice*. 5th ed. St. Louis: Mosby, 1998:1063-72.
2. Schuberth KC, Lichtenstein LM, Kagey-Sobotka A, Szklo M, Kwiterovich KA, Valentine MD. An epidemiologic study of insect allergy in children. *J Pediatr* 1982;100:546-51.
3. Hoffman DR, Dove DE, Moffitt JE, Stafford CT. Allergens in Hymenoptera venom. *J Allergy Clin Immunol* 1988;82(5 pt 1): 828-34.
4. Hamilton RG, Wisenauer JA, Golden DB, Valentine MD, Adkinson NF Jr. Selection of Hymenoptera venoms for immunotherapy on the basis of patient's IgE antibody cross-reactivity. *J Allergy Clin Immunol* 1993;92:651-9.
5. deShazo RD, Butcher BT, Banks WA. Reactions to the stings of the imported fire ant. *N Engl J Med* 1990;323:462-6.
6. Golden DB, Marsh DG, Kagey-Sobotka A, Freidhoff L, Szklo M, Valentine MD, et al. Epidemiology of insect venom sensitivity. *JAMA* 1989;262:240-4.
7. Graft DF, Schuberth KC, Kagey-Sobotka A, Kwiterovich KA, Niv Y, Lichtenstein LM, et al. A prospective study of the natural history of large local reactions after Hymenoptera stings in children. *J Pediatr* 1984;104:664-8.
8. Mauriello PM, Barde SH, Georgitis JW, Reisman RE. Natural history of large local reactions from stinging insects. *J Allergy Clin Immunol* 1984;74(4 pt 1):494-8.
9. Barnard JH. Studies of 400 Hymenoptera sting deaths in the United States. *J Allergy Clin Immunol* 1973;52:259-64.
10. Schwartz JH, Sutheimer C, Gauerke B, Zora JA, Yunginger JW. Venom-specific IgE antibodies in postmortem sera from victims of sudden unexpected death [Abstract]. The American Academy of Allergy and Immunology forty-first annual meeting. *J Allergy Clin Immunol* 1984;73(1 pt 2):189.
11. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amadio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978;299:157-61.
12. Golden DB. Stinging insect vaccines: patient selection and administration of Hymenoptera venom immunotherapy. *Immunol Allergy Clin North Am* 2000;20:553-70.
13. 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(3 pt 1):335-9.
14. Valentine MD, Schuberth KC, Kagey-Sobotka A, Graft DF, Kwiterovich KA, Szklo M, et al. The value of immunotherapy with venom in children with allergy to insect stings. *N Engl J Med* 1990;323:1601-3.
15. Golden DB, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Do children outgrow insect sting allergy? [Abstract]. American Academy of Allergy, Asthma and Immunology, 55th annual meeting. *J Allergy Clin Immunol* 1999;103(1 pt 2):S182.
16. The use of epinephrine in the treatment of anaphylaxis. *J Allergy Clin Immunol* 1994;94:666-8.
17. The diagnosis and management of anaphylaxis. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 1998;101(6 pt 2):S465-528.
18. Simons FE, Roberts JR, Gu X, Simons KJ. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998;101(1 pt 1):33-7.
19. Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. *J Allergy Clin Immunol* 1986;78(1 pt 1):76-83.
20. Portnoy JM, Moffitt JE, Golden DB, Bernstein IL, Berger WE, Dykewicz MS, et al. Stinging insect hypersensitivity: a practice parameter. *J Allergy Clin Immunol* 1999;103(5 pt 1):963-80.
21. Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Insect sting allergy with negative venom skin test responses. *J Allergy Clin Immunol* 2001;107:897-901.
22. Golden DB, Schwartz HJ. Guidelines for venom immunotherapy. *J Allergy Clin Immunol* 1986;77:727-8.
23. Golden DB, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Dose dependence of Hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 1981;67:370-4.
24. Rueff F, Wenderoth A, Przybilla B. Patients still reacting to a sting challenge while receiving conventional Hymenoptera venom immunotherapy are protected by increased venom doses. *J Allergy Clin Immunol* 2001;108:1027-32.
25. Lockey RF, Turkeltaub PC, Olive ES, Hubbard JM, Baird-Warren IA, Bukantz SC. The Hymenoptera venom study. *J Allergy Clin Immunol* 1990;86:775-80.
26. Golden DB, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of Hymenoptera venom immunotherapy. *Ann Intern Med* 1980;92:620-4.
27. Muller U, Hari Y, Berchtold E. Premedication with antihistamines may enhance efficacy of specific-allergen immunotherapy. *J Allergy Clin Immunol* 2001;107:81-6.
28. Brockow K, Kiehn M, Riethmuller C, Vieluf D, Berger J, Ring J. Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy. *J Allergy Clin Immunol* 1997;100:458-63.
29. The discontinuation of Hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 1998;101:573-5.
30. Golden DB, Kwiterovich KA, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Discontinuing venom immunotherapy: outcome after five years. *J Allergy Clin Immunol* 1996;97:579-87.
31. Golden DB, Johnson K, Addison BL, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Clinical and immunologic observations in patients who stop venom immunotherapy. *J Allergy Clin Immunol* 1986;77:435-42.
32. Reisman RE, Dvorin DD, Randolph CC, Georgitis JW. Stinging insect allergy. *J Allergy Clin Immunol* 1985;75:735-40.
33. Golden DB, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. *J Allergy Clin Immunol* 2000;105 (2 pt 1):385-90.
34. Bellinghausen I, Metz G, Enk AH, Christmann S, Knop J, Saloga J. Insect venom immunotherapy induces interleukin-10 production and a Th2-to-Th1 shift, and changes surface marker expression in venom-allergic subjects. *Eur J Immunol* 1997;27:1131-9.