

Rostrum

Negative venom skin test results in patients with histories of systemic reaction to a sting

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For more than 20 years venom immunotherapy has been the preferred treatment for Hymenoptera allergy and venom skin testing the preferred diagnostic test. Most allergists consider venom skin tests to be highly accurate and interpret a negative venom skin test result to indicate the absence of insect allergy. Furthermore, current practice guidelines do not adequately address the question of how best to manage the patient with a convincing history of insect allergy but negative skin test results. Recent case reports and published studies have forced us to reexamine this important management issue and to consider what role in vitro venom testing might have in the management of insect allergy. We reviewed the current status of what is known about the management of individuals with a history of insect allergy but negative venom skin test results and suggested modifications of current working guidelines. (*J Allergy Clin Immunol* 2003;112:495-8.)

Key words: Skin test, insect venom, insect sting, Hymenoptera, anaphylaxis, venom immunotherapy, RAST

Most allergists consider venom skin tests to be highly accurate.¹ When a venom skin test result is negative, most interpret this result to indicate that the patient has no allergy to insect stings or that the patient has lost sensitivity to the venom and has, therefore, no risk of systemic reaction to a sting. Furthermore, because skin tests are more sensitive than the RAST, allergists and the American Academy of Allergy, Asthma and Immunology (AAAAI) have not recommended the serologic measurement of venom-specific IgE antibodies for patients who have had negative results on venom skin tests. In addition, there has been controversy over the optimal diagnostic concentration for venom skin testing.² We now recognize that we need additional research in this area as well as revised guidelines for diagnosing insect sting allergies.

Abbreviation used

AAAAI: American Academy of Allergy, Asthma and Immunology

BACKGROUND

Insect sting allergies can have serious impact on affected individuals. They can cause severe local swelling and can produce systemic reactions, including 1 or more of the signs and symptoms of anaphylaxis. Approximately 1% of children and 3% of adults have had systemic reactions to insect stings.^{3,4} Every year in the United States alone, insect sting allergy causes an estimated 50 fatal reactions,⁵ and this is most likely an underestimate.^{6,7} But even the patients who only have severe local swelling (that is, large local reactions) share some of the morbidity and altered quality of life associated with insect sting allergy.

Because insect sting allergies are so troubling—even life threatening—and so prevalent, it is fortunate that highly effective prophylactic treatment is available. Venom immunotherapy can be 97% effective in preventing systemic reactions to stings. As a result, allergists must detect, with optimal sensitivity, all patients who are at risk for potentially life-threatening reactions, so the physician can inform the patients of the availability and benefit of venom immunotherapy. However, allergists want to treat primarily those who are at greatest risk and not necessarily those with minimal risk, so they must interpret the clinical history and diagnostic test results with optimal specificity.

Ideally, what we need then is a diagnostic test with optimal sensitivity but also high specificity. However, these criteria must be compared against some other measure, usually the history of previous sting reactions or the outcome of future exposure. The differences between the history, the test result, and the outcome of future stings affect the clinical diagnosis and the recommendations the physician makes to the patient.

DIAGNOSTIC METHODS (SKIN TEST VERSUS IN VITRO)

To confirm insect sting allergy in patients with a history of systemic reaction to Hymenoptera stings, the recommended diagnostic method is intradermal skin testing

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with Hymenoptera venoms, and this should be performed before the physician recommends and initiates venom immunotherapy. Our current methods for diagnosing insect sting allergy are good, but no diagnostic test is perfect. In the majority of patients with a convincing history, skin test results are clearly positive, but many are clearly negative. Why does this occur? In the days or weeks after a sting reaction, skin test results could appear to be negative because of a refractory period of anergy. In this situation the skin test should be repeated in these patients after 4 to 6 weeks.⁸ Alternatively, a negative skin test result in a patient who has a positive history could be caused by a loss of sensitivity over time or could indicate a non-IgE-mediated reaction (eg, mastocytosis).⁹

In vitro methods might have an important role in evaluating the patient with insect allergy. However, venom skin tests and venom-specific IgE assays correlate imperfectly.^{4,10-13} The in vitro assay results are negative in approximately 20% of subjects with positive skin test results, and venom skin test results are negative in approximately 10% of persons with elevated venom-IgE antibodies. We do not always know the clinical significance of a positive IgE antibody assay with a negative skin test result, but it is clearly associated with a risk of systemic reaction to a sting.^{10,14,15} We should particularly note that venom skin test and in vitro results do not reliably predict the severity of the reaction to future stings. In fact, some of the patients with the most severe systemic reactions have minimal venom-specific IgE antibodies.

Although often considered less sensitive than skin tests, in vitro tests might be positive in 11% to 16% of patients with negative skin test results.^{4,10,12,13} Patients with a positive history and negative venom skin test results might have a positive in vitro test result or show positive results when skin tests are subsequently repeated. There is variability between commercial laboratories, but there are sufficient data to suggest that in vitro testing is an important diagnostic adjunct in patients who have negative venom skin test results and a convincing history of a severe or life-threatening reaction. In 1 report of frequent negative venom skin test results, the RAST (or in vitro assay) in an academic laboratory was positive in more than 40% of cases.¹⁴ It requires clinical judgment to choose the optimal timing for repeat skin or in vitro tests, but the tests should be at least 6 weeks after any sting to allow for any post-sting refractory period and for the sting-induced immune response to appear. Because neither venom skin tests nor in vitro methods alone can detect all cases of insect sting allergy, each test might be useful as a supplement to the other.

CURRENT RECOMMENDATIONS AND CHANGING PERSPECTIVES

We wish to make clear that the thesis of this report is that we simply do not know as much as we once thought we knew and that as a result, physicians should exercise much more caution in diagnosing and treating insect sting allergies. Venom skin tests are the recommended standard diag-

nostic method for insect sting allergy. Individuals with positive venom skin test results, regardless of their history, have at least a 10% chance of systemic reaction to a subsequent sting. However, patients with recent severe reactions and positive venom skin test results might have a 40% to 70% chance of systemic reaction to their next sting. Yet patients with any severity of history might have negative venom skin test results; the frequency of this dilemma is uncertain. Although some investigators found few cases of negative venom skin test results in patients with a positive history,^{10,11,16,17} some large research studies reported that as many as one third of subjects recruited for a history of systemic reaction had negative venom skin test results.^{14,18} Furthermore, since the inception of venom extracts for diagnosis and treatment there have been reports that a few patients can have negative skin test results and still have severe—or even fatal—reactions to stings.^{10,11,14,16,17,19-21} In fact, in cases of fatal sting anaphylaxis, in vitro methods showed the levels of venom-specific IgE antibodies to be very low in 24% and undetectable in another 10%, whereas only 43% had levels above 1.1 ng/mL.²²

In the past when the intradermal skin test results have been negative, physicians have often advised patients that they had “outgrown” the allergy or that the reaction might have been of a toxic nature (especially with multiple stings). Published practice guidelines and parameters state that patients with negative skin test results are not candidates for immunotherapy, but they provide no guidance for managing these patients.^{1,23} Allergists generally told such patients that they showed no evidence of venom allergy and thus had no need to carry an Epi-Pen (Dey Laboratories, Napa, Calif) injector, because they were perceived to be at no greater risk of anaphylaxis than the general population.

Recent and past observations of the possibility of anaphylactic reactions to Hymenoptera stings in a few patients with negative venom skin test results might lead some to question the utility of the currently recommended diagnostic methods and materials. However, venom skin tests are still relevant and useful because they are positive in more than 65% of adults with positive history, compared to only 15% of adults with negative history.⁴ When venom skin test results are negative in adults with a history of systemic reaction, the chance of another systemic reaction to a sting is relatively small (5% to 10%) compared to the risk associated with positive venom skin test results (25% to 70%).¹⁴

Finally, in patients who have been on maintenance venom immunotherapy, we have thought in the past that negative skin test results indicate that treatment could be safely discontinued. However, this is not necessarily true, because there have been reports of fatal and near-fatal reactions to stings after these patients stopped immunotherapy.^{20,24,25} Thus we again must make clear that a negative skin test result is not a guarantee of safety, and patients with a history of severe or life-threatening reactions or with a high risk of subsequent sting should be counseled about emergency management, insect avoidance, epinephrine kit use, and follow-up care.

SENSITIVITY VERSUS SPECIFICITY

Diagnostic tests would ideally have perfect sensitivity and specificity, but this is rarely achieved. In the case of insect sting allergy, there are conflicting merits to these ideals. It is obviously desirable to avoid the cost and inconvenience of treating patients who would be reasonably safe without treatment, suggesting that optimal specificity of the diagnostic tests is required. However, the potential for life-threatening reactions would argue that sensitivity is perhaps even more important. Unfortunately, current materials and methods have fallen somewhat short in both respects.

Although venom skin tests have a 90% to 95% sensitivity, some cases might be missed by using the commercial venom products with the recommended concentrations of up to 1.0 $\mu\text{g/mL}$.^{14,19,20} The nonallergenic components in Hymenoptera venoms, which can cause false-positive reactions at concentrations higher than 1.0 $\mu\text{g/mL}$, place a practical limit on the diagnostic range of venom skin tests. Although limiting the skin tests to concentrations of 0.1 $\mu\text{g/mL}$ or less increases the specificity of the test,^{26,27} it also will miss up to 25% of the patients who have positive test results at 1.0 $\mu\text{g/mL}$, including some with severe reactions to stings.^{28,29} Despite concerns about the lower specificity of venom skin tests with the 1.0 $\mu\text{g/mL}$ concentration, we must give precedence in this disease to the need for the greatest sensitivity. The *in vitro* assays have been claimed to be a more specific test, but this too might depend on the threshold of the assays for detection of venom-specific IgE antibodies in most commercial laboratories.^{10,30} In fact, neither the venom skin test nor *in vitro* methods have optimal sensitivity; thus the diagnosis of Hymenoptera sensitivity in some patients might require the use of both tests.

NEW RECOMMENDATIONS

The Insect Committee recognizes that current practice guidelines do not address the management and evaluation of patients with a positive history of systemic reaction to a sting who have negative venom skin test results. On the basis of current evidence, it is clear we need modified working guidelines. There are limited published reports, and this field is still a work in progress. Until new studies present additional data for review and until researchers develop a better prognostic test, the committee concludes that in current practice:

1. Negative venom skin test results in patients with a positive history (of systemic reaction to a sting) might be more common than previously thought and might not exclude the presence of venom-specific IgE antibodies.
2. In some clinical situations, venom skin tests and *in vitro* measurement of venom-specific IgE antibodies might be complementary and might need to be repeated for confirmation, notably in patients with a history of severe life-threatening reactions.

3. A negative venom skin test or *in vitro* assay result is not a guarantee of safety, and patients with suspected higher risk should be counseled about avoidance strategies, use of epinephrine injectors, and the emergent and follow-up care of the acute allergic reaction.
4. The management of patients with positive history and negative venom skin test results requires clinical judgment and ongoing research.

REFERENCES

1. Portnoy JM, Moffitt JE, Golden DBK, Bernstein IL, Berger WE, Dykewicz MS, et al. Stinging insect hypersensitivity: a practice parameter. *J Allergy Clin Immunol* 1999;103:963-80.
2. Reisman RE. Venom hypersensitivity. *J Allergy Clin Immunol* 1994;94:651-8.
3. Settipane GA, Boyd GR. Prevalence of bee sting allergy in 4991 Boy Scouts. *Acta Allergol* 1970;25:286.
4. Golden DBK, Marsh DG, Kagey-Sobotka A, Addison BI, Freidhoff L, Szklo M, et al. Epidemiology of insect venom sensitivity. *JAMA* 1989;262:240-4.
5. Barnard JH. Studies of 400 Hymenoptera sting deaths in the United States. *J Allergy Clin Immunol* 1973;52:259-64.
6. Hoffman DR, Wood CL, Hudson P. Demonstration of IgE and IgG antibodies against venoms in the blood of victims of fatal sting anaphylaxis. *J Allergy Clin Immunol* 1983;71:193.
7. Schwartz HJ, Sutheimer C, Gauerke B, Zora JA, Yunginger JW. Venom-specific IgE antibodies in postmortem sera from victims of sudden unexpected death. *J Allergy Clin Immunol* 1984;73:189.
8. Goldberg A, Confino-Cohen R. Timing of venom skin tests and IgE determinations after insect sting anaphylaxis. *J Allergy Clin Immunol* 1997;100:183-4.
9. Fricker M, Helbling L, Schwartz L, Muller U. Hymenoptera sting anaphylaxis and urticaria pigmentosa: clinical findings and results of venom immunotherapy in ten patients. *J Allergy Clin Immunol* 1997;100:11-5.
10. Day J, Buckeridge D, Welsh A. Risk assessment in determining systemic reactivity to honeybee stings in sting-threatened individuals. *J Allergy Clin Immunol* 1994;93:691-705.
11. Parker JL, Santrach PJ, Dahlberg MJE, Yunginger JW. Evaluation of Hymenoptera-sting sensitivity with deliberate sting challenge. *J Allergy Clin Immunol* 1982;69:200-7.
12. Sobotka AK, Adkinson NF Jr, Valentine MD, Lichtenstein LM. Allergy to insect stings, IV: diagnosis by radioallergosorbent tests (RAST). *J Immunol* 1978;121:2477-84.
13. Hoffman DR. Comparison of the radioallergosorbent test to intradermal skin testing in the diagnosis of stinging insect venom allergy. *Ann Allergy* 1979;43:211-3.
14. Golden DBK, Kagey-Sobotka A, Hamilton RG, Norman PS, Lichtenstein LM. Insect allergy with negative venom skin tests. *J Allergy Clin Immunol* 2001;107:897-901.
15. Santrach PJ, Peterson LG, Yunginger JW. Comparison of diagnostic tests for Hymenoptera sting allergy. *Ann Allergy* 1980;45:130-6.
16. Georgitis J, Reisman R. Venom skin tests in insect-allergic and insect non-allergic populations. *J Allergy Clin Immunol* 1985;76:803-7.
17. vanderLinden PG, Hack CE, Struyvenberg A, vanderZwan JK. Insect-sting challenge in 324 subjects with a previous anaphylactic reaction: current criteria for insect-venom hypersensitivity do not predict the occurrence and the severity of anaphylaxis. *J Allergy Clin Immunol* 1994;94:151-9.
18. Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978;299:157-61.
19. Selcow J, Mendelson L, Rosen J. Anaphylactic reactions in skin test-negative patients. *J Allergy Clin Immunol* 1980;67:400.
20. Light WC. Insect sting fatality 9 years after venom treatment. *J Allergy Clin Immunol* 2001;107:925.
21. Blaauw PJ, Smithuis LOMJ. The evaluation of the common diagnostic methods of hypersensitivity for bee and yellow jacket venom by means of an in-hospital insect sting. *J Allergy Clin Immunol* 1985;75:556-62.

22. Hoffman DR. Fatal reactions to Hymenoptera stings. *Asthma Allergy Proc* 2003;24:116-20.
23. Muller U, Mosbech H. Position paper: immunotherapy with Hymenoptera venoms. *Allergy* 1993;48:37-46.
24. Golden D, Kagey-Sobotka A, Lichtenstein L. Survey of patients after discontinuing venom immunotherapy. *J Allergy Clin Immunol* 2000;105:385-90.
25. Golden DBK. Fatal insect allergy after discontinuing venom immunotherapy (letter). *J Allergy Clin Immunol* 2001;107:925-6.
26. Day J. A comparison of venom concentrations of 0.1 µg/mL and 1.0 µg/mL as indicator of sensitivity to honeybee stings. *J Allergy Clin Immunol* 1986;77:142.
27. Reisman RE, Georgitis JW. Frequency of positive venom skin tests in insect-allergic and non-allergic populations. *J Allergy Clin Immunol* 1984;73:187.
28. Hunt KJ, Valentine MD, Sobotka AK, Lichtenstein LM. Diagnosis of allergy to stinging insects by skin testing with Hymenoptera venoms. *Ann Intern Med* 1976;85:56-9.
29. Schwartz HJ, Lockey RF, Sheffer AL, Parrino J, Busse WW, Yunginger JW. A multicenter study on skin test reactivity of human volunteers to venom as compared with whole body Hymenoptera antigens. *J Allergy Clin Immunol* 1981;67:81-5.
30. Reisman RE. Insect sting allergy: the dilemma of the negative skin test reactor. *J Allergy Clin Immunol* 2001;107:781-2.