

V. Clinical Sciences

A. Allergic Diseases and Related Disorders

1. Upper airway disease

a. Clinical skills and interpretive strategies for diagnosis of upper airway diseases: skin testing (epicutaneous and intracutaneous); cytology of nasal secretions; understanding of indications for and methodology of nasal challenges; rhinoscopy; nasal and ear examination; gross assessment of upper airway imaging studies.

i. Skin testing

latter and needs to be done for skin tests as well. With use of a combination of history and appropriate

LANDMARK ARTICLE:

Malling HJ

Proposed guidelines for quantitative skin prick test procedure to determine the biological activity of allergenic extracts using parallel line assay, Allergy; 1987;42, 391-4

Guidelines are proposed for determining the potency of allergenic extracts in relation to a reference extract using parallel line bio-assay. The practical performance, limitations, and advantages of skinprick test are discussed.

2. Lower respiratory tract disease

a. Specific skills and practical management : chest exam, interpretation of pulmonary function testing, bronchial challenges, sputum and exhaled breath analysis, and gross interpretation of imaging studies.

i. Long Acting beta agonists

LANDMARK ARTICLE:

Nelson HS

The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol.

Chest. 2006;129:15-26

STUDY OBJECTIVE: To compare the safety of salmeterol xinafoate or placebo added to usual asthma care. **DESIGN:** A 28-week, randomized, double-blind, placebo-controlled, observational study. **SETTING:** Study subjects were seen once in the study physician's office for screening and were provided all blinded study medication for the entire study period. Follow-up by telephone was scheduled every 4 weeks. **PARTICIPANTS:** Subjects (> 12 years old) with asthma as judged by the study physician were eligible. Individuals with a history of long-acting beta2-agonist use were excluded. **INTERVENTIONS:** Salmeterol, 42 mug bid via metered-dose inhaler (MDI), and placebo bid via MDI. **MEASUREMENTS AND RESULTS:** Following an interim analysis in 26,355 subjects, the study was terminated due to findings in African Americans and difficulties in enrollment. The occurrence of the primary outcome, respiratory-related deaths, or life-threatening experiences was low and not significantly different for salmeterol vs placebo (50 vs 36; relative risk [RR] = 1.40; 95% confidence interval [CI], 0.91 to 2.14). There was a small, significant increase in respiratory-related deaths (24 vs 11; RR, 2.16; 95% CI, 1.06 to 4.41) and asthma-related deaths (13 vs 3; RR, 4.37; 95% CI, 1.25 to 15.34), and in combined asthma-related deaths or life-threatening experiences (37 vs 22; RR, 1.71; 95% CI, 1.01 to 2.89) in subjects receiving salmeterol vs placebo. The imbalance occurred largely in the African-American subpopulation: respiratory-related deaths or life-threatening experiences (20 vs 5; RR, 4.10; 95% CI, 1.54 to 10.90) and combined asthma-related deaths or life-threatening experiences (19 vs 4; RR, 4.92; 95% CI, 1.68 to 14.45) in subjects receiving salmeterol vs placebo.

CONCLUSIONS: For the primary end point in the total population, there were no significant differences between treatments. There were small, but statistically significant increases in respiratory-related and asthma-related deaths and combined asthma-related deaths or life-threatening experiences in the total population receiving salmeterol. Subgroup analyses suggest the risk may be greater in African Americans compared with Caucasian subjects. Whether this risk is due to factors including but not limited to a physiologic treatment effect, genetic factors, or patient behaviors leading to poor outcomes remains unknown.

ii. Genetic polymorphisms and beta agonists

LANDMARK INVESTIGATION:

Martinez FD.

Association between genetic polymorphisms of the b2-adrenoceptor and response to albuterol in children with and without a history of wheezing.

J Clin Invest 1997;100:3184-3188.

The beta2-adrenergic receptor (beta2AR) agonists are the most widely used agents in the treatment of asthma, but the genetic determinants of responsiveness to these agents are unknown. Two polymorphic loci within the coding region of the beta2AR have been recently described at amino acids 16 and 27. It has been reported that glycine at codon 16 (Gly-16) is associated with increased agonist-promoted downregulation of the beta2AR as compared with arginine-16 (Arg-16). The form of the receptor with glutamic acid at codon 27 (Glu-27), on the other hand, has been shown to be resistant to downregulation when compared with glutamine-27 (Gln-27), but only when coexpressed with Arg-16. To assess if different genotypes of these two polymorphisms would show differential responses to inhaled beta2AR agonists, we genotyped 269 children who were participants in a longitudinal study of asthma. Spirometry was performed before and after administration of 180 microg of albuterol, and a positive response was considered an increase of >15.3% predicted FEV1. There was marked linkage disequilibrium between the two polymorphisms, with 97.8% of all chromosomes that carried Arg-16 also carrying Gln-27. When compared to homozygotes for Gly-16, homozygotes for Arg-16 were 5.3 times (95% confidence interval 1.6-17.7) and heterozygotes for beta2AR-16 were 2.3 times (1.3-4.2) more likely to respond to albuterol, respectively. Similar trends were observed for asthmatic and nonasthmatic children, and results were independent of baseline lung function, ethnic origin, and previous use of antiasthma medication. No association was found between the beta2AR-27 polymorphism and response to albuterol. These results may explain some of the variability in response to therapeutic doses of albuterol in children.

3. Drug allergy

a. General reviews and susceptibility states

LANDMARK PUBLICATION:

Brown BC, Price EV, Moore MD

Penicilloyl-polylysine as an intradermal test of penicillin sensitivity.

JAMA 1964;189:599-604.

4. Anaphylaxis and anaphylactoid reactions

LANDMARK PUBLICATION:

Smith PL, Kagey-Sobotka A, Bleecker ER, et al. Physiologic manifestations of human anaphylaxis. J Clin Invest 1980;66:1072-80.

The authors conducted a controlled study to evaluate different forms of immunotherapy for subjects with insect-sting hypersensitivity, and observed 11 subjects who had generalized urticaria and 3 subjects who experienced anaphylactic shock characterized by severe hypotension attributed to peripheral vasodilation. Plasma histamine levels correlated with the severity and duration of the cardiopulmonary

changes observed during anaphylactic shock. The two subjects with the most severe shock showed reductions in Factor V, Factor VIII, fibrinogen, and high molecular weight kininogen, as well as changes in complement components. This study also documents the paradoxical occurrence of bradycardia in the setting of anaphylactic shock (one subject).

5. Insect hypersensitivity

LANDMARK PUBLICATION:

Hunt KJ, Valentine MD, Sobotka AK et al

A controlled trial of immunotherapy in insect hypersensitivity

N Engl J Med 1978;299:157-161

Insect hypersensitivity is currently treated by immunization using whole-body extracts. We compared this regimen with immunotherapy using insect venoms or placebo in groups of 20 patients matched for history and sensitivity, as judged by venom skin test, histamine release and IgE antibody to venom. After six to 10 weeks of immunization, systemic reactions to stings occurred in seven of 12, seven of 11, and one of 18 patients treated with placebo, whole-body extract, and venom, respectively. Placebo and wholebody extract gave similar results and were significantly less effective than venom immunotherapy (P less than 0.01). The 14 patients with failure of treatment with wholebody extract and placebo were subsequently provided with venom immunotherapy; one reacted to a subsequent sting. We conclude that venom immunotherapy is clinically superior to therapy on whole-body extract or placebo.

LANDMARK PUBLICATION:

Barnard JH

Studies of 400 Hymenoptera sting deaths in the United States

J Allergy Clin Immunol 1973;52:259-64

Data from 400 cases of Hymenoptera sting deaths in the United States have been collected. These included 100 cases seen at autopsy and the results of postmortem abnormalities and certain other correlations are tabulated.

a. Skin prick, intradermal and in vitro testing to stinging insects

LANDMARK PUBLICATION:

Golden DBK, Marsh DG, Freidhoff LR, et al.

Natural history of Hymenoptera venom sensitivity in adults

J Allergy Clin Immunol 1997;100:760-6

Background: Epidemiologic studies of Hymenoptera venom allergy in adults show a prevalence of positive venom skin test results, RASTs of 15% to 25%, or both, but most such individuals have had no systemic reactions to stings. The clinical significance and natural history of this apparently common sensitivity is uncertain. Objective: We sought to determine the natural history of venom sensitization by observing the rate of decrease or increase in sensitivity in normal adults over 5 to 10 years. The clinical significance of these findings is related to the frequency of systemic reactions to stings during the period of observation. Methods: Serial observations were planned in 520 volunteers and randomly selected subjects. Two follow-up visits were attempted, once after 2 to 3 years and again after 5 to 9 years, to perform repeat venom skin tests and RASTs and to review any history of interim stings and their outcomes. Results: Follow-up visits were conducted with 398 subjects (375 early visits and 205 late visits). Overall, in the 398 subjects with one or more visits after a mean of 4 years, skin test responses changed from positive to negative in 44 of 98 (45%) and from negative to positive in 27 of 309 (8.7%) of the subjects. Skin test responses changed from positive to negative in 29 of 87 (33%) subjects after 2.5 years and in 43 of 54 (80%) after 6.8 years. Even when the skin test response became negative, venom-specific IgE remained positive in 11 of 29 (38%) subjects after 2.5 years and in 13 of 43 (30%) after 6.8 years. The rate of loss of sensitivity was 12% per year, similar to retrospective estimates. Skin test sensitivity to venoms disappears more rapidly in these subjects without symptoms (half-life, 4 years)

than in patients receiving venom immunotherapy (half-life, 7 years). Skin test responses changed from negative to positive in 23 of 288 (8%) subjects after 2.5 years and in 9 of 151 (6%) after 6.8 years. Insect stings caused no reaction in 120 subjects with a negative skin test response, but 17% (11 of 65) of subjects with a positive skin test response (but with a negative history) had systemic reactions when stung. There was no difference between the early and late visits in the frequency of systemic reactions reported. The risk may be higher than 17% for the specific individuals (67% after 2.5 years and 20% after 6.8 years) whose positive skin test responses persist for years. This risk is lower than that of patients with a positive history (50%) but higher than that of "normal" adults or venom-treated patients (<2%). It is still not clear whether any subset of adults with a positive skin test response but a negative history can be identified, in whom the risk of systemic sting reaction would justify venom immunotherapy even before any reaction occurs. Conclusion: Asymptomatic venom sensitization in adults is common but transient, disappearing at the rate of 12% per year. However, the risk of a systemic reaction to a subsequent sting is significant in adults without symptoms but with positive venom skin test responses (17%) and may be higher when skin test sensitivity does persist for years.

b. Predictive value of clinical history and testing for adult and pediatric population

LANDMARK PUBLICATION:

Outcomes of Allergy to Insect Stings in Children, with and without Venom Immunotherapy

Golden DBK, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM

N Engl J Med 2004;351:668-74.

Background - Children are thought to "outgrow" the allergy to insect stings, but there are no reports documenting the natural history of this reaction. We studied the outcome of allergic reactions to insect stings in childhood 10 to 20 years afterward in patients who had not received venom immunotherapy and in those who had been treated. Methods - Between 1978 and 1985, we diagnosed allergic reaction to insect stings in 1033 children, of whom 356 received venom immunotherapy. We conducted a survey of these patients by telephone and mail between January 1997 and January 2000, to determine the outcome of stings that occurred in the period from 1987 through 1999. Results - Of the 1033 patients, 512 patients (50 percent) responded, with a mean follow-up period of 18 years, a mean duration of venom immunotherapy of 3.5 years in treated patients, and an incidence of stings of 43 percent. Systemic reactions occurred less frequently in patients who had received venom immunotherapy (2 of 64 patients, or 3 percent) than in untreated patients (19 of 111 patients, or 17 percent; $P=0.007$). Patients - with a history of moderate-to-severe reactions had a higher rate of reaction if they had not been treated (7 of 22 patients, or 32 percent) than if they had received venom immunotherapy (2 of 43 patients, or 5 percent; $P=0.007$). In patients who had been treated and who had a history of mild (cutaneous) systemic reaction (i.e., one with only cutaneous manifestations), none of the 21 subjects who received stings had a systemic reaction. Conclusions - A clinically important number of children do not outgrow allergic reactions to insect stings. Venom immunotherapy in children leads to a significantly lower risk of systemic reaction to stings even 10 to 20 years after treatment is stopped, and this prolonged benefit is greater than the benefit seen in adults.

c. Venoms, formulation, schedule and duration of immunotherapy.

LANDMARK PUBLICATION:

Freeman TM, Hylander R, Ortiz A, Martin ME

Imported fire ant immunotherapy: m Effectiveness of whole body extracts

J Allergy Clin Immunol 1992;90:210-5

The purpose of this study was to determine if whole body extract (WBE) immunotherapy for Imported fire ant (IFA) hypersensitivity is effective. This evaluation was carried out by retrospectively interviewing 76 patients with a history of generalized allergic reactions to IFA stings and positive skin tests to IFA-WBE. The study groups consisted of 65 patients on immunotherapy and 11 similar patients who were not treated for various reasons. In addition, an IFA sting challenge was performed in 30

volunteers of the 65 patients on immunotherapy. The retrospective review showed that of the 65 patients on immunotherapy there had been 112 Subsequent field-sting episodes in 47 patients. Only one sting episode in this group (2.1%) produced an anaphylactic reaction. Six of the 11 patients not on immunotherapy have had subsequent field re-sting episodes, and each has had a systemic reaction. Repeat skin testing on 31 of the 65 patients in the immunotherapy group showed persistent positive responses in five (16%), but each was at a lower dilution than initially. Responses of the other 26 of the 31 patients who had skin testing had become negative. The four untreated patients who were available for skin testing continued to have positive responses at comparable dilutions on skin testing. Sting challenges carried out on 30 volunteers from the 65 patients (all from the 31 who had repeat skin tests) on immunotherapy resulted in only local reactions. Therefore it appears IFA-WBE is effective in decreasing the incidence of anaphylaxis during subsequent field stings; reducing specific immunoglobulin E as demonstrated by skin testing; and protecting against systemic reactions provoked by a sting challenge with a single IFA.

LANDMARK PUBLICATION:

Golden DBK, Kagey-Sobotka A, Lichtenstein LM

Survey of patients after discontinuing venom immunotherapy

J Allergy Clin Immunol 2000;105:385-90

Background: Venom immunotherapy rapidly reduces the risk of a systemic sting reaction in adults from 30% to 70% to less than 2%. When venom immunotherapy is stopped after 5 years or longer, the risk of a systemic sting reaction is 5% to 15% during the first few years after stopping treatment. It is uncertain whether systemic sting reactions will occur more than 5 years after discontinuing venom immunotherapy and whether treatment can be safely stopped in some patients after less than 5 years. Objective: The purpose of this study is to estimate the risk of systemic reaction to a sting 10 years after discontinuing treatment and the relative risk after 3 years of treatment compared with that after 5 years or more of treatment. Methods: Among all patients who had venom immunotherapy at our center, we identified 395 patients who stopped treatment: some had dropped out of therapy early (6-24 months), some stopped after 3 to 4 years, and most completed 5 years or more of venom immunotherapy and were advised to stop by the allergist (many as part of our reported studies of discontinuing venom immunotherapy). Results: Contact was made with 194 patients, including telephone interviews for sting history and requests to visit the office for skin testing and blood sampling. Of these patients, 74 had been included in our original study of patients who had 5 years or more of venom immunotherapy and had sting challenges after 1 to 5 years off venom immunotherapy, as previously reported. Of the 74 in that original study, 61 were reached for this survey, and 30 reported recent stings, with 5 systemic sting reactions. Another 133 patients who had stopped venom immunotherapy were reached: 82 had 5 or more years of venom immunotherapy, 20 had 3 to 4 years of venom immunotherapy, and 31 had less than 2 years of venom immunotherapy. Of 51 patients stung from this group, 27 had 5 or more years of venom immunotherapy (no systemic sting reactions), and 24 had less than 5 years of venom immunotherapy (3 systemic sting reactions). We have now observed a total of 113 patients who had 5 or more years of venom immunotherapy and were stung after stopping. Sixteen (14%) had systemic sting reactions; most were mild, but 4 were severe. Systemic sting reactions occurred in 12 (10.7%) of 112 patients stung in the first 4 years off venom immunotherapy and 5 (10%) of 50 stung more than 5 years off venom immunotherapy. In 4 of 8 patients with current systemic sting reactions, the skin test response was negative, although the venom-IgE response was positive at the previous encounter. All systemic sting reactions were similar in pattern and severity to pre-venom immunotherapy reactions in the same patient. Conclusions: We conclude that the risk of systemic sting reactions when venom immunotherapy is stopped after 5 years or longer remains in the reported range of 5% to 15% in the 5 to 10 years after stopping venom immunotherapy. This risk of systemic sting reactions does not seem to decrease over time, unlike the progressive decline in immunologic markers (skin test and venom-IgE responses). To prospectively assess the risk of recurrent systemic sting reactions, there is a need for sting challenge

studies of patients who have been off venom immunotherapy for 5 to 10 years and patients who have stopped venom immunotherapy after just 3 to 4 years treatment.

LANDMARK PUBLICATION:

Rüeff 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

Background: Up to 20% of patients allergic to Hymenoptera venom are not protected by conventional venom immunotherapy (VIT) with 100 µg of any single venom. Objective: We sought to evaluate the efficacy of an increased venom dose in patients allergic to Hymenoptera venom still reacting systemically to a sting challenge despite immunotherapy with 100 µg of venom every 4 weeks.

Methods: In this retrospective study patients were included who still had reacted systemically to a sting challenge with a living bee or wasp despite VIT with a maintenance dose of 100 µg every 4 weeks. The maintenance dose was increased to 150 or 200 µg every 4 weeks, and a second sting challenge was performed. If a patient reacted again, the dose was further increased. Baseline mast-cell tryptase levels were assessed by using a fluoroenzyme immunoassay in stored patient sera. Results: While receiving a maintenance dose of 100 µg of venom every 4 weeks for 7 to 38 months, 18 patients reacted systemically to a bee sting and 22 reacted to a wasp sting. After an increase of the maintenance dose to 150 µg, 2 of 4 patients allergic to bee venom (BV) and 6 of 6 patients allergic to yellow jacket venom (YJV) no longer reacted systemically to the sting challenge. The respective rates of full protection were 13 of 14 and 15 of 16 in patients with an increase of the maintenance dose to 200 µg from the start. Of those 4 individuals not protected by the first dose increase, one patient allergic to BV (prior dose of 150 µg) and one patient allergic to YJV (prior dose of 200 µg) did not react systemically to a further sting challenge while receiving 200 µg of BV or 250 µg of YJV, respectively. One patient allergic to BV who had a systemic reaction to the sting challenge while receiving 150 µg was not protected after a dose increase to 200 µg; she later received a dose of 400 µg of BV, and no further sting challenge was performed. The patient allergic to BV who still reacted systemically after a first dose increase to 200 µg was a female patient with urticaria pigmentosa. She had repeated systemic adverse reactions to further BV immunotherapy, necessitating discontinuation of the treatment; however, she tolerated well VIT with 200 µg of YJV. In all other patients, no unusual adverse reactions to the increased venom doses were observed. Baseline serum tryptase levels were elevated above 13.5 µg/L (95th percentile in normal subjects) in 9 (28.1%) of 32 patients. Conclusions: The majority of patients allergic to Hymenoptera venom who still reacted systemically to a sting challenge despite VIT with a dose of 100 µg every 4 weeks can be fully protected by an increased maintenance dose. This dose increase is well tolerated by most patients. The rather high proportion of patients with elevated baseline serum tryptase levels necessitates further investigation of a possible association between mastocytosis and treatment failure of conventionally dosed VIT.