

ALLERGYWATCH®

"10th Anniversary Volume"

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

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Peanut OIT Protocol Shows Good Safety Profile. . .

ORAL immunotherapy (OIT) may offer a useful new alternative for the treatment of peanut allergy. The possibility of serious adverse reactions to orally ingested peanut allergen raises obvious safety concerns. This study evaluated the safety of a peanut OIT protocol in children.

The study included 28 patients, mean age 4.8 years, with confirmed peanut allergy. All received peanut OIT, with an initial escalation day followed by a buildup phase and home dosing phase, up to a peanut protein dose of 300 mg. Skin, upper respiratory tract, chest, and abdominal symptoms were documented after each dosing, with daily diaries used during the home phase.

Twenty patients completed all phases of the OIT protocol. Most patients had symptoms during the initial escalation day, including upper respiratory symptoms in 79% and abdominal symptoms in 68%. Eighteen per-

cent of patients had mild wheezing during the escalation day.

During the buildup phase, there was a 46% rate of post-dose symptoms, including a 29% rate of upper respiratory symptoms and a 24% rate of skin symptoms. During the home phase, the risk of reactions was 3.5%, with a 1.2% rate of upper respiratory symptoms and a 1.1% rate of skin symptoms. Overall, treatment was needed after 0.7% of home doses. Two patients required epinephrine treatment (one time each) after a home dose.

The results support the safety of an OIT protocol for peanut-allergic children. Most allergic reactions occur during the initial escalation day, when patients are in a controlled setting under the care of trained personnel. The rate of allergic symptoms during the home phase of the protocol is low, with most reactions being mild.

COMMENT: This article presents safety and efficacy data for an OIT protocol for children with peanut protein allergy. Although substantial numbers of ►►

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children had significant reactions during the initial escalation and buildup phase, the end result was that 93% were able to tolerate approximately 10 peanuts at the conclusion of the buildup. This OIT protocol offers hope to the many families with peanut-allergic children.

S.M.F.

Hofmann AM, Scurlock AM, Jones SM, et al: Safety of a peanut oral (OIT) protocol in children with peanut allergy.

J Allergy Clin Immunol 2009;124:286-291.



... Along with Efficacy and Immune Effects

ORAL immunotherapy has the potential to induce clinical desensitization in patients with peanut allergy. Clinical and immunologic responses to an OIT protocol in children with peanut allergy are reported.

The analysis included 29 children undergoing OIT for peanut allergy, median age 57.5 months. On food challenge performed at the end of the OIT protocol, all but 2 patients were able to ingest 3.9 g of peanut protein.

Evaluation of immunologic responses showed a significant reduction in titrated skin prick tests by 6 months, along with reduced basophil activation. A reduction in peanut-specific IgE was noted at 12 to 16 months, with an accompanying increase in IgG₄. In an in vitro binding assay, formation of IgE-peanut complexes was inhibited in the presence of serum factors. From 6 to 12 months, secretion of interleukin (IL)-10, IL-5, interferon-γ, and tumor necrosis factor-α increased significantly. On flow cytometry, peanut-specific forkhead box protein 3 (FoxP3+) T-cells increased from 6 to 12 months, decreasing thereafter. Microarray assays showed downregulation of genes in T-cell apoptotic pathways.

The OIT protocol induces clinical desensitization to peanut, with humoral and cellular immune responses occurring over the long-term. The documented effects on T-cell apoptotic pathways may help to explain the mechanism of OIT's clinical efficacy.

COMMENT: Food anaphylaxis is frightening and sometimes fatal. Avoidance is difficult. Peanut allergy is the "poster child" for this group, because of its prevalence and severity. This study of 29 children shows that an OIT regimen resulted in clinical desensitization of all children who completed at least 8 months of the regimen. Oral challenge doses of 3.9 grams of peanut protein were tolerated by 27 of 29 patients. There remain many unanswered questions, and the procedure is not ready for general use by any means, but these data are very promising.

R.J.M.

Jones SM, Pons L, Roberts JL, et al: Clinical efficacy and immune regulation with peanut oral immunotherapy.

J Allergy Clin Immunol. 2009;124:292-300.



Steep Rise in Allergic Sensitization in Swedish Children

MOST studies of the recent increase in allergic disease have focused on asthma, with few objective data on allergic sensitization. The few studies of sensitization trends have yielded conflicting results, with little information on the reasons for change. Data from two cohort studies were used to analyze changes in the prevalence of allergic sensitization among Swedish children over the past decade.

Skin prick tests were performed in large groups of 7- to 8-year-old children in Northern Sweden in 1996 and 2006. The cohorts included 2,148 and 1,700 children, respectively; participation rates were around 90%. The two studies used identical methods to document sensitization to 10 common airborne allergens. Allergic disease symptoms and risk factors were ►►

assessed by a detailed parental questionnaire.

The percentage of children with at least one positive skin prick test increased from 21% in 1996 to 30% in 2006. At both times, cat was the most frequent sensitizing allergen, with an increase from 13% to 19%. Other sensitization patterns were also similar, with low rates of sensitization to mites and mold in both cohorts.

Children with a family history of allergies were more likely to be sensitized, odds ratio 1.7. In 1996, children in rural areas and those with multiple siblings were at lower risk; by 2006, these factors were no longer protective. During the decade studied rates of respiratory infections and parental smoking decreased, while other risk factors remained similar. The prevalence of wheezing was unchanged: about 12% in both cohorts. Rates of rhinitis and eczema remained similar as well.

Over the past decade, the rate of allergic sensitization among Swedish schoolchildren increased by nearly 50%. Yet there is no apparent change in clinical allergy symptoms, possibly reflecting reductions in certain environmental factors. The authors predict that further follow-up will show a continuous increase in allergic disease as the children enter their preteen and adolescent years.

COMMENT: *In this unique report, similar cohorts of children were studied at a 10-year interval for evidence of allergies. It is somewhat surprising that, although the prevalence of positive allergy skin tests increased 45% during that interval, the prevalence of clinical allergy symptoms didn't change. The authors suggest that improvements in lifestyle or environment—including significant reductions in parent smoking and respiratory infections—may help reduce clinical symptoms in allergic children.*

S.M.F.

Rönmark E, Bjerg A, Perzanowski M, et al: Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden.

J Allergy Clin Immunol. 2009;124:357-363. ◆◆

Basic Science of Atopic Dermatitis: What's New?

PREVIOUS studies have linked atopic dermatitis (AD) to mutations of the filaggrin gene (*FLG*). This suggests a primary barrier abnormality, although the mechanism provoking inflammation is unknown. This issue was addressed using a mouse model of *FLG* deficiency.

The experiments used the "flaky tail" mouse, which has a frameshift mutation in the profilaggrin gene similar to some mutations observed in humans with AD. The *flg* deficiency in this model produced a significant permeability barrier abnormality, localized to the extracellular membranes of the stratum corneum. This barrier abnormality was associated with low-grade inflammation with increased bidirectional, paracellular permeability of water-soluble xenobiotics, the result of impaired lamellar body secretion.

In these *flg*-deficient mice, repeated exposure to low-dose haptens led to inflammatory changes similar to human AD, with further worsening of barrier function. Similar hapten exposure produced no inflammation in wild-type mice. The inflammation was associated with certain Th2 characteristics.

The findings in flaky-tail mice suggest that *FLG* deficiency produces a paracellular barrier abnormality, resulting in lower inflammatory thresholds in topical irritants or haptens. This may explain the enhanced antigen penetration reported in human AD associated with *FLG* deficiency.

COMMENT: *Atopic dermatitis is associated with allergies, and accumulating evidence indicates an "outside-in" direction of sensitization. In other words, the dermatitis may precede the allergy, rather than the other way around. In the stratum corneum, filaggrin is a structural protein, deficiency of which causes a barrier defect that permits increased passage of environmental and food proteins into the deeper skin, where sensitization probably occurs. This study in a mouse model supports the theory.*

R.J.M.

Scharschmidt TC, Man M-Q, Hatano Y, et al: Filaggrin deficiency confers a paracellular barrier abnormality that reduces inflammatory thresholds to irritants and haptens.

J Allergy Clin Immunol. 2009;124:496-506. ◆◆

FILAGGRIN deficiency has been reported in up to 20% of patients with AD. Recent studies have reported interleukin (IL)-17-producing cells in the dermis of acute AD lesions; along with other findings, this suggests involvement of local and systemic Th17 as well as Th2 responses. The flaky tail mouse model was used to assess the role of filaggrin deficiency in skin inflammation and epicutaneous sensitization to protein antigen.

Filaggrin-deficient flaky tail mice developed eczematous skin lesions by 28 weeks, accompanied by progressive increases in serum IgE and IgG₁. Apparently normal skin from 8-week-old animals showed epidermal thickening, increased dermal infiltration with CD4⁺ cells, and expression of IL-17, IL-6, and IL-23 mRNA. At 32 weeks, skin lesion samples showed similar but increased changes, along with increased IL-4 mRNA.

When ovalbumin was epicutaneously applied to the skin of 8-week-old flaky tail mice, the result was epidermal thickening, dermal infiltration by CD4⁺ cells, and expression of IL-17, IL-6, IL-23, IL-4, and interferon- γ mRNA. Splenocytes from these animals secreted cytokines when stimulated with ovalbumin; their sera showed ovalbumin-specific IgE and IgG₁. These responses did not occur in wild-type controls.

Filaggrin-deficient flaky tail mice develop a Th17-dominated pattern of skin inflammation and eczematous lesions as they reach maturity. These animals also develop sensitization in response to skin contact with protein antigens that are excluded by normal skin barrier function. ➤➤

TWO common mutations of the filaggrin gene (*FLG*)-R501X and 2282del4--have been identified as genetic risk factors for AD. Atopic dermatitis eczema herpeticum (ADEH), resulting from disseminated cutaneous infection with herpes simplex virus, is a rare but serious complication of AD. Mutations of *FLG* were evaluated as a risk factor ADEH in European American and African American populations.

FLG genotyping was performed in 278 European American patients with AD, 112 of whom had ADEH, and in 157 controls. Both common loss-of-function mutations were associated with AD, with odds ratios (ORs) of 7.1 for R501X and 5.6 for 2282del4. Among AD patients, the R501X allele was more frequent in those with ADEH: 25% versus 9%, OR 3.4. Allele frequencies in the AD group were 7.8% and 8.8%, respectively. The association was even stronger for subjects with both mutations, OR 10.1.

A replication study was performed in 339 African American patients: 187 with ADEH, of whom 32 had ADEH. The R501X mutation was found in 3.2% of AD patients, including 9.4% of those with AD, compared to none of the healthy control group. None of the African-American ADEH patients, and less than 1% of the controls, had the 2282del4 mutation.

The findings confirm the association between the R501X mutation and AD, and suggest an even stronger association with ADEH. The association between R501X and ADEH is found in both European American and African American populations. Abnormal skin barrier function appears to be a key contributor to ADEH.

COMMENT: *The preceding two studies investigate the role of filaggrin in AD. Changes in the gene encoding the epidermal structural protein FLG have been known as major risk factors for skin barrier dysfunction and subsequent development and progression of AD. Oyoshi et al found that flaky tail mice, which are a model for AD, develop FLG deficiency and a Th17-dominated cytokine response as their skin lesions progress. Gao et al used data from the Atopic Dermatitis and Vaccinia Network to characterize the frequency of the genetic mutation R501X, which encodes FLG. This mutation is a strong predictor of severity of AD and, more importantly, the risk for eczema herpeticum in various populations. Understanding the role of FLG can help us understand the skin barrier dysfunction in our patients with AD.*

S.M.F.

Oyoshi MK, Murphy GF, Geha RS: Filaggrin-deficient mice exhibit Th17-dominated skin inflammation and permissiveness to epicutaneous sensitization with protein antigen.

J Allergy Clin Immunol. 2009;124:485-493.

Gao P-S, Rafaels MR, Hand T, et al: Filaggrin mutations that confer risk of atopic dermatitis confer greater risk for eczema herpeticum.

J Allergy Clin Immunol. 2009;124:507-513. ♦♦

AUTOREACTIVE serum IgE antibodies have been identified in patients with AD, and linked to AD severity. Although a number of different self-antigens

have been reported, the full range of IgE-binding self-antigens associated with AD remains unclear. This study sought to estimate the repertoire size of autoreactive proteins related to AD, and to evaluate the humoral and T-cell responses to these self-antigens.

High-throughput techniques were used to screen a human phage surface-displayed cDNA library using serum IgE from patients with AD. Through the use of affinity selection and high-density arrays, the investigators identified 140 distinct sequences encoding potential IgE self-binding antigens associated with AD, including 16 previously reported self-antigen sequences. Another 86 sequences encoded known human proteins, 28 showed sequence identify with genomic contigs, 7 predicted proteins, and 3 were homologous with environmental allergens.

The proteins encoded by 5 of the putative IgE-binding self-antigens were cloned to assess their IgE-binding ability. Immunoblotting and enzyme-linked immunosorbent assays demonstrated IgE antibodies to these proteins in sera from patients with AD. In further experiments, the antibodies induced mediator release from basophils from these sensitized patients.

High-throughput screening techniques identify a wide range of IgE-binding self-antigens associated with AD. Evaluation of immune responses suggests that the antigens may contribute to skin inflammation via IgE antibody binding or specific T-cell activation. The discovery of these self-antigens may help to clarify the autoimmune factors involved in chronic allergic diseases.

COMMENT: *The immunopathogenesis of AD is very complex, and recent information on autoreactive IgE to skin self-antigens makes the picture even more complex. This study identified 140 potential self-antigens associated with AD. A few of them were homologous with environmental antigens, but most were known human proteins. It can't be said how these auto-reactive IgE antibodies are related to AD.*

R.J.M.

Zeller S, Rhyner C, Meyer N, et al: Exploring the repertoire of IgE-binding self-antigens associated with atopic eczema.

J Allergy Clin Immunol. 2009;124:278-285. ♦♦

Obstructive Sleep Apnea Linked to Increased Urinary LTE₄

PATIENTS with obstructive sleep apnea (OSA) are at increased risk of cardiovascular disease and death from cardiovascular causes. The frequent association of OSA with obesity makes it difficult to assess the inflammatory contribution to this association. Urinary leukotriene E₄, a marker of proinflammatory cysteinyl leukotriene production, was evaluated in patients with OSA.

Liquid chromatography-tandem mass spectrometry was performed to measure urinary LTE₄ levels in 40 nonobese patients with OSA and 25 controls matched for age, sex, and body mass index. Urinary LTE₄ >>>

was significantly elevated in the OSA group, and correlated with the percentage of total sleep time at an oxygen saturation of less than 90%. Urinary LTE₄ was unrelated to metabolic parameters.

The contribution of obesity and other potential confounders was evaluated in a larger cohort of 72 OSA patients. Urinary LTE₄ was independently associated with BMI and time at an oxygen saturation of 90%—as a predictor of LTE₄, BMI was stronger than hypoxia severity.

A peripheral blood mononuclear cell assay showed that urinary LTE₄ was related to expression of 5-lipoxygenase activating protein mRNA. A trial of continuous positive airway pressure resulted in a significant 22% reduction in urinary LTE₄, but only in OSA patients with normal BMI.

Patients with OSA show increased urinary LTE₄, suggesting activation of the cysteinyl leukotriene pathway. The increase in LTE₄ is strongly associated with obesity and to a lesser extent with nocturnal oxygen desaturation. Cysteinyl leukotrienes could be an important contributor to the increased cardiovascular disease risk in OSA.

COMMENT: Urinary LTE₄, a biomarker of inflammation, is elevated in allergic patients and in those with coronary artery disease, cardiac ischemia, and diabetes. In this carefully selected, nonobese study population, increased production of LTE₄ was associated with OSA, particularly when associated with hypoxia. This suggests that in patients with OSA there is activation of the cysteinyl leukotriene pathway, which could be a contributing factor to the cardiovascular morbidity associated with OSA.

S.M.F.

Stanke-Labesque F, Bäck M, Lefebvre B, et al: Increased urinary leukotriene E₄ excretion in obstructive sleep apnea: effects of obesity and hypoxia.

J Allergy Clin Immunol. 2009;124:364-370. ♦♦

Disease Control Hard to Predict in Well-Treated Urban Youth with Asthma

TREATMENT consistent with evidence-based guidelines is a major priority in the management of adolescents with asthma. However, little is known about the factors associated with asthma control in patients receiving guideline-based care. Predictors of disease control were evaluated in a large sample of young inner-city patients receiving guideline-based therapy for asthma.

The study included 546 patients with persistent asthma, aged 10 to 20, enrolled in the Asthma Control Evaluation study at centers in 10 U.S. cities. African Americans accounted for 64% of participants and Hispanics for 23%. After extensive baseline evaluation, participants received 46 weeks of guideline-based, optimal asthma management. Potential predictors of future asthma control were evaluated, including exhaled nitric oxide, total and specific IgE, skin test reactivity, asthma symptoms, and pulmonary function.

Treatment adherence averaged 87% at follow-up, yet 72% of participants had at least one visit with poor asthma control. The baseline factors evaluated were not strong predictors of disease control—they accounted for only 11.4% of the variance in maximum symptom days and 12.6% of the variance in exacerbations. Asthma symptoms, albuterol use, previous exacerbations, and lung function had some predictive value for exacerbations. Asthma symptoms, albuterol use, and previous exacerbations were also modest predictors of maximum symptom days, but lung function was not.

In this study of inner-city youth with high adherence to guideline-based asthma care, the baseline factors typically associated with future disease control have only low predictive value. More complex indicators, including exhaled nitric oxide and markers of atopy, are also of limited value. As efforts to increase guideline-based care for this patient population increase, better clinical predictors of asthma control are needed.

COMMENT: What is the best measure of asthma control? In this population of 546 inner-city adolescents with well-controlled persistent asthma, none of our usual markers were predictive for future symptoms and exacerbations. These markers included lung function, allergic sensitivity, exhaled NO, and airway hyperreactivity. We do need a good measure to predict impairment and risk in our chronic asthmatic patients, particularly those who are adherent to our therapy recommendations.

S.M.F.

Gruchalla RS, Sampson HA, Matsui E, et al: Asthma morbidity among inner-city adolescents receiving guidelines-based therapy: Role of predictors in the setting of high adherence.

J Allergy Clin Immunol. 2009;124:213-221. ♦♦

Asthma Can Be 'Th2-High' or 'Th2-Low'

THE proinflammatory T-helper 2 cytokines interleukin (IL)-4, IL-5, and IL-13 are potentially important therapeutic targets in asthma. However, a growing body of evidence suggests that some cases of asthma are driven by other types of inflammation. This study sought to determine whether clinical variations in asthma are related to heterogeneity in Th2 inflammation.

Based on microarray and polymerase chain reaction assays, 42 patients with mild to moderate asthma (and 28 controls) were classified as having low or high expression of IL-13-inducible genes. This classification was then compared with cytokine expression in bronchial biopsies, markers of airway inflammation and remodeling, and response to inhaled corticosteroids.

Based on gene expression studies, 22 asthma patients were classified as having a high Th2 signature. The remaining 20 patients had a low Th2 signature—a pattern identical to that found in nonasthmatic controls. The patients with Th2-high vs Th2-low asthma were similar in terms of demographic characteristics, severity, and bronchodilator responsiveness, although the ►►

high-Th2 group had worse airway hyperresponsiveness. Only patients with high-Th2 asthma had the expected improvement in lung function in response to inhaled corticosteroids.

The two groups also showed significant differences in expression of IL-5 and IL-13 in bronchial biopsies, serum IgE level, blood and airway eosinophilia, subepithelial fibrosis, and airway mucin gene expression. The Th2 markers were reproducible on repeat examination.

Asthma can be classified into two distinct molecular phenotypes, based on the degree of Th2 inflammation. These findings suggest that treatments targeting Th2 cytokines will only be effective in about half of patients with mild to moderate asthma. More research is needed to explain the large number of cases of non-Th2-driven asthma.

COMMENT: *This extremely interesting article sets the immunologic basis for response to commonly used controller medications. It continues to refine our understanding of the groups of patients who are not likely to respond to current therapies. We hope studies like this will provide the foundation for significant therapeutic advances.*

B.E.C.

Woodruff PG, Modrek B, Choy DF, et al: T-helper type 2-driven inflammation defines major subphenotypes of asthma.

Am J Respir Crit Care Med. 2009;180:388-395. ♦♦

Why Don't Mucus Plugs Dissolve in Acute Asthma?

AIRWAY mucus plugs--composed of mucin glycoproteins mixed with plasma proteins--are a major contributor to airway obstruction in acute asthma. Despite their importance, these plugs are not addressed by current treatments. This study sought evidence of impaired airway mucus clearance in acute severe asthma.

Samples of airway mucus were obtained from patients with acute severe asthma at various times during the exacerbation and from healthy controls. The physical properties of the mucus gel, the size profile of the mucins, and the degradation products of albumin were compared between the two groups of samples.

The findings in nonasthmatic subjects suggested that proteases normally degrade mucus gel, and that this process is inhibited by albumin. The degradation process was inhibited in mucus samples obtained during the height of the acute asthma exacerbation, and returned to normal during the recovery period. Immunoblotting showed that albumin was a substrate of neutrophil elastase, and that albumin degradation products were abundant in the airway during asthma exacerbations.

Acute severe asthma is associated with inhibition of normal mucin degradation in the airway, resulting from a protease-dependent excess of plasma proteins. The findings raise the possibility of effective new mucolytic therapy approaches to acute asthma.

COMMENT: *The inhibition of protease-dependent mucin digestion in acute asthma and the role that plasma proteins play in this process are an evolving story. These data provide mechanistic insight into the pathophysiology of mucous impaction in the airways in acute asthma. They also help to define the contribution of neutrophil protease in restoring airway patency by digesting mucous plugs.*

B.E.C.

Innes AL, Carrington SD, Thornton DJ, et al: Ex vivo sputum analysis reveals impairment of protease-dependent mucus degradation by plasma proteins in acute asthma.

Am J Respir Crit Care Med. 2009;180:203-210. ♦♦

Same-Day Changes in Pollutant Levels Affect Diurnal FEV₁

SEVERAL studies have shown the adverse effects of air pollution on respiratory health. Most of these studies have compared daily pollution levels with daily mortality or hospitalization data; there are few data on how air pollution affects within-day variations in lung function. The relationship between hourly air pollution data and pulmonary function was assessed in a sample of children with asthma.

For 28 consecutive days, 128 children with asthma in Windsor, Ontario, underwent morning and evening measurement of FEV₁. The diurnal change (morning to evening) in FEV₁ was compared with hourly monitoring data on air pollutant levels.

An interquartile range increase in the mean concentration of fine particulates 2.5 µm in diameter (PM_{2.5}) over the previous 24 hours--equivalent to 6.0 µg/m³--was associated with a 0.54% decrease in evening FEV₁. Similar associations were noted in two-pollutant models including ozone, nitrogen, and sulfur dioxide. An interquartile range increase in mean daytime concentration of PM_{2.5}--equivalent to 6.5 µg/m³--was associated with a 0.73% decrease in FEV₁ from morning to evening. This pattern was expressed by the equation 100 x (FEV₁ evening - FEV₁ morning)/FEV₁ morning.

Even relatively minor increases in air pollutant levels may lead to significant reductions in asthmatic children--even within a single day. Fine particulate pollution appears to have the greatest impact on diurnal change in FEV₁.

COMMENT: *This article summarizes the effect of even very low concentrations of urban air pollution to worsening lung function. The degree of pulmonary function change is significant even with a very short exposure time. It should be noted that these effects were blocked in patients taking bronchodilators.*

B.E.C.

Dales R, Chen L, Frescura AM, et al: Acute effects of outdoor air pollution on forced expiratory volume in 1 s: a panel study of schoolchildren with asthma.

Eur Respir J. 2009;34:316-323. ♦♦

Predicting Egg Tolerance in Egg Allergy

CHILDREN with egg allergy need regular follow-up until they become tolerant of egg, as most eventually do. If skin prick testing (SPT) and specific IgE levels could accurately identify patients with persistent egg allergy, the risks associated with challenge testing could be avoided. The predictive value of SPT and specific IgE levels were assessed in children with egg allergy.

The prospective study included 157 children under age 16 with IgE-mediated egg allergy and at least 6 months on a strict egg-avoidance diet. Sixty-one percent of the patients were boys and the median age was 2.5 years; two-thirds had atopic dermatitis. All children underwent SPT, measurement of specific IgE levels to egg allergens, and double-blind placebo-controlled egg challenge. All tests were interpreted without knowledge of the other results. The diagnostic performance of the SPT and specific IgE levels was assessed by receiver operating characteristic curve analysis.

The results of oral egg challenge were positive in 63.7% of children. Both SPT and specific IgE measurement were significant predictors of positive oral challenge. On egg white SPT, positive predictive value (PPV) was 92.3% for a 7 mm response and 95.6% for a 9 mm response. On egg-specific IgE measurement, positive predictive values were 90.4% at a level of 1.5 kU/L and 100% at 25 kU/L. Accuracy was lower with yolk and ovalbumin SPTs, and lowest with ovotransferrin and lysozyme SPTs.

This prospective study confirms the value of SPT and specific IgE measurement in assessing persistence of egg allergy in children. The presented cutoff values identify patients with a 90% or higher likelihood of positive egg challenge. The accuracy of SPT is highest when egg white complete extract is used.

COMMENT: This very thorough study from Madrid focused on children with a history of proven clinical allergy and helps confirm both skin testing and in vitro specific IgE thresholds for predicting tolerance versus persistent clinical allergy. Take-home messages: 1. Egg white is the most helpful extract to use for testing; 2. Two-thirds of children with either a current skin test wheal less than 7mm or specific IgE less than 1.3 kU/L tolerated egg challenge without symptoms; 3. When either the skin test or in vitro test results were above these thresholds, there was a 90% chance of a clinical reaction to egg.

S.A.T.

Diéguez M^aC, Cerecedo I, Muriel A, et al: Utility of diagnostic tests in the follow-up of egg-allergic children. *Clin Exp Allergy*. 2009;39:1575-1584. ♦♦

Sensitizations Shift and Change during Childhood

CHILDHOOD allergic rhinitis and asthma follow a dynamic course, associated with IgE responses to aeroallergens. However, there are few data on the nat-

ural history of allergen-specific IgE levels. This study tracked changes in specific IgE levels in children from birth to age 10.

The study included 273 children from the Multi-Centre Allergy Study, some of whom had risk factors for atopy. At age 2, 5, 7, and 10, the children underwent measurement of IgE levels against common airborne allergens (house dust mite, cat, dog, and birch and grass pollen). The evolution of new and persistent sensitization to aeroallergens was assessed. Associations with clinical allergic rhinoconjunctivitis and asthma at age 13 were evaluated as well.

For each allergen, sensitization rates increased steadily throughout childhood. Grass had the highest sensitization prevalence, followed by birch, mite, cat and dog. This pattern was established at age 5 and persisted through age 10. Sensitization generally began with a single allergen, but children remained monosensitized for a relatively short time, adding new sensitizations frequently.

Weak sensitizations (UNICAP class 1 or 2) frequently went into remission, especially in children under 5. In contrast, stronger sensitizations (with IgE levels greater than 3.5 kU/L) almost always persisted. Children who became sensitized at younger ages were more likely to have polysensitization at age 10, and to have allergic rhinoconjunctivitis and/or asthma at age 13.

This study documents the dynamic evolution of allergic sensitization during childhood. Sensitization to one allergen may be shortly followed by sensitization to additional allergens. Weak sensitizations are likely to fade, but stronger sensitizations with higher IgE levels are more likely to persist and to be associated with clinical allergic disease.

COMMENT: This German birth cohort study followed serial in vitro specific IgE levels to inhalant allergens through age 10 and assessed clinical allergy at age 13. Factors predictive of symptomatic respiratory allergy at age 13 included early sensitization and a specific IgE level greater than 3.5 kU/L at any age. Lower-level sensitivities were often short-lived. These authors argue that multiple allergy testing assessments during childhood are necessary to establish an optimal management plan.

S.A.T.

Matricardi PM, Bockelbrink A, Keil T, et al: Dynamic evolution of serum immunoglobulin E to airborne allergens throughout childhood: results from the Multi-Centre Allergy Study birth cohort.

Clin Exp Allergy. 2009;39:1551-1557. ♦♦

Changes in Facilitated Allergen-IgE Binding after VIT

IMMUNOTHERAPY for bee venom allergy is associated with increased venom-specific IgG4 levels, but this change is unrelated to the clinical response. After grass pollen immunotherapy, increases in IgG4 occur along with increases in IgG-dependent serum inhibitory activity for IgE-facilitated binding between allergen-IgE complexes and B cells. Serum inhibitory activity >>>

for IgE-facilitated antigen binding (FAB) was assessed during and after venom immunotherapy in children.

The study included 10 children, mean age 9.3 years, undergoing VIT for moderate to severe bee venom allergy. Another 7 children who had completed VIT 2 years earlier were also studied, along with 10 matched nonallergic controls. In the FAB assay, allergen-IgE binding to B-cells decreased from 104% at baseline to 46% after 2 years of VIT. This change was accompanied by an increase in IgG4 levels, from 8.6 to 26.7 AU.

Both of these findings were significant compared to controls and patients studied after VIT withdrawal. The latter group showed a progressive decline in IgE levels: from 44 AU at baseline, to 25 AU after 2 years of VIT, to 10 AU at 2 years after the end of VIT.

Venom immunotherapy, like grass pollen immunotherapy, is associated with decreased facilitated allergen-IgE binding to B-cells, increased IgG4 antibody, and decreased IgE antibody. However, 2 years after the end of VIT, the changes in IgG4 and IgE are not sustained. The findings may have implications for the long-term clinical efficacy of VIT.

COMMENT: *This study reminds us that although the principles of administration of immunotherapy for venoms and inhalants are similar, there are also important differences. The authors speculate that these differences may be explained by post-immunotherapy natural allergen exposure—ie, pollen exposure continues each year while repeat stings occur infrequently.*
S.A.T.

Varga E-M, Francis JN, Zach MS, et al: Time course of serum inhibitory activity for facilitated allergen-IgE binding during bee venom immunotherapy in children. *Clin Exp Allergy*. 2009;39:1353-1357. ♦♦

Neuroticism, Stress May Cause New-Onset Adult Asthma

STRESS is a well-recognized trigger for worsening of existing asthma. Some studies suggest that stress could also contribute to the development of incident asthma, possibly via an inflammation-related pathway. Few studies have examined the possible causative role of stress, or of stress-related personality traits such as neuroticism or extraversion.

In a prospective study, 5,114 middle-aged adults completed questionnaires assessing personality traits, lifestyle factors, and health in 1992-95. Of these, 4,010 completed follow-up questionnaires in 2002-03. Neuroticism, extraversion, and stressful life events (unemployment, breaking off a life partnership, or death of a family member or close friend) were evaluated as predictors of incident asthma.

Over a median follow-up of 8.5 years, the incidence of new-onset asthma was 1.8%. Asthma was more likely to develop in respondents with high neuroticism, relative risk 3.07, and in those who had broken off a life partnership, relative risk 2.24. Asthma risk was not significant related to extraversion or to other types of stressful life events studied.

High neuroticism is associated with a threefold increase in the risk of new-onset adult asthma. Getting

divorced or breaking off other life partnerships may also increase asthma risk. The results add to previous evidence linking interpersonal conflicts to increased asthma risk, possibly through an immunologic pathway.

COMMENT: *Although emotional stress is a well-accepted trigger of acute symptoms in asthma patients, psychosocial stress as a cause of new-onset asthma remains controversial. This population based prospective study from Germany administered questionnaires to more than 5,000 adults at baseline, more than 4,000 of whom completed the follow-up questionnaire 3 years later. New-onset asthma was more likely among those who scored highly on a scale of neuroticism and those who had recently ended a life partnership (divorce, death, estrangement from parents). Perhaps stress is more than a trigger of pre-existing asthma after all.*
S.A.T.

Loerbroeks A, Apfelbacher CJ, Thayer JF, et al: Neuroticism, extraversion, stressful life events, and asthma: a cohort study of middle-aged adults. *Allergy*. 2009;64:1444-1450. ♦♦

Churg-Strauss Syndrome May Emerge in Omalizumab Users

CHURG-Strauss syndrome (CSS) is a rare systemic vasculitis associated with asthma. This condition often occurs after withdrawal of inhaled or systemic corticosteroids; recently, cases have been reported in patients using leukotriene modifiers. Cases of CSS associated with another new type of asthma treatment, anti-IgE therapy, are reported.

Review of a drug company's global safety database identified 34 potential cases of CSS among patients receiving the anti-IgE antibody omalizumab. On analysis of clinical data, 13 cases met at least four of six of the American College of Rheumatology's classification criteria for CSS. The patients were 9 men and 4 women, most between age 40 and 60.

Of these 13 definite or probable cases, 8 showed symptoms of CSS before starting omalizumab or developed initial symptoms after corticosteroid weaning. Six patients had received corticosteroids for apparent severe asthma; when corticosteroid tapering was performed in conjunction with omalizumab treatment, CSS symptoms appeared just after tapering. Of the remaining 21 potential cases, 4 were classified as possible CSS.

Most patients who develop CSS in association with omalizumab therapy have pre-existing evidence of CSS. The underlying eosinophilic disorder may be unmasked by withdrawal of corticosteroids, or by delays in corticosteroid therapy. Physicians treating moderate to severe asthma should be alert for signs and symptoms of CSS: vasculitis and/or infiltration of extrapulmonary tissue eosinophilia.

COMMENT: *Daily use of oral steroids for treatment of asthma has decreased dramatically since widespread use of inhaled corticosteroids. Churg-Strauss Syndrome has been associated with specific treatments, but is more likely associated with systemic steroid with- ➤➤*

drawal or tapering. This review of a large database of patients receiving omalizumab is consistent with previous studies implying that steroid withdrawal or delay in the use of oral corticosteroids is associated with CSS. Since there are systemic steroid effects with high-dose ICS, are some of these patients at risk for CSS if their inhaled steroids are tapered?

S.F.W.

Wechsler ME, Wong DA, Miller MK, et al: Churg-Strauss syndrome in patients treated with omalizumab. *Chest*. 2009;136:507-518. ♦♦

Therapeutic Misconception Affects Recruitment for Clinical Trials in Children

FEW studies have explored psychologic factors affecting the decision to enroll in clinical research, particularly pediatric trials. This study looked for possible differences between parents who did vs did not choose to enroll their food-allergic child in a trial of food-specific oral immunotherapy (OIT).

Parents of 1- to 12-year-old children receiving outpatient allergy clinic care for peanut allergy were offered the opportunity to enroll their children in a trial of OIT. Twenty-five parents agreed to enroll their child and 40 declined. Responses to questionnaires assessing health-related quality of life were compared between groups.

The two groups were similar in terms of the children's age and sex distribution, number of food allergies, symptom severity, and socioeconomic status. There was no difference in the parents' ratings of how their child's health-related quality of life was affected by food allergy. However, parents who consented to enrollment perceived their child as being at higher risk of severe reaction or death: odds ratio 6.75. This single factor was 90% accurate in predicting parental consent.

Parents who believe their child is at higher risk of negative outcomes of food allergy are more likely to enroll their child in a clinical trial of OIT. The findings raise some important ethical concerns in recruitment for pediatric trials, highlighting the need for measures to avoid unintended coercion.

COMMENT: This particular research is of initial interest as the study looks at characteristics of families enrolling their food-allergic children in an OIT trial. That trial, however, is not the focus of this report. Instead, the study queries the psychologic factors motivating parents to enroll their children in clinical studies. In the concept of "therapeutic misconception," families envision a greater benefit to being in a study versus not participating, while minimizing the actual study risks. The most anxious families in particular may be vulnerable to this belief; as allergists, we can certainly understand this vulnerability in parents of food-allergic children. Recruiters for clinical trials must be sensitive to this issue, but how exactly to resolve the problem remains elusive.

K.R.M.

DunnGalvin A, Chang WC, Laubach S, et al: Profiling families enrolled in food allergy immunotherapy studies. *Pediatrics*. 2009;124:e503-e509. ♦♦

Is Levalbuterol More Effective than Racemic Albuterol, as Continuous Therapy?

THERE is continuing debate over the therapeutic effects of racemic albuterol (RAC) vs levalbuterol (LEV), the single active (R) enantiomer. No previous studies have compared these two forms for use in high-dose continuous therapy in children hospitalized for status asthmaticus.

This randomized, double-blind trial included 81 children—aged 6 to 18, mainly African-American—admitted to an urban children's hospital with severe asthma. All were receiving high-dose continuous beta-agonist therapy after nonresponse to standard treatment with RAC and systemic steroids in the emergency department. Patients were assigned to receive equipotent doses of RAC, 20 mg/h, or LEV, 10 mg/h, in a standardized inpatient protocol.

Baseline characteristics were similar between groups. Both forms of high-dose continuous therapy were well tolerated. Changes in heart rate and serum potassium and glucose levels were not significantly different between groups. Serum (S)-albuterol levels were higher in patients assigned to RAC.

There was no significant difference in time to discontinuation of continuous therapy: 18.3 hours in the RAC group and 16.0 hours in the LEV group. Other clinical outcomes, including time to readiness for discharge, were similar as well.

In children hospitalized for status asthmaticus, clinical outcomes are similar for those receiving high-dose continuous therapy with LEV vs RAC. Both treatments are well tolerated, with few complications and similar effects on heart rate and serum potassium and glucose levels. Further studies of treatment for pediatric status asthmaticus are needed, including initial therapy with LEV.

COMMENT: The clinical debate about the efficacy of levalbuterol vs racemic albuterol will continue, but in this study the continuous use of levalbuterol did not confer any advantage in a group of hospitalized asthmatic children. One must give Sepracor credit—it funded a much-needed study, in the absence of previous data, comparing continuous high-dose levalbuterol versus standard racemic albuterol in children.

Given the high percentage of African-American subjects here, a question arises whether these results can be extrapolated to the general pediatric population; pharmacologically important beta-receptor polymorphism differences may exist. Regarding (S)-albuterol, the authors are very methodical in their attempt to tease out an early influence (via the initial racemic epinephrine treatment in the ED, prior to study randomization) on subsequent results. But we cannot know with certainty whether this initial treatment somehow skewed the findings. Look for additional studies to address these questions—in other words, to be continued . . .

K.R.M.

Andrews T, McGintee E, Mitall MK, et al: High-dose continuous nebulized levalbuterol for pediatric status asthmatics: a randomized trial.

J Pediatr. 2009;155:205-210. ♦♦

How Does SIT Change Th1, Th2, and Treg Responses?

RECENT studies of the immunologic mechanisms of specific immunotherapy have shown a shift from the Th2 to a Th1 cytokine response to allergen, as well as induction of CD4+CD25+ T regulatory (Treg) cells. Most of these studies have been limited to the first treatment year, and have not included monitoring of allergy symptoms. This 3-year follow-up study monitored allergen-induced Th2-, Th1, and Treg-immune responses in patients receiving SIT for allergic rhinitis.

The study included 20 Finnish patients undergoing SIT with birch and/or timothy. Peripheral blood mononuclear cells were collected for assessment of Th2-type (interleukin [IL]-4 and IL-5), Th1-type (interferon [IFN]- γ , IL-18, and the signaling lymphocytic activation molecule [SLAM]), and Treg-type (IL-10) mRNA responses to allergen stimulation. The findings were correlated with the SIT-related improvement in allergic rhinitis symptoms.

After 3 years of SIT, the patients had significant increases in mRNA expression of IL-18, SLAM and IL-10, with peak expression at 1 year. One-year follow-up showed a decrease in IL-5 expression and an increase in IFN- γ expression, but both of these changes were transient. The increase in IL-18 and SLAM expression were unrelated to symptom improvement. However, good symptom responses to SIT were significantly correlated with 1-year decreases in IL-4 expression and in the IL-4/IFN- γ ratio.

In patients with allergic rhinitis, SIT is associated with significant increases in Treg- and Th1-type immune responses, which are still present after 3 years. In contrast, decreases in Th2-type responses are seen only during after 1 year of SIT. The findings help to clarify the immunologic mechanisms by which SIT reduces allergic symptoms.

COMMENT: Increased Treg- and Th1-type immune responses in allergen-stimulated PBMC after 1 and 3 years of SIT are not associated with the therapeutic outcome of SIT for allergic rhinitis. The findings suggest that early induction of these responses, rather than their sustained increase, might have a greater impact on the ultimate clinical efficacy of SIT.

M.F.

Nieminen K, Laaksonen K, Savolainen J: Three-year follow-up study of allergen-induced in vitro cytokine and signalling lymphocytic activation molecule mRNA responses in peripheral blood mononuclear cells of allergic rhinitis patients undergoing specific immunotherapy.

Int Arch Allergy Immunol. 2009;150 370-376. ◆◆

CLINICAL TIDBITS

New Method of Predicting Omalizumab Response

THE dosage of anti-IgE therapy with omalizumab is calculated according to the baseline serum IgE level and body weight. This study assessed the size of the IgE antibody fraction--ie, the percentage of IgE antibody out of "total IgE"--as a predictor of response to omalizumab.

The double-blind, placebo-controlled trial included 59 patients receiving omalizumab for allergic rhinoconjunctivitis and/or asthma associated with IgE antibodies to cat. The percentage of IgE antibodies to cat was classified as high (over 3.8%) in 31 patients and low (less than 1%) in 28 patients. Both groups had a significant reduction in basophil allergen threshold sensitivity in response to omalizumab, but not placebo.

However, the response to omalizumab differed for patients in the high vs low groups. Thirteen of 18 patients with a low percentage of IgE antibodies to cat became negative, compared to none of those with a high percentage of IgE antibodies to cat.

At currently recommended doses, omalizumab is very effective in eliminating disease-relevant IgE antibodies when such antibodies account for a low percentage of total IgE. In contrast, when the IgE antibody fraction is higher, omalizumab has reduced efficacy. Further study is needed to determine whether this sizable group of patients can benefit from an increased dose of anti-IgE therapy.

COMMENT: Predicting which patients will benefit the most from omalizumab has been difficult. These authors used an in vitro surrogate for clinical efficacy to show that cat-allergic patients with a low ratio of cat-specific IgE to total IgE (IgE antibody fraction) respond better to omalizumab than patients with a high antibody fraction. If confirmed using symptoms and target organ endpoints, these findings may lead to more effective use of omalizumab.

S.A.T.

Johannson SGO, Nopp A, Öman H, et al: The size of the disease relevant IgE antibody fraction in relation to 'total IgE' predicts the efficacy of anti-IgE (Xolair®) treatment.

Allergy. 2009;64:1477-1477. ◆◆

Food Allergies Go to College

CHILDREN who don't "outgrow" their food allergies may continue to be at risk as they reach college age. This study assessed trends and attitudes toward food allergy on a university campus.

The analysis included 513 University of Michigan undergraduates who completed an Internet questionnaire (response rate 3.5%). Fifty-seven percent reported food allergies, of whom 36% reported symptoms consistent with anaphylaxis. About half reported hav- ➤➤

ing some form of emergency medication. Although 21% said they had self-injectable epinephrine, only about 7% always carried it with them. Only 40% of students said they always avoided foods to which they were allergic. Good medication maintenance habits were less likely for students who did not have a history of reactions while enrolled at university or a history of anaphylactic symptoms.

Most college students with self-reported food allergies do not practice allergen avoidance or carry self-injectable epinephrine, placing them at risk of allergic reactions. Potentially life-threatening reactions to foods are occurring on U.S. college campuses.

COMMENT: *Food allergies can cause fatal anaphylaxis. College students are at an age when risk-taking behaviors are common. This important study confirms what might be intuited: 60% of college students with food allergies don't practice allergen avoidance and more than 75% don't carry self-injectable epinephrine. Colleges should be more proactive in managing this potentially-catastrophic allergy problem.*

R.J.M.

Greenhawt MJ, Singer AM, Baptist AP: Food allergy and food allergy attitudes among college students.

J Allergy Clin Immunol. 2009;124:323-327. ◆◆

The Return of Bocavirus

THE role of respiratory viral infections as triggers of asthma exacerbations is well recognized. The recently discovered human bocavirus was evaluated as a contributor to asthma exacerbations in children.

Nasopharyngeal aspirate specimens were obtained from 166 children over age 2 (mean age 6.5) hospitalized for acute asthma. Polymerase chain reaction detected human bocavirus in 12.7% of children (mean age 3.5). There was a seasonal effect, with most bocavirus-positive cases identified in the winter months and none in the summer. Forty-eight percent of children positive for bocavirus required at least 48 hours of oxygen therapy, and 2 were admitted to the pediatric ICU.

In contrast, bocavirus was found in only 1 out of a sample of 50 ambulatory children with stable asthma. These findings implicate human bocavirus as an important cause of severe asthma exacerbations in children.

COMMENT: *As you may recall, bocavirus received mention in the May/June 2008 issue of Allergy Watch as a potential mimicker of pertussis. Despite being newly isolated in 2005, this parvovirus has quickly become recognized as a serious pathogen. It is now identified second only to respiratory syncytial virus in children hospitalized with respiratory tract infections. Based on this newer data, bocavirus is also--not surprisingly--identified as a major trigger of asthma exacerbations requiring hospitalization in children.*

K.R.M.

Vallet C, Pons-Catalano C, Mandelcwaig A, et al: Human bocavirus: a cause of severe asthma exacerbation in children.

J Pediatrics. 2009;155:286-288. ◆◆

Asthma: Yet another Cause of Social Anxiety among Teens

ASTHMA may place adolescents at risk of social anxiety. For example, asthma may lead to impairment in physical or social activities or, if teens are self-conscious about taking medications in front of peers, contribute to treatment noncompliance. The relationship between social anxiety and asthma was assessed in a sample of 765 high school students.

Based on questionnaire responses, about 15% of students had clinically significant social anxiety while 11% had current asthma. Students with a current asthma diagnosis and symptoms had increased symptoms of social anxiety, apparently related to fear of negative evaluations and general discomfort in social settings. Twenty-one percent of this group had social anxiety scores in the clinical range, compared to 13% of students without asthma.

Current asthma may contribute to social anxiety in adolescents. Referral for mental health evaluation should be considered when social anxiety seems to be causing problems with asthma management in teens.

COMMENT: *Teenagers in general have many concerns about what their peers are thinking about them. As if adolescents don't have enough to worry about, those with current asthma symptoms are at increased risk of social anxiety. In such a setting, the potential for underutilization of relief medication exists, and an already problematic situation has the possibility of becoming worse.*

K.R.M.

Bruzzese J-M, Fisher PH, Lemp N, Warner CM: Asthma and social anxiety in adolescents.

J Pediatr. 2009;155:398-403. ◆◆

Exhaled NO Can Help in Diagnosing Pediatric Asthma

A simpler test for assessing airway inflammation in children would aid in making the diagnosis of asthma. The role of exhaled nitric oxide (eNO) measurement in children remains unclear.

The investigators measured eNO in 150 consecutive children referred for evaluation of possible asthma. Other assessments included sputum induction for eosinophil count and spirometry. At 18 months' follow-up, 69 children were diagnosed as having steroid-naïve asthma while 37 had asthma requiring inhaled corticosteroids.

Children with steroid-naïve asthma had elevated eNO and sputum eosinophil percentage. Areas under the receiver operative curve were 0.906 for eNO and 0.921 for eosinophil percentage, compared to 0.606 for FEV₁. At a cutoff of 19 ppb, eNO had sensitivity of 80%, specificity of 92%, and positive and negative predictive value of 89% and 86%, respectively.

Exhaled NO measurement may aid in early diagnosis of asthma in children. This test is best reserved for children in whom the diagnosis is unclear after initial clinical assessment. ►►

COMMENT: Measurement of eNO may yet prove a useful tool in the diagnosis and management of asthma. Threshold levels of eNO for diagnosis of asthma are becoming better defined. This study compares induced sputum for eosinophils and eNO as diagnostic tools in symptomatic school-aged children, seen before the establishment of an asthma diagnosis. In this group of patients, eNO may be especially helpful in difficult cases, where early diagnosis can be elusive.

K.R.M.

Sivan Y, Gadish T, Fireman E, Soferman R: The use of exhaled nitric oxide in the diagnosis of asthma in school children.

Pediatrics. 2009;155:211-216. ♦♦

Exhaled NO Reflects AHR in Children, but Not Teens, with Asthma

RECENT studies have questioned the extent to which airway inflammation affects airway hyperresponsiveness (AHR) in children and adults with asthma. There are few data on how this relationship is affected by age. This study examined the relationship between AHR and airway inflammation, as measured by exhaled nitric oxide (eNO), in asthmatic children and adolescents.

The acetylcholine chloride challenge test was used to assess AHR in 267 young asthma patients, aged 5 to 20. Each subject also underwent eNO measurement, performed before the acetylcholine test. The relationship between AHR and eNO was compared for children (under age 12) and adolescents (aged 12 to 20).

In children, increasing AHR (lower PC₂₀) was significantly related to higher eNO. By comparison, in adolescents, AHR was only weakly related to eNO.

In the older group, increased AHR was associated with indicators of peripheral airway obstruction: FEV₁ and forced expiratory flow at 25% and 50% of forced vital capacity.

In children with asthma, AHR is significantly associated with airway inflammation. In contrast, in asthmatic adolescents, AHR appears more strongly related to structural changes reflecting chronic airway remodeling than to inflammation.

COMMENT: This study explored the relationship between AHR by acetylcholine inhalation and inflammation by measurement of eNO between children and adolescents. Children evidenced higher eNO, in correlation with AHR. In contrast, adolescents with AHR demonstrated less inflammation. This may reflect structural changes in adolescents resulting from chronic inflammation or duration of disease.

S.F.W.

Motomura C, Odajima H, Tezuka J, et al: Effect of age on relationship between exhaled nitric oxide and airway hyperresponsiveness in asthmatic children.

Chest. 2009;136:519-525. ♦♦

REVIEWS OF NOTE

COMMENT: How effective are school-based asthma education programs at improving asthma management? This meta-analysis attempts to answer the question. On the whole, the results are encouraging for asthma knowledge and self-efficacy. More disappointing are the effects on asthma outcomes. Short-term, school-based interventions may be unable to yield enduring changes in asthma outcome—changes are also hindered by multiple potential factors and barriers outside the school setting. Improving the outcome of asthma requires a host of coordinated interventions, and it remains unlikely that focus on one segment, in isolation, will reap optimal benefit.

K.R.M.

Coffman JM, Cabana MD, Yelin EH: Do school-based asthma education programs improve self-management and health outcomes?

Pediatrics. 2009;124:729-742. ♦♦

COMMENT: Here is an excellent pro-con debate regarding the roles of dust mites in inception and persistence of asthma. These editorials are well worth reading.

B.E.C.

von Hertzen L, Haahtela T: Con: House dust mites in atopic diseases: accused for 45 years but not guilty? and Platts-Mills TA, Erwin EA, Heymann PW, Woodfolk JA: Pro: The evidence for a causal role of dust mites in asthma.

Am J Respir Crit Care Med. 2009;180:109-121. ♦♦

COMMENT: This is an excellent review of what is known and not known about the natural history and epidemiology of hymenoptera allergy, including that at least 50% of insect sting fatalities would have been prevented if patients treated for systemic reactions had been appropriately referred to an allergist.

S.A.T.

Bilò MB, Bonifazi F: The natural history and epidemiology of insect venom allergy:

clinical implications. 2009;39:1467-1476. ♦♦

COMMENT: Allergen levels in schools can be higher than in homes. Some parents challenge schools to reduce their allergen loads. This article reviews what is, and isn't, known about allergen sources and measures to reduce them. Interventions are described, and you will be surprised by the outcomes.

R.J.M.

Salo PM, Sever ML, Zeldin DC: Indoor allergens in school and day care environments.

J Allergy Clin Immunol. 2009;124:185-192. ♦♦