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*A Synopsis of Allergy and
Asthma Literature,
Resulting from an Unbiased,
Comprehensive Review of
Nineteen Major Medical Journals.*

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Which Is More Effective for Grass Pollen Allergy--SCIT or SLIT?

BOTH subcutaneous and sublingual immunotherapy--SCIT and SLIT--have recognized efficacy for treatment of seasonal allergic rhinitis grass pollen. Because of increased safety and ease of administration, there is a trend toward increased prescription of SLIT. However, the relative efficacy of the two routes of administration remains unclear. An updated meta-analysis of SCIT versus SLIT for grass pollen allergy is presented.

The investigators performed an indirect meta-analysis of randomized, double-blind, placebo-controlled trials of SCIT or SLIT for the treatment of seasonal allergic rhinitis to grass pollen. The analysis included 22 trials of SLIT and 14 of SCIT, including a total of 3,014 immunotherapy-treated and 2,768 placebo-treated patients. Standardized mean differences (SMDs) in symptom and medication scores with active treatment

versus placebo were calculated to compare the efficacy of the two treatments.

The results showed a significantly larger effect size of SCIT for symptom score: SMD -0.92, compared to 0.25 for SLIT administered via drops and -0.40 via tablets. The SMDs for medication score were -0.58 for SCIT versus -0.37 for SLIT drops and -0.30 for SLIT tablets. Rates of treatment-emergent adverse events were 0.86 events per patient with SCIT versus 2.13 with SLIT. Anaphylactic events were more frequent with SCIT: 12 episodes versus 1.

The analysis shows "indirect but solid evidence" that SCIT is more effective than SLIT for the treatment of seasonal allergic rhinitis to grass pollen. The authors note significant heterogeneity between trials, particularly for SCIT studies. They outline suggestions for a direct comparative trial of SCIT versus SLIT.

COMMENT: *Which works better, SLIT or SCIT? That is a question many allergists and patients are asking. This meta-analysis analyzed 36 randomized >>>*

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controlled trials and found indirect but solid evidence that SCIT is more effective than SLIT in controlling symptoms and reducing medication use in patients with allergic rhinoconjunctivitis during grass pollen season. Interestingly, the evidence was stronger in adults, possibly because of a larger data pool. The rate of serious adverse reactions was markedly higher with SCIT, which is one of the reasons SLIT is an appealing alternative. Ideally, future prospective studies will help answer the question.

S.M.F.

DiBona D, Plaia A, Leto-Barone M, et al: Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison.

J Allergy Clin Immunol 2012;130:1097-1107. ◆◆

Kinetics of Omalizumab Therapy for Peanut Allergy

ANTI-IgE monoclonal antibodies are clinically effective in patients with peanut allergy. However, there are questions about the kinetics of the clinical response, as well as the association with mast cell or basophil responses to allergen. These issues were addressed in a study of omalizumab therapy for peanut allergy.

The study included 14 adults with peanut allergy undergoing 6 months of treatment with omalizumab. Baseline assessments included double-blind, placebo-controlled oral food challenge, skin prick test titration (SPTT), and basophil histamine release (BHR) to peanut. The BHR test was repeated regularly until the value decreased to 20% of baseline (or after 8 weeks). Food challenge and SPTT were repeated at that point, and again at 6 months.

The threshold dose of peanut inducing allergic symptoms decreased from 80 mg at baseline to 6,500 mg at follow-up challenge. Five patients had complete suppression of peanut-induced BHR, while the other nine had more than a tenfold increase in the amount of allergen needed to induce maximal BHR. There was no significant change in SPTT responses.

There was no further change in the threshold dose on oral challenge or in BHR through 6 months of omalizumab treatment. However, suppression of the peanut allergen SPTT became significant: mean wheal size was 5.6 mm at baseline versus 3.8 mm at the end of treatment.

The results suggest that the clinical response to omalizumab in peanut-allergic patients occurs early in the course of treatment, when basophils are suppressed but mast cells are not. The findings are consistent with a role of basophils in acute food reactions. Anti-IgE therapy is associated with a sharp increase in the threshold dose of peanut inducing allergic reactions, within the first 8 weeks of treatment.

COMMENT: *These authors had previously shown that the basophil response to allergen was suppressed early in the course of treatment with omalizumab, although nasal mast cells were not affected. The new study in patients with peanut allergy demonstrates that the basophil suppression response to omalizumab occurs early; again, the mast cell response is unaffected. In an impressive clinical response, the threshold challenge dose increased 56-fold--from 1 peanut to 21 peanuts--after treatment with omalizumab. The authors suggest that basophil hyporesponsiveness to allergen may be an indicator that food-allergic patients could tolerate an oral food challenge. These findings also suggest that clinical benefit from omalizumab may occur earlier than previously thought.*

S.M.F.

Savage JH, Courneya J-P, Sterba PM, et al: Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy.

J Allergy Clin Immunol. 2012;130:1123-1129. ◆◆

New Additions to the Asthma Outcome Measurements Armamentarium

VARIOUS tools for classifying asthma severity and disease activity exist, but there is a need for weighted, composite measures that consider the wide range of clinical variables evaluated. The Asthma Disease Activity Score (ADAS) was evaluated as a weighted, responsive tool for measuring asthma disease activity.

Data from two large, phase 3 trials of montelukast were used to develop six- and four-item versions of the ADAS. The ADAS-6 showed content validity in that it assessed a range of asthma manifestations: FEV₁, the Asthma Quality of Life Questionnaire-Symptom domain, rescue beta-agonist use, nighttime awakenings, and diurnal variability in peak expiratory flow and rescue beta-agonist use. It also showed cross-sectional and longitudinal validity.

The ADAS-6 discriminated different levels of disease activity and responses to different treatment intensities, with comparable findings in an independent clinical trial. It outperformed other commonly used scores in demonstrating treatment effects. If the original montelukast trials had used the ADAS-6 as the primary endpoint, a similar effect on outcomes would have been demonstrated in a smaller sample size. Higher ADAS-6 scores also predicted a higher risk of future asthma attacks. The simplified ADAS-4 showed similar performance.

The ADAS-6 and ADAS-4 provide potentially useful tools for measuring asthma disease activity. The weighted composite measures demonstrate multiple aspects of validity and are highly sensitive to change. The authors believe these new scores will improve on the ability to estimate asthma disease burden and to assess treatment responses.

THE Asthma Symptom Utility Index (ASUI) is a promising tool for assessment of asthma symptoms in clinical research, but has yet to be adequately validated. The authors report a further evaluation of the ASUI's reliability, validity, and responsiveness to change, including establishment of the minimal important difference (MID).

The analysis included 1,648 adult asthma patients from two previous randomized trials. Along with other assessments, ASUI scores were obtained at baseline and follow-up; patients also completed daily asthma diaries. The ASUI showed good psychometric properties in both samples, including good construct validity, test-retest reliability, and discriminant validity. Baseline ASUI scores significantly predicted the risk of asthma exacerbations over the subsequent 2 weeks. The tool also showed good responsiveness to change, with ASUI scores reflecting differences of 10% in percent predicted FEV₁ and 0.5 points in Asthma Control Questionnaire scores. On a 0-to-1 scale, the MID of the ASUI was set at 0.09 points.

The study demonstrates the reliability, validity, and change responsiveness of the ASUI for assessment of

asthma symptoms. The reported MID value will aid in interpreting clinical research and improving asthma symptom monitoring. Further studies are needed to evaluate the ASUI's psychometric properties in other groups of asthma patients, including children.

COMMENT: *The 2010 Asthma Outcomes Workshop, assembled by the National Institutes of Health and the Agency for Healthcare Research and Quality, made recommendations on outcome measures for federally funded asthma clinical research in seven areas, ranging from biomarkers to disease effect on quality of life. Two recent articles--accompanied by an illuminating editorial by Wilson (J Allergy Clin Immunol 2012;130:1085-1086)--add two new tools and insights to our asthma outcomes assessment armamentarium. While the expert group suggested that evaluation of symptoms was an important outcome measurement, they did not endorse any specific measurement instrument or procedure. The ASUI is the most widely used retrospective symptom recall questionnaire for adults. It has good reported measurement characteristics, but information on essential psychometric properties was missing.*

Bime et al provide new evidence affirming the measurement properties of the ASUI using data from the Study of Acid Reflux and Asthma (SARA) and Safety of Inactivated Influenza Vaccine in Asthma (SIIVA) trials. Of note, the ASUI is not copyrighted, although scoring requires use of a computer since it is not a mere summation of responses.

Greenberg et al evaluate the ADAS, a composite measure that integrates data on multiple constructs typically obtained from multiple measurement procedures. The six-item ADAS-6 provides a continuous score with acceptable internal consistency reliability, is responsive to treatment, discriminates adequately between differing severity of asthma (as does the ADAS-4), and is predictive of future exacerbations. Although the ADAS was designed to measure "disease activity"--a different construct from "asthma control"--the information entered into the ADAS overlaps that of the Asthma Control Test and Asthma Control Questionnaire. It remains to be seen whether the use of diary data and differential weighting of components in the ADAS will provide additional unique predictive information.

C.D.

Bime C, Wei CY, Holbrook JT, et al: Asthma Symptom Utility Index: Reliability, validity, responsiveness, and the minimal important difference in adult asthmatic patients. J Allergy Clin Immunol. 2012;130:1078-1084. Greenberg S, Liu N, Kaur A, et al: The Asthma Disease Activity Score: A discriminating, responsive measure predicts future asthma attacks.

J Allergy Clin Immunol. 2012;130:1071-1077. ♦♦

Should We Dispense or Prescribe ICS to Children with Asthma in the ED?

CHILDREN making emergency department (ED) visits for asthma have low rates of outpatient fol- ➤➤

low-up and inhaled corticosteroids (ICS) prescription. Three different strategies for ICS delivery to asthmatic children seen in the ED were evaluated for clinical effectiveness and cost-effectiveness.

The decision tree analysis used published data to compare three ED-based options for ICS delivery to asthmatic children: usual care, ie, recommending outpatient follow-up; and uniformly prescribing or dispensing ICS to all patients. Projected rates of ED relapse visits and hospitalizations within 1 month were compared, considering the expected rates of follow-up, prescription filling, and medication compliance.

Predicted rates of repeat ED visits within 1 month (per 100 patients) were 10.6 with usual care, 9.4 with ICS prescribing and 8.4 with ICS dispensing. Hospitalization rates were 2.4, 2.2, and 1.9 per 100 patients, respectively. Direct costs were \$23,400 in the usual care group versus \$20,800 with the prescribing strategy and \$19,100 with the dispensing strategy. Indirect costs were \$27,100, \$22,000, and \$20,100, respectively, including parents' missed work time. Overall, the dispensing strategy would save \$7,000 per 100 patients, compared to simply recommending outpatient care.

The model results support a strategy of ED prescribing or dispensing ICS for children with acute asthma. Both strategies produce significant reductions in repeat ED visits and hospitalizations, with attendant reductions in costs. By improving ICS use among asthmatic children, these options offer "an effective way to deliver preventive care in the acute care setting."

COMMENT: For decades, ICS have been the primary controller medication for persistent asthma. However, acute asthma is still seen in the ED. Three paradigms were tested to determine if referring to primary care physician, prescribing ICS, or dispensing ICS could prevent costly outcomes in the month following the ED visit. Dispensing ICS (at a 40% discount) was associated with less direct and indirect costs, most noticeably from return ED visits. The authors propose a larger role of the ED in chronic care than currently established. This study brings to surface a discussion over who should be delivering care to patients with asthma. Let's wait and hear from the pediatricians.
S.F.W.

Andrews AL, Teufel RJ II, Basco WT Jr, Simpson KN: A cost-effectiveness analysis of inhaled corticosteroid delivery for children with asthma in the emergency department.

J Pediatr. 2012;161:903-907. ◆◆

Gabapentin Is Effective for Refractory Chronic Cough

REFRACTORY chronic cough poses a challenge in diagnosis and management. Like neuropathic pain, refractory chronic cough is associated with central reflex sensitization, suggesting a potential role of neuro-modulator therapy. This study evaluated gabapentin for the treatment of refractory chronic cough.

The randomized double-blind trial included 62

adults with refractory chronic cough lasting longer than 8 weeks. All patients were free of infection or other respiratory disease. After stratification by sex, patients were assigned to treatment with gabapentin or placebo. The main outcome of interest was the change in cough-specific quality of life, as measured by the Leicester cough questionnaire (LCQ), after 8 weeks of treatment.

Fifty-two patients completed the study. Gabapentin was associated with significant improvement in cough-specific quality of life; compared to placebo, the between-group difference in LCQ score was 1.80. The number needed to treat to produce improvement in 1 patient was 3.58. Thirty-one percent of patients in the gabapentin group experienced side effects--most commonly nausea and fatigue. Side effects occurred in 10% of the placebo group.

Gabapentin is an effective and well-tolerated treatment for patients with refractory chronic cough. The benefits shown in this placebo-controlled trial provide support for a mechanism of central reflex sensitization in refractory chronic cough.

COMMENT: Allergists frequently are asked to see patients whose chief complaint is cough. We diligently work them up but sometimes they actually don't have asthma, reflux, postnasal drip syndrome, malignancy or any other documented cause for their cough. This is the first double-blind randomized controlled trial in subjects with refractory chronic cough that has met the primary efficacy variable as well as important secondary endpoints. Gabapentin has a central mechanism of action. When more subjects are studied, gabapentin may prove useful in patients with this condition.

S.F.W.

Ryan NM, Birring SS, Gibson PG: Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial.

Lancet. 2012;380:1583-1589. ◆◆

Peanut Oral Immunotherapy Improves QOL

PEANUT allergy is an increasingly common condition for which allergen avoidance is the only available treatment. Oral immunotherapy has emerged as a promising new treatment, with the potential to improve quality of life (QOL) for affected patients. This study evaluated the effects of oral immunotherapy on food-specific quality of life in children and adolescents with peanut allergy.

The open-label trial included 100 pediatric patients with known peanut allergy--age range 5 to 18 years. All patients received peanut oral immunotherapy, with a target maintenance daily dose of 450 mg of peanut protein. Patients were assessed using validated, age-specific food allergy QOL questionnaires at baseline and after completing immunotherapy.

The target maintenance dose was achieved by 90 patients: 76 children (up to 12 years old) and 14 adolescents. The children showed significant improvement in all domains of food-specific QOL: allergen avoid- ➤➤

ance, dietary restriction, risk of accidental exposure, emotional impact, food-related anxiety, and social and dietary limitations. For adolescents, improvement was significant in all domains except emotional impact.

For children aged 5 to 12 years, parent reports showed significant improvement for 30 out of 30 questions. Improvement was reported on 22 out of 24 questions for children aged 8 to 12 years, and for 12 out of 18 questions for adolescents aged 13 to 18 years.

The open trial suggests significant improvements in food-specific QOL for children and adolescents receiving oral immunotherapy for peanut allergy. The emotional impact appears less for adolescents than for younger children. The authors note the high rate of adverse reactions to peanut oral immunotherapy, indicating that treatment "should not be undertaken lightly."

COMMENT: *This study evaluated the effect of oral immunotherapy to peanut on food-specific QOL in 90 children with peanut allergy. The results showed dramatic improvements in all allergen avoidance, dietary restriction, accidental exposure risk, emotional impact, anxiety associated with foods, and social and dietary limitations. Parents, children, and adolescents alike indicated improved QOL overall. Practicing allergists should be cognizant of the benefits of this investigational treatment.*

C.C.R.

Factor JM, Mendelson L, Lee J, et al: Effect of oral immunotherapy to peanut on food-specific quality of life.

Ann Allergy Asthma Immunol. 2012;109:348-352. ♦♦

Vitamin D Sufficiency Affects Response to SIT

RECENT studies have found that vitamin D promotes tolerogenic dendritic cells, leading to induction of Foxp3-positive regulatory cells and inhibition of Th1 and Th2 immune responses. This raises the possibility that vitamin D status could influence the clinical response to allergen specific immunotherapy (SIT). The current study evaluated the effects of serum 25-hydroxyvitamin D (25[OH]D) level on the response to SIT in asthmatic children.

The researchers analyzed data from two previous randomized, placebo-controlled trials of allergen SIT in children with moderate asthma who were sensitized to house dust mite. The studies followed an identical protocol, including at least 12 months of immunotherapy for children assigned to placebo. Serum 25(OH)D levels were measured at the initial visit and during the SIT buildup phase. The clinical and immunologic effects of SIT were analyzed in relation to vitamin D status.

Children with higher serum 25(OH)D levels had better responses to SIT. This included a greater reduction in asthma symptoms and an increased steroid-sparing effect. Higher vitamin D levels were also associated with greater transforming growth factor- β production and increased induction of Foxp3. The steroid-sparing effect was significantly correlated to 25(OH)D level at baseline and after 3 months of SIT, as well as with the change in

serum 25(OH)D during the buildup phase. Patients with a 25(OH)D level greater than 30 ng/mL had a better clinical response to SIT.

This retrospective study suggests that vitamin D status influences the outcomes of allergen SIT in children with asthma. Serum 25(OH)D levels greater than 30 ng/mL appear to facilitate an "optimal effect" of SIT. The authors recommend monitoring 25(OH)D in children receiving SIT, particularly in those at risk of vitamin D insufficiency.

COMMENT: *This intriguing study demonstrates that a sufficient level of vitamin D correlates with optimal effect of immunotherapy. Individuals with serum 25(OH)D levels greater than 30 ng/mL had a more significant decline in asthma symptom scores and a greater steroid-sparing impact of SIT. They also showed greater transforming growth factor- β production and enhanced Foxp3 induction in response to SIT. The allergist should be aware that serum 25(OH)D levels greater than 30 ng/mL ml provide for an optimal outcome of allergen immunotherapy.*

C.C.R.

Majak P, Jerzyńska J, Smejda K, et al: Correlation of vitamin D with Foxp3 induction and steroid-sparing effect of immunotherapy in asthmatic children.

Ann Allergy Asthma Immunol. 2012;109:329-335. ♦♦

Can Hand Symptoms Predict Latex Sensitization?

IgE-mediated allergy to latex has become a common and potentially serious problem among health care workers (HCWs). Diagnosis of latex allergy relies on a comprehensive medical history and testing, typically skin-prick testing (SPT). Some efficient means of screening for latex allergy would be of value. This study evaluated HCW-reported hand symptoms for use in monitoring for latex sensitization.

A total of 804 HCWs at two hospitals completed a questionnaire including items related to latex glove use, symptoms related to wearing gloves, and history of allergic disease. Reported hand symptoms were evaluated for association with the presence of latex sensitization, as diagnosed by SPT.

Workers reporting increased use of latex gloves were more likely to have hand symptoms. The presence of hand symptoms was also closely related to the occurrence of glove-related respiratory and systemic symptoms. The rate of positive SPT to latex was 5% overall, and increased with the number of hand symptoms: 1.6% for HCWs with no hand symptoms, 3.4% for those with one or two symptoms, and 19.0% for those with three or more symptoms.

The presence of three or more symptoms was associated with an 11.0 odds ratio for latex sensitization. Rash with hives was the symptom most specific for positive SPT results.

Hand symptoms reported by HCWs in response to a questionnaire are closely related to latex sensitization, as confirmed by SPT. The presence of hand symptoms may be useful in screening for latex allergy among >>>

HCWs who use latex gloves. A small number of workers have latex sensitization even without hand symptoms.

COMMENT: Hand symptoms reported on a questionnaire survey are closely related to latex sensitization in HCWs. Hand symptoms reported by workers wearing latex gloves were highly associated with positive SPT to latex. Workers reporting more than two hand symptoms were 11 times more likely to have a positive SPT, compared to those with two or fewer symptoms. The practicing allergist should know that hand symptoms in HCWs wearing latex gloves are highly associated with latex sensitization.

C.C.R.

Wang ML, Kelly KJ, Klancik M, Petsonk EL: Self-reported hand symptoms: a role in monitoring health care workers for latex sensitization?

Ann Allergy Asthma Immunol. 2012;109:314-318. ♦♦

Exhaled Mediators of EIB in Asthmatic Children

EXERCISE-induced bronchoconstriction (EIB) is an important contributor to the burden of childhood asthma. Increased knowledge of the pathogenesis of EIB is needed to aid in the diagnosis and treatment of asthma. Two potential exhaled markers of EIB--RANTES (regulated on activation, normal T-cell expressed and secreted) and interleukin (IL)-4--were evaluated in children with asthma.

Fifty-six asthmatic children performed a treadmill exercise challenge. Exhaled breath condensates were collected at baseline and at 30 minutes after exercise challenge. Specific immunoassays were used to measure RANTES and IL-4 levels. These exhaled markers and other variables associated with the occurrence and severity of EIB were analyzed.

Exercise challenge in asthmatic children was associated with a significant increase in exhaled RANTES level. This was so in the 31 children without EIB, as well as the 25 children with EIB. Exhaled RANTES level was significantly correlated with FEV₁, exacerbation frequency, serum IgE, and body mass index. There was no significant change in exhaled IL-4 after exercise challenge.

The maximal drop in FEV₁ after exercise challenge was significantly related to total eosinophil count as well as the baseline ratio of FEV₁ to forced vital capacity (FVC). On multivariate analysis adjusted for age and sex, both eosinophil count and FEV₁/FVC were significantly associated with EIB.

Exercise challenge in children with asthma is associated with an increase in the exhaled RANTES level, consistent with the hyperosmolar theory of EIB. Exhaled RANTES is correlated with serum IgE, asthma severity, FEV₁/FVC, and body mass index, but neither RANTES nor IL-4 is independently associated with EIB. Eosinophil count and FEV₁/FVC ratio may be useful predictors of EIB in children with asthma.

COMMENT: What are the mediators exhaled by children with asthma during exercise challenge? The

authors demonstrate that during exercise challenge the hyperosmolar stimulus results in enhanced exhaled RANTES levels. These levels correlate with serum IgE, asthma severity, the FEV₁/FVC ratio, and body mass index. While RANTES and IL-4 may not be separate predictors, eosinophil count and FEV₁/FVC are predictive indices of presence and severity of EIB in children with asthma. The allergist should be cognizant that eosinophil count and FEV₁/FVC can be predictive of EIB in asthmatic children.

C.C.R.

Keskin O, Keskin M, Kucukosmanoglu E, et al: Exhaled RANTES and interleukin 4 levels after exercise challenge in children with asthma.

Ann Allergy Asthma Immunol. 2012;109:303-308. ♦♦

Can Micro-Syringe Venom Administration Replace Live Bee Sting Challenge?

IN patients with Hymenoptera venom allergy, sting challenge with live honeybees can evaluate the effects of a field sting under controlled conditions. Although this test is useful to confirm protection in some situations, the need for live insects poses difficulties. This study evaluated micro-syringe injection of venom as an alternative to sting challenge.

The study included 19 patients, mainly beekeepers, who were receiving venom immunotherapy for honeybee. All were free of systemic reactions to field stings. All patients underwent live bee sting challenge, with up to 48 hours of observation for large local reactions. Patients without systemic reactions proceeded to micro-syringe challenge designed to mimic natural bee sting, consisting of 0.5 µL of fresh unfiltered bee venom injected to a depth of 2 mm. Reactions were again monitored. Bee-specific immunoglobulin E (IgE) and tryptase were measured after both challenges.

Of the 19 patients, 4 had immediate systemic reactions to live bee sting challenge. The remaining 15 patients had large local reactions and underwent micro-syringe challenge. Maximum area of the large local reactions was similar between challenges: 231 cm² after sting challenge and 240 cm² after micro-syringe challenge. Serum tryptase and specific IgE responses were similar as well.

The preliminary study demonstrates the feasibility of performing micro-syringe challenge as an alternative to live bee sting challenge in patients receiving venom immunotherapy. The results of the two challenges are "indistinguishable," suggesting that injection may provide a more practical alternative to challenge with live bees. Because the study excluded patients with systemic reactions, no assumptions can be made regarding the test's predictive value.

COMMENT: Venom immunotherapy is effective in the treatment of patients with stinging insect allergy. However, in some patients at risk for repeat stinging--due to occupation, for example--confirmation of protection may be needed. The use of live bees for sting challenge poses several difficulties for the allergist, >>>

including high cost and time needed to perform the challenge. This study investigated the use of micro-syringe administration of venom as a challenge in patients with large local reactions during live bee sting challenge. Although patients with systemic reactions during live bee challenge were excluded, the reactions in the remaining patients were similar with either live sting or micro-syringe venom administration. The authors also suggest the possibility of freezing the venom, thus offering allergists a more practical form of challenge, when needed.

V.H.-T.

Cortellini G, Severino N, Francesato E, et al: Evaluation and validation of a bee venom sting challenge performed by a micro-syringe.

Ann Allergy Asthma Immunol. 2012;109:438-441. ♦♦

Can Skin Prick Tests Predict Response to Baked Milk Challenge?

RECENT studies have shown that many children with IgE-mediated cow's milk allergy can tolerate baked milk products. Little is yet known about predictive factors for passing a baked milk food challenge. This study evaluated the ability of skin prick test (SPT) and specific IgE levels to predict the results of baked milk challenge.

The researchers retrospectively analyzed the results of 35 baked milk challenges (muffins or cupcakes) in children with cow's milk allergy. Twenty-nine children passed the open baked milk challenge. Of the remaining children, 3 passed the clinic challenge but had symptoms in response to ongoing exposure at home during the subsequent weeks or months. One child in the latter group had a reaction requiring treatment with epinephrine.

Skin prick test results, specific IgE levels, and demographic factors predictive of the response to baked milk challenge were analyzed. Median age was 8.9 years for children who passed the challenge, compared to 3.7 years for those who failed. More than 90% of children with a milk SPT wheal smaller than 12 mm, and 100% with a wheal smaller than 7 mm, passed the baked milk challenge. The challenge was also passed by more than 90% of children with a casein SPT wheal of 9 mm, a milk specific IgE level of 1.0 kU/L, and a casein specific IgE level of 0.9 kU/L.

In this study, more than 80% of children with cow's milk allergy were able to pass a baked milk challenge. Wheal size in response to milk SPT is more reliable than specific IgE level in predicting the response to baked milk challenge. Some children who pass the clinic challenge will have late reactions to ongoing baked milk exposure at home.

COMMENT: This study, like others, found that many patients with cow's milk allergy will pass an oral challenge with baked milk products. In contrast to previous studies reporting the use of serum specific IgE levels during food challenge, this study raises the possibility that wheal size during SPT to cow's milk may better predict whether patients will tolerate baked milk challenge. The authors remind us to discuss the possibility

of late reactions with the patients. They also highlight the need to ensure that the baked milk products are not undercooked. Because of the small sample size, further studies are needed.

V.H.-T.

Bartnikas LM, Sheehan WJ, Hoffman EB, et al: Predicting food challenge outcomes for baked milk: role of specific IgE and skin prick testing.

Ann Allergy Asthma Immunol. 2012;109:309-313. ♦♦

Egg in Baked Foods Does Not Affect Skin Test

MOST children with egg allergy can safely eat baked goods containing egg. Recent studies suggest that regularly eating small amounts of baked egg may lead to immunomodulatory changes similar to those associated with development of allergen tolerance. This study evaluated changes in skin prick test (SPT) wheal size in egg-allergic children who regularly ate baked egg products.

The retrospective analysis included children with challenge-confirmed egg allergy who underwent at least two egg SPTs at one pediatric allergy department between 1996 and 2005. Rates of decline in egg SPT wheal size were compared for children with different frequencies of baked egg ingestion, as reported by parents: frequent, more than once per week; regular, more than once every 3 months; or "strict avoidance," no more than once every 3 months. Associations were adjusted for potential confounders.

Of the 125 children in the study, 17% had frequent baked egg ingestion, 30% had regular ingestion, and 54% had strict avoidance. The overall mean rate of decline in egg SPT size was 0.7 mm/year. This rate did not differ significantly by frequency of baked-egg exposure: 0.4 mm/year with frequent exposure, 0.9 mm/year with regular exposure, and 0.7 mm/year with strict avoidance.

The frequency of baked egg ingestion does not affect the rate of decline in egg SPT size in children with confirmed egg allergy. The results suggest that children who can tolerate baked egg should be allowed to incorporate these foods into their diet. Unlike some previous reports, the study did not find faster resolution of egg sensitization in children who ate baked eggs more frequently.

COMMENT: The dogma regarding how to safely avoid symptoms and also facilitate oral tolerance in egg allergic children has shifted dramatically in recent years. No longer are we necessarily recommending strict avoidance of all forms of egg in the diet. This study confirms that at least skin test wheal diameter does not increase over time while allowing egg allergic children to regularly eat baked foods containing egg. Ongoing studies should clarify whether allowing baked eggs in the diet actually speeds the development of clinical tolerance.

S.A.T.

Tey D, Dharmage SC, Robinson MN, et al: Frequent baked egg ingestion was not associated with change in rate of decline in egg skin prick test in children >>>

with challenge confirmed egg allergy.
Clin Exp Allergy. 2012;42:1782-1790. ◆◆

Hygiene Hypothesis Applies to Egg Allergy

DESPITE the high frequency of egg allergy in infants and young children, little is known about the risk factors for its development. Risk factors for egg allergy in infants were analyzed in a population-based study.

The analysis included 5,276 infants enrolled in HealthNuts, an Australian population-based study of food allergy. Egg white skin prick testing (SPT) was performed when the infants were 12 months old. Oral food challenge was performed in 699 of 873 infants with a detectable wheal on egg SPT. Of these, 453 had confirmed egg allergy, defined as a positive challenge plus SPT of 2 mm or larger. Demographic and environmental factors associated with the development of egg allergy were analyzed.

Risk of developing egg allergy by age 1 was significantly lower for infants with older siblings and for those who had a dog at home: adjusted odds ratio (OR) 0.72 for each. Risk was unaffected by cesarean delivery, exposure to antibiotics during infancy, attending child-care, and maternal age. The presence of allergy in an immediate family member was strongly associated with egg allergy, OR 1.82. Children of parents born in East Asia were at even higher risk: OR 3.30.

Exposure to older siblings and having a dog at home are associated with a lower risk of developing egg allergy in infants. Risk is increased for infants with a family history of allergy and those with parents born in East Asia. These risk factors can be added to later introduction of egg in the diet, noted in previous reports from the HealthNuts study.

COMMENT: *Although egg-allergic children have an increased risk of developing respiratory allergy, the risk factors for developing egg allergy have been less well established. This large population-based study of infants used skin testing, oral food challenge, and questionnaires to show that having older siblings and/or a dog in the first year of life was associated with a decreased risk of developing egg allergy. The hygiene hypothesis is alive and well!*

S.A.T.

Koplin JJ, Dharmage SC, Ponsonby A-L, et al: *Environmental and demographic risk factors for egg allergy in a population-based study of infants.*

Allergy. 2012;67:1415-1422. ◆◆

Finally, a Practical Role for eNO?

NOT using inhaled corticosteroids (ICS) as prescribed is a major contributor to treatment failure in asthma. Assessing ICS nonadherence is a clinical challenge; no simple, objective measure is available. This study evaluated measurement of exhaled nitric oxide (eNO) as a test for assessing ICS in difficult asthma.

The study included 22 patients with difficult asthma, defined as persistent symptoms despite Global Initiative for Asthma Step 4 and 5 treatment, and eNO greater than 45 ppb. All received 7 days of directly observed inhaled corticosteroids (DOICS), consisting of budesonide 1,600 µg. Based on the magnitude of eNO suppression after DOICS, patients were prospectively classified as ICS-adherent or ICS-nonadherent. This classification was then validated against the patients' prescription records, prednisolone assay, and concordance interview.

Thirteen patients were classified as adherent, filling more than 80% of ICS prescriptions; and 9 as nonadherent, filling less than 50% of prescriptions. After DOIC, the nonadherent group has a 47% reduction in eNO compared to baseline, versus a 79% reduction in the adherent group. The difference was significant within 5 days; an eNO test for nonadherence was developed, with an area under the curve of 0.86.

In a prospective validation phase including 40 patients, 13 were identified as nonadherent by the eNO test. Of these, 8 admitted to nonadherence in interviews, including 3 patients with high prescription filling rates. Another 5 patients denied nonadherence; of these 2 had unintentional nonadherence related to poor inhaler technique.

The eNO test suggested adherence in 27 patients, which was confirmed in 21. Of 5 patients who admitted poor ICS adherence, 4 had good adherence to oral steroids and 1 to omalizumab.

The eNO test evaluated in this study appears to provide an objective method of identifying ICS-adherent versus ICS-nonadherent patients with difficult asthma. Measuring eNO after DOICS can identify nonadherence even in patients who fill their prescriptions but don't use their medication. With further validation, the eNO test may help in providing appropriately tailored asthma management.

COMMENT: *Whether to incorporate eNO measurement into routine practice has been a difficult decision for many asthma specialists, and it seems that the more thought that is put into the decision, the more difficult it becomes. Beyond the inconsistencies, quirks, expenses, and inconveniences of measuring eNO, clarifying nonadherence to inhaled corticosteroids in poorly controlled asthmatic patients may be its most valuable potential role, at least in the subset of patients with persistently elevated eNO. This study provides useful information for those of us who struggle with deciding which patients are truly refractory to corticosteroids.*

S.A.T.

McNicholl DM, Stevenson M, McGarvey LP, Heaney LG: *The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma.*

Am J Respir Crit Care Med. 2012;186:1102-1108. ◆◆

CLINICAL TIDBITS

Fish Oil Supplementation in Infancy

DECLINING intake of omega 3 polyunsaturated fatty acids (n-3 PUFA) is a potential contributor to the rising prevalence of allergic disease. This suggests a possible preventive benefit of fish oil supplementation for primary prevention of allergy.

Four hundred twenty healthy infants born to allergic mothers were randomly assigned to a daily fish oil supplement containing docosahexanoic acid 280 mg and eicosapentanoic acid 110 mg; or a control supplement containing olive oil. At age 6 months, infants receiving fish oil had higher plasma and erythrocyte levels of the n-3 PUFAs, as well as lower erythrocyte arachidonic acid levels. Infants with higher n-3 PUFA levels were less likely to have eczema or recurrent wheezing. However, the association with eczema became nonsignificant after multiple comparisons. Overall, there were no significant between-group differences in sensitization, eczema, asthma, or food allergies.

Fish oil supplementation does not reduce the risk of childhood allergic disease in high-risk infants, despite improvement in the infants' n-3 PUFA status. Ongoing studies will help to determine whether there is any "window of opportunity" for allergy intervention using fish oil supplementation.

COMMENT: *Dr. Susan Prescott's group in Perth, Australia, continues to research potential modifiable factors responsible for allergic disease in children. Previous studies of fish oil supplementation have yielded mixed results, with the timing of supplementation perceived as the critical variable. It will be interesting to see the effects of supplementation in early infancy followed in these same groups at 2.5 and 5 years of age.*

K.R.M.

D'Vaz N, Meldrum SJ, Dunstan JA, et al: Postnatal fish oil supplementation in high-risk infants to prevent allergy.

Pediatrics. 2012;130:674-682. ◆◆

Cord Blood Vitamin D Linked to Atopic Dermatitis in Infancy

VITAMIN D insufficiency is being investigated as a possible predisposing factor to childhood allergy. Exposure to vitamin D during gestation, as measured by cord blood 25-hydroxyvitamin D₃ (25[OH]D₃) levels, was evaluated for associations with allergic disease in infancy.

The study included 231 infants at high risk of allergy, drawn from an Australian birth cohort. Cord blood 25(OH)D₃ was analyzed for association with the development of eczema, allergic sensitization, and IgE-mediated food allergy during the first year of life. Cord blood 25(OH)D₃ was significantly associated with maternal use of vitamin D supplements, but not with dietary vitamin D intake. Seasonal variations were observed, suggesting that maternal sunlight exposure affected vitamin D sta-

tus during gestation. Eczema was more than twice as likely to develop in infants with cord blood 25(OH)D₃ levels of less than 50 nmol/L: odds ratio 2.66, compared to concentrations of 75 nmol/L or greater. Cord blood vitamin D status was unrelated to allergen sensitization, food allergy, or eczema severity.

Reduced exposure to vitamin D in utero is associated with a higher risk of developing eczema during the first year of life. Randomized trials are needed to assess the preventive benefits of interventions to improve vitamin D status during pregnancy.

COMMENT: *Vitamin D insufficiency and deficiency have been associated with atopic disease, but there are numerous unanswered questions. One of the most important questions centers on whether there is a critical "window" for vitamin D intake during development, which might reduce subsequent disease. This is one of a series of studies by Dr. Susan Prescott's group assessing potential modifiable factors responsible for pediatric allergic disease.*

K.R.M.

Jones AP, Palmer D, Zhang G, Prescott SL: Cord blood 25-hydroxyvitamin D₃ and allergic disease during infancy.

Pediatrics. 2012;130:e1128-1135. ◆◆

Risk Factors for Eczema Herpeticum Hospitalization in Children

ECZEMA herpeticum occurs when herpes simplex virus 1 or 2 infection is superimposed on atopic dermatitis. There are no clear guidelines as to which children can be managed as outpatients with oral acyclovir, and which should be hospitalized for IV acyclovir.

Risk factors for hospitalization were retrospectively analyzed in a series of 79 patients with eczema herpeticum at a tertiary pediatric care center. Seventy-six percent of patients had a generalized eruption at presentation. Fever was present in 56% of children, systemic symptoms in 37%, and eye involvement in 10%. Fifty-seven percent were admitted to the hospital.

Hospitalization was more likely for boys, odds ratio (OR) 3.09; patients with fever, OR 5.75, or systemic symptoms, OR 2.98; and infants less than 1 year old, OR 7.17. There was a 8.9% rate of recurrence within 1 month and a 16% rate of repeat episodes after 1 month. Hospitalized children were more likely to have repeat episodes, OR 8.25. Early recurrence was more likely for those with previous eczema herpeticum, OR 6.80; or repeat episodes, OR 9.43.

The study identifies risk factors for hospitalization in children with eczema herpeticum. Children with repeated episodes of eczema herpeticum are at risk of future episodes, suggesting a possible susceptible phenotype.

COMMENT: *Eczema herpeticum is a particularly severe viral complication of atopic dermatitis, with a reported incidence of up to 6%. Anticipating which children may be at higher risk of hospitalization or recurrence is aided by this relatively large retrospective study.* ➤➤

K.R.M.

Luca NJC, Lara-Corrales I, Pope E: *Eczema herpeticum in children: clinical features and factors predictive of hospitalization.*

J Pediatr. 2012;161:671-675. ◆◆

'What We Have Here... Is Failure to Communicate'

CURRENT guidelines for asthma management address patient-provider communication, including asking the patient and family to contribute their views on the asthma treatment plan. Communication during pediatric asthma visits was evaluated in a study using audiotape recordings.

Audio recordings were made during office visits with 259 children and adolescents, aged 8 through 16 years, at five pediatric practices. At home interviews 1 month later, the children reported an average 72% adherence to asthma control medications over the preceding week, while caregivers reported average 85% adherence. Both adherence reports were significantly associated with the patient's asthma management self-efficacy.

Providers asked for the child's and caregiver's input on the asthma management plan in less than 10% of office visits. Caregiver-reported adherence was higher when providers asked for the caregivers' input during the visit.

Asking caregivers for input into the management plan may help to promote medication adherence in children with asthma. The authors believe providers should talk directly to older children about their adherence to asthma control medications, with the goal of assessing potential barriers to medication use.

COMMENT: *With a nod to the movie Cool Hand Luke, we have great potential for a "failure to communicate" when discussing asthma medications and management, as this general pediatric practice study shows. Improving adherence takes an actual discussion, as opposed to dispensing one-way advice. Hopefully, we allergists take the time to really listen to our patients and their families!*

K.R.M.

Sleath B, Carpenter DM, Slota C, et al: *Communication during pediatric asthma visits and self-reported asthma medication adherence.*

J Pediatr. 2012;161:627-633. ◆◆

Can Young Children 'Outgrow' Fear of SCIT Injections?

SUBCUTANEOUS immunotherapy (SCIT) is not currently recommended for very young children, partly because of psychologic distress associated with repeated needle injections. The authors report the first prospective study of fear and distress associated with SCIT injections in children younger than age 4.

The study included 18 children, mean age 37 months,

receiving a total of 788 SCIT injections. For each injection, the parent and nurse graded the child's fear on a 0-to-10 scale. The children made a median of 49 injection visits over a median of 81.5 weeks.

During this time, 83% of the children lost their fear of injections; mean time to achieve a fear score of 0 was 8.4 visits. Children who missed more visits were more likely to have persistent fear of injections. Fear scores were unrelated to the child's age, adverse events, number of injections, and change of injection personnel.

Very young children undergoing SCIT appear to lose their fear of injections over time. Even at the first injection, moderate to high fear scores (4 to 6 or higher) are uncommon. Children with longer intervals between visits are more likely to exhibit fear of injections.

COMMENT: *This study addressed the effects of fear in young children during immunotherapy. Because of the potential benefits of SCIT, the results are especially important to allergists who care for the youngest patients. All but one child lost "the fear" of injections over time. Interestingly, the longer the intervals between injections, the more likely the patients would have fear of the injection. This article reminds us that even young patients may lose their fear of SCIT injections, and become emotionally "tolerant" of injections over time.*

V.H.-T.

de Vos G, Shankar V, Nazari R, et al: *Fear of repeated injections in children younger than 4 years receiving subcutaneous allergy immunotherapy.*

Ann Allergy Asthma Immunol. 2012;109:465-469. ◆◆

Allergy Linked to Mood Disorders

SOME research has linked allergy to depression and anxiety disorders, although the nature and mechanisms of these associations remain unclear. Data from a large population survey were used to assess the relationship between allergies and mood and anxiety, including the effects of allergy treatment.

The study included data on 4,181 adult participants (age 18 to 65 years) in the German National Health Interview and Examination Survey. Associations between physician-diagnosed allergy and mental disorders were analyzed.

Participants with allergic diagnoses were more likely to have any anxiety disorder, odds ratio (OR) 1.3; panic attacks and panic disorder, OR 1.6; generalized anxiety disorder, OR 1.8; any mood disorder and depression, OR 1.4; and bipolar disorder, OR 2.0. All associations became nonsignificant after adjustment for desensitization treatment. Allergy treatment was associated with a lower prevalence of any mood or anxiety disorder: OR 0.65.

These population-based data support an association between physician-diagnosed allergy and the presence of mood and anxiety disorders. Treatment may mitigate the psychologic associations with allergy; more study is needed to clarify the sequence of allergy, allergy treatment, and mental disorders. ➤➤

COMMENT: *Depression and anxiety have been previously shown to be more symptomatic among patients with allergic rhinitis symptoms. In this study, patients receiving allergy treatment were less likely to have anxiety or depression. These results remind us to include consideration of relevant symptoms other than congestion, rhinorrhea, and sneezing when deciding whether to treat rhinitis.*

S.A.T.

Goodwin RD, Galea S, Perzanowski M, Jacobi F: *Impact of allergy treatment on the association between allergies and mood and anxiety in a population sample.* Clin Exp Allergy. 2012; 42:1765-1771. ◆◆

Link between Rhinitis and Otitis Media May Require Allergy

ALLERGIC inflammation may contribute to the very common problem of otitis media with effusion (OME). This issue was addressed using strict definitions of atopic disease and OME in 6-year-old children from a birth cohort study.

The analysis included 291 children in the sixth year of life, enrolled in the Copenhagen Prospective Study on Asthma in Childhood 2000 birth cohort. Tympanometry and other objective assessments were used to determine the presence of OME; pre-defined algorithms were followed for prospective diagnosis of asthma, eczema, allergic rhinitis, and nonallergic rhinitis. Associations between OME and allergic disease were analyzed, with adjustment for pet and smoking exposure, paternal atopy, household income, older siblings, sex, and number of acute OME episodes.

The diagnosis of OME was made in 39% of children. There was a significant association between OME and allergic rhinitis: adjusted odds ratio 3.36. Otitis media with effusion was unrelated to the other allergic diagnoses assessed, or to nasal eosinophilia or mucosal swelling.

The close association between OME and allergic rhinitis in young children suggests a contribution of allergic inflammation, rather than nasal mucosal swelling. The findings highlight the need for increased attention to OME among children with allergic rhinitis.

COMMENT: *The correlation between recurrent otitis media and allergic rhinitis has long been assumed to occur due to mechanical obstruction of the eustachian tubes. In this birth cohort study there was a strong correlation between OME and allergic rhinitis, but not with nonallergic rhinitis or physical findings of nasal turbinate edema. Additional studies are required to clarify whether aeroallergens have a direct effect on the middle ear.*

S.A.T.

Kreiner-Möller E, Chawes BLK, Caye-Thomasen P, et al: *Allergic rhinitis is association with otitis media with effusion: a birth cohort study.*

Clin Exp Allergy. 2012;42:1615-1620. ◆◆

Positive Exercise Test Predicts Persistent Asthma 20 Years Later

ASTHMA is common in early adulthood, but little is known about long-term risk factors for persistent asthma. This issue was addressed in a study of military conscripts with asthma, including the predictive significance of spirometry and an exercise test.

The study included 119 Swedish male military conscripts referred for evaluation of asthma between 1987 and 1990. The results of asthma evaluation at that time were compared with the findings on a follow-up visit 20 years later, at approximately age 40.

Overall, asthma was less severe at follow-up: 11.8% of men were in remission, 42.0% had intermittent asthma, 10.9% had mild persistent asthma, and 35.3% had moderate/severe persistent asthma. On multivariate analysis, men with a positive exercise test at baseline were more likely to have persistent asthma at follow-up: odds ratio 3.2. Significant spirometric predictors were a decreased FEV₁/FVC ratio, OR 4.0; and a decreased FEF_{50%}, OR 2.8.

In this sample of asthmatic young men, nearly half have persistent asthma 20 years later. A positive exercise test and obstructive findings on spirometry may be useful long-term prognostic factors for asthma severity.

COMMENT: *In this study of Swedish male conscripts with asthma, positive results on a standardized free-running field exercise challenge at baseline predicted asthma at 20 years' follow-up. Likelihood of persistent asthma was increased 3-fold for a positive exercise test, 4-fold for a decreased FEV₁/FVC, and 3-fold for a decreased FEF_{50%}. In the 50% of these men with persistent asthma 20 years later, spirometry with obstruction and positive exercise challenge at baseline were predictive of persistence and severity of asthma. The take-home message is that a positive exercise challenge at baseline and obstructive results on spirometry may be prognostic indices for persistence and severity of asthma even 20 years later.*

C.C.R.

Lindström I, Suojalehto H, Lindholm H, et al: *Positive exercise test and obstructive spirometry in young male conscripts associated with persistent asthma 20 years later.*

J Asthma. 2012;49:1051-1059. ◆◆

Some Adults with Lactose Intolerance Have Milk Allergy

LACTOSE intolerance due to hypolactasia is a common condition. In adults reporting adverse reactions to cow's milk, physicians may not consider or test for the possibility of IgE-mediate cow's milk allergy. This may result in diagnostic bias, with patients being labeled as lactose intolerant without appropriate allergy testing. A series of adult patients with refractory lactose intolerance were tested for allergy to cow's milk.

The study included 46 adult patients with convincing clinical histories of adverse reactions to cow's milk ►►

who were having continued symptoms despite a lactose-free diet. All had lactose intolerance confirmed by hydrogen breath testing. The patients underwent skin prick and immunoblot testing for cow's milk allergy. Twenty subjects with clinical tolerance to cow's milk were studied as controls.

Of this group of patients with lactose intolerance, 69.5% had positive skin-prick tests to whole cow's milk. The patients also had high rates of positive skin-prick tests to other milk proteins, including alpha-lactalbumin in 36.9%, beta-lactoglobulin and caseins in 56.5% each, goat's milk in 54.3%, and soy in 50%.

Skin reactions to casein were observed in 78.2% of patients who reacted to soy and 34.7% of those who did not react to soy. Immunoblot testing for specific IgE was positive for alpha-lactalbumin in 21.7% of patients, beta-lactoglobulin in 63%, caseins in 67.3%, and bovine serum albumin in 2.1%. Just 5 patients had no evidence of IgE-mediated sensitization--a rate of 10.8%.

Many adult patients with lactose intolerance may also have IgE-mediated sensitization to milk proteins. Testing for cow's milk allergy may aid diagnostic in treatment decision-making in patients with "lactose intolerance" who do not respond to a lactose-free diet.

COMMENT: *This thought-provoking study investigated adults with lactose intolerance who remained symptomatic despite following a lactose-free diet. Most patients with symptoms had positive skin-prick tests to cow's milk. Some also had positive tests to other milk proteins; in contrast, patients who tolerated cow's milk had negative results to all milk proteins on skin testing. The authors recommend consideration of testing to cow's milk proteins in patients whose symptoms persist despite a lactose-free diet. Although the patients may not be truly allergic to cow's milk, sensitization was seen in these patients; this additional information may improve their quality of life.*

V.H.-T.

Olivier CE, Lorena SLS, Pavan CR, et al: Is it just lactose intolerance?

Allergy Asthma Proc. 2012;33:432-436. ◆◆

REVIEWS OF NOTE

COMMENT: *Allergy/immunology specialists are increasingly called upon to manage dermatologic conditions suspected to have an allergic etiology or component. This review systematically outlines the evaluation and management of hand eczema, using the example of a 33-year-old nurse and mother with nickel allergy, history of childhood eczema, and current hand eczema. Vivid photos of the conditions to be considered in the differential diagnosis as well as algorithms on management options make this a must-read for praallergists.*

C.D.

Coenraads P-J: Hand eczema.

N Engl J Med. 2012;367:1829-1837. ◆◆

COMMENT: *Since the introduction of immunoglobulin replacement therapy in the 1950s, more than a dozen new and improved preparations suitable for intravenous administration have been approved for the treatment of primary immunodeficiency diseases. This informative review of the mechanisms and use of intravenous gammaglobulin in a wide variety of autoimmune and inflammatory disorders--ranging from blistering skin diseases to transplant rejection--is supplemented by lucid illustrations and informative tables.*

C.D.

Gelfand EW: Intravenous and immune globulin in autoimmune and inflammatory diseases.

N Engl J Med. 2012;367:2015-2025. ◆◆

COMMENT: *These two "Images in Clinical Medicine" features provide descriptive graphics and concise summaries illustrating the presentation, evaluation, and management of a patient presenting with anaphylaxis to blue dye and another with suspected type III hereditary angioedema.*

C.D.

Gil-Moreno A, Perez-Benavente A: Anaphylaxis associated with blue dye.

N Engl J Med. 2012;367:2026.

Ebo DG, Bridts CH: Disfiguring angioedema.

N Engl J Med. 2012;367:1539. ◆◆

COMMENT: *This exciting review article addresses the use of new antagonists of CRTH2 (chemoattractant receptor homologous molecule expressed on Th2 cells) as a treatment option for patients with allergic disease. As a recently described prostaglandin D2 receptor, CRTH2 plays an important role in allergic disease because of its effects on activation and chemotaxis of Th2 cells, eosinophils, and basophils. The authors review the decrease in serum IgE production in CRTH2-deficient mice. They also discuss the use of CRTH2 antagonist OCOO459 in patients with asthma, which produced statistically significant improvement in nighttime symptoms as well as decreases in IgE levels. It also appears promising for the treatment of patients with nasal polyps. This review is a reminder that new therapeutic options continue to aid in the treatment of our allergic patients, as new receptors and targets are described.*

V.H.-T.

Townley RG, Agrawal S: CRTH2 antagonists in the treatment of allergic responses involving TH2 cells, basophils, and eosinophils.

Ann Allergy Asthma Immunol. 2012;109:365-374. ◆◆