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# AllergyWatch®

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

A Publication of The American College of Allergy, Asthma & Immunology

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## Peanut Allergy Predictive Value: Is Ara h 6 as Good as Ara h2?

MEASUREMENT of specific IgE to Ara h 2 has emerged as a valuable test for diagnosis of peanut allergy. So far, few studies have compared the diagnostic value of Ara h 2 with that of Ara h 6, another 2S albumin. This issue was addressed in a series of patients with suspected peanut allergy.

The study included 124 adults, median age 24 years, undergoing double-blind, placebo-controlled food challenge (DBPCFC) as part of clinical evaluation for suspected peanut allergy. Measurements of f specific IgE to both Ara h 2 and Ara h 6 were performed using ImmunoCAP ISAC 112, and the findings compared with the results of DBPCFC.

The rate of positive DBPCFC was 61%. The two 2S albumins had comparable discriminative ability; area under the curve values were 0.81 for Ara h 2 and 0.82 for Ara h 6. At a cutoff of 1 ISU/L or greater, both tests had positive predictive value of 95%.

Sensitivity was low: 58% for Ara h 2 and 62% for Ara h 6. However, both tests had 95% specificity. At a cutoff of 0.3 ISU/L, the two tests gave conflicting results in 5% of patients.

In testing for suspected peanut allergy in adults, measurement of IgE for Ara h 6 and Ara h 2 yields comparable diagnostic performance. Although combining Ara h 6 and Ara h 2 does not improve accuracy, the researchers note the potential for misdiagnosis if only one test is used.

**COMMENT:** *Sometimes lost in the furor over the dire risks of food allergy is the fact that our current testing methods are essentially screening tests. Arguably, there are more patients out there who unnecessarily avoid foods because of false-positive test-* ➤➤

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*ing than there are patients who are truly allergic to the food. Peanut allergen component testing is now widely available, and Ara h 2 is regarded as the most specific for predicting systemic clinical reactions to peanut. This study analyzed banked sera from adults who underwent oral challenge to peanut and found that measuring Ara h 6-specific IgE correlated very strongly with measuring Ara h2, although measuring both was better than choosing one or the other. We still need a practical tool to sort out these patients!*
*S.A.T.*
*Klemans RJB, Knol EF, Bruijnzeel-Koomen CAFM, Knulst AC: The diagnostic accuracy of specific IgE to Ara h 6 in adults is as good as Ara h 2.* **Allergy**. 2014;69:1112-114. ♦♦

## FROM THE EDITOR

*This is my final issue as editor of* AllergyWatch, *as my term is expiring. It has been my privilege to serve the College as editor, but we leave the publication in expert and able hands as Steve Tilles assumes editorship in 2015. I would like to thank the College administrative staff as well as our associate and assistant editors for their valuable support. I look forward to continuing as a faithful subscriber and reader.*

*Warm Regards,*
Anthony Montanaro MD

## Focus on Food Allergy— Three New Clinical Guidelines

**COMMENT**: *Food Allergy is the greatest unmet need facing our specialty, and the prevalence of food allergy continues to increase. Multiple guideline documents have been published in recent years but the field is progressing rapidly, and therefore it's a good idea to keep abreast of new guidelines. Three new food allergy guideline documents have been published recently, including an updated practice parameter in* The Journal of Allergy and Clinical Immunology. *The Workgroup Chair and first author of this consensus document is Hugh Sampson. The parameter features a total of 64 Summary Statements covering many important issues that we regularly face in clinic, including when and how to test, when to challenge, and updated diagnostic and treatment recommendations about eosinophilic esophagitis. In general, summary statements have been carefully worded as "actionable" to enhance their applicability to clinical practice. For example, one statement reads, "Advise patients with seafood allergy that they are not at increased risk of a reaction to radiocontrast media."*

*The other two recent food allergy guideline documents are position papers from the European Academy of Allergy and Clinical Immunology, which are published in the same issue of* Allergy. *These documents represent the European perspective on managing food allergy both in clinic and in community settings--schools, restaurants, packaged food labels, etc. Recommendations are presented in easy-to-read tables, including a specific recommendation not to routinely prescribe oral immunotherapy to foods.*

*We strongly recommend that* AllergyWatch *readers download these important and practical references. They are available for free download at http://allergyparameters.org and http://onlinelibrary.wiley.com.*
*S.A.T.*
*Sampson HA, Aceves S, Bock SA, et al: Food allergy: A practice parameter update--2014.* **J Allergy Clin Immunol**. *2014;134:1016-1025.e43. Aug 28. pii: S0091-6749(14)00672-1. doi: 10.1016/j.jaci.2014.05.013. [Epub ahead of print].*
*Muraro A, Agache I, Clark A, et al: EAACI Food Allergy and Anaphylaxis Guidelines: managing patients with food allergy in the community.* **Allergy**. *2014;69:1046-1057.* ►►

*Muraro A, Werfel T, Hoffmann-Sommergruber K, et al: EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy.*
**Allergy**. 2014;69:1008-1025. ♦♦

## Vitamin D Status Linked to Food Allergy and Atopic Dermatitis in Infants

INTERVENTIONS directed at risk factors for sensitization to food allergens might be effective in preventing allergic diseases. Previous research has linked vitamin D to the development of allergic disease in children, including studies showing a link between vitamin D deficiency and the severity of atopic dermatitis (AD). This study evaluated the relationship of vitamin D status in infants with food allergen sensitization and AD severity.

The study included 26 Korean infants evaluated for AD or suspected food allergy, who had not recently received vitamin supplementation. Serum hydroxyvitamin D (25[OH]D) levels were measured, along with IgE to common or suspected food allergens. Atopic dermatitis severity was assessed using the Scoring Atopic Dermatitis index. Food allergen sensitization was categorized in terms of the number of allergens involved and the degree of sensitization.

Low levels of 25(OH)D were associated with an increased risk of food allergen sensitization and increased severity of AD. Infants with polysensitization to food allergens had lower 25(OH)D levels than nonsensitized or monosensitized infants. Measured 25(OH)D levels were also lower for infants with high-level food sensitization, compared to those with low-level or no sensitization.

Vitamin D deficiency was significantly associated with food allergen sensitization. The strongest associations were noted for milk and wheat: odds ratios 5.0 and 4.2, respectively. The association between 25(O)HD and AD severity remained significant after adjustment for the level of food allergen sensitization.

The results suggest that low 25(O)HD in infants is associated with increased risk of food allergen sensitization and increased severity of AD. The degree of allergen sensitization is also related to AD severity. The results show a possible nonlinear association between vitamin D status and AD.

**COMMENT:** *Here comes the vitamin D connection to allergic disorders again. The authors present data linking low vitamin D to higher severity of AD and IgE food sensitization in infants. They note that vitamin D is important for skin barrier function as well as affecting Treg induction, which connects the dots between immune and barrier dysfunction. The clinical relevance may be in ensuring adequate vitamin D supplementation in infancy.*
*S.F.W.*
*Baek JH, Shin YO, Chung IH, et al: The link between serum vitamin D level, sensitization to food allergens, and the severity of atopic dermatitis in infancy.*
**J Pediatr**. 2014;165:849-854. ♦♦

## Vitamin D Added to Asthma Controllers Improves Lung Function

SEVERAL studies have found associations between vitamin D and asthma, including reports linking low vitamin D levels to poor asthma control and reduced lung function. However, few trials have evaluated the possible effects of vitamin D supplementation on asthma control and severity. This randomized trial assessed the impact of adding supplemental vitamin D to asthma controller medications.

The study included 130 patients, aged 10 to 50 years, with mild to moderate persistent asthma. Patients were seen over 24 weeks at a referral hospital in Tehran, Iran. All patients received budesonide along with formoterol, indicated by their disease status. In addition, patients in the intervention group received open-label treatment with vitamin D: a 100,000 U IM bolus followed by 50,000 orally per week. Spirometry was performed before and after 8 and 24 weeks of treatment.

At 8 weeks, significant improvement in $FEV_1$ was noted in both groups of patients, with or without supplemental vitamin D. However, by 24 weeks, $FEV_1$ improved significantly only in the vitamin D group; there was no further change among the patients receiving controller medications only. Vitamin D status was positively correlated with $FEV_1$ at 24 weeks.

Adding vitamin D supplementation to controller medications can improve $FEV_1$ in patients with mild to moderate persistent asthma. Vitamin D may provide further improvement in lung function at 24 weeks, after medications have achieved their effect at 8 weeks. The authors note that their study did not include a measure of asthma control.

**COMMENT:** *In this open-label trial of subjects with persistent asthma, there was a positive correlation between vitamin D level and $FEV_1$ after 24 weeks of therapy ($p < 0.001$, $r = 0.366$). This suggests that vitamin D supplementation may result in improved and prolonged response to asthma controller therapy in some patients. Further studies are needed to evaluate dose response.*
*C.C.R.*
*Arshi S, Fallahpour M, Nabavi M, et al: The effects of vitamin D supplementation on airway functions in mild to moderate persistent asthma.*
**Ann Allergy Asthma Immunol**. 2014;113:404-409. ♦♦

## Clinical Factors Predict Response to Baked Cow's Milk Challenge

MULTIPLE studies have found that many children with cow's milk allergy (CMA) can tolerate extensively heated cow's milk in the form of baked foods, such as muffins. Questions remain about the safety of open food challenge (OFC) to baked cow's milk, and whether clinical characteristics can help in predicting the response to OFC. These issues were addressed in a single-center challenge series.

The experience included 70 children, median ►►

age 5.3 years, with confirmed CMA who were following complete dietary avoidance of cow's milk. Thirty-four percent of the children had a history of anaphylaxis, and 59% had a history of asthma. Patients underwent formal OFC to baked cow's milk at a referral allergy clinic. The challenge consisted of incremental doses of baked muffin, up to one whole muffin. The investigators evaluated the safety of OFC, as well as clinical factors predicting reactions, including anaphylaxis, to baked cow's milk.

Seventy-three percent of children tolerated the OFC and subsequently incorporated baked cow's milk into their diet. The remaining 27% had clinical reactions, including anaphylaxis requiring epinephrine in 4 patients. Clinical factors associated with reactions to OFC were history of asthma, use of an asthma preventer, history of anaphylactic reactions to cow's milk, and IgE-mediated allergy to three or more food groups. Skin prick test wheal size did not predict the response to oral challenge.

Asthma, history of anaphylaxis, and multiple food sensitivities are associated with an increased risk of positive reactions to baked cow's milk OFC. While these factors shouldn't be regarded as contraindications, caution should be observed when they are present. The authors emphasize that challenge should be performed under medical supervision in children with CMA who have been strictly avoiding cow's milk.

**COMMENT:** *In this study of 86 children with confirmed CMA, 27% reacted to formal open food challenge with extensively heated (baked) cow's milk. Predictors of reactivity were asthma, particularly requiring controller therapy; sensitivity to more than three food groups; and history of anaphylaxis to cow's milk. The implications for performing supervised introduction of foods containing based cow's milk are discussed.*
*C.C.R.*
*Mehr S, Turner PJ, Joshi P, et al: Safety and clinical predictors of reacting to extensively heated cow's milk challenge in cow's milk-allergic children.*
**Ann Allergy Asthma Immunol**. 2014;113:425-429. ♦♦

## Delayed Diagnosis in Children with FPIES

CHILDREN with food protein-induced enterocolitis syndrome (FPIES) have delayed vomiting and other symptoms, typically 2 to 4 hours after ingestion of the culprit food. These non-IgE-mediated reactions are often misdiagnosed, with delayed presentation to an allergist or gastroenterologist. A referral clinic experience was reviewed to analyze patterns of clinical presentation and referral in children with FPIES.

Between 2010 and 2013, a total of 54 cases of FPIES were diagnosed at a London pediatric allergy clinic. Average age at onset was 8 months; 59% of patients were boys. Patients saw an average of two medical professionals before referral to an allergist or gastroenterologist. Symptoms were present for a mean of 20.2 months before allergy referral.

Vomiting was the most common presenting symptom, occurring in 81% of patients. Signs of shock or hypotension occurred in 59% of children and diarrhea in 19%. Conditions considered in the differential diagnosis included gastroenteritis, sepsis, and surgical abnormalities. Cow's milk was the most common eliciting allergen, with a frequency of 46%. Other allergens identified in more than 10% of FPIES cases were fish, egg, soy, and wheat.

The experience illustrates a pattern of multiple presentations and incorrect diagnoses in children with FPIES. The authors note that the children's initial presentation was equally divided between primary and secondary care physicians. All medical practitioners who treat children need enhanced education regarding the variable presentation of FPIES.

**COMMENT:** *These UK authors report that FPIES symptoms typically begin by 8 months. There is a significant delay in diagnosis, despite episodic flaring. The findings remind us to be aware of this important but fortunately rare syndrome.*
*C.C.R.*
*Ludman S, Harmon M, Whiting D, et al: Clinical presentation and referral characteristics of food protein-induced entercolitis syndrome in the United Kingdom.*
**Ann Allergy Asthma Immunol**. 2014;113:290-294 ♦♦

## In Children with Asthma, Most Chest X-Rays Don't Affect Treatment

PREVIOUS reports suggest that chest radiographs are performed in many children presenting to the emergency department (ED) with asthma--despite guidelines stating that this test should be used selectively. The use of chest x-rays in children hospitalized for asthma exacerbations was analyzed, focusing on how the radiographic findings affect the treatment plan.

The experience included 405 children, aged 2 to 19 years, admitted from a children's hospital ED for acute asthma exacerbation or status asthmaticus over a 12-month period. The study excluded children who had been taking antibiotics before their ED visit, who had received continuous albuterol or intravenous magnesium in the hospital, or who had other chronic diseases affecting lung function.

Chest x-rays were obtained in 180 children--a rate of 44%. However, only 18 of the x-rays obtained led to alterations in the patient's treatment plan. The abnormal x-ray findings were 6 cases of radiologist-diagnosed pneumonia, 9 cases of atelectasis treated with antibiotics, and 3 cases of pneumothorax. Chest x-rays were more likely to be ordered for children with fever at home or in the ED, odds ratio (OR) 4.5; triage oxygen saturation of 92% or less, OR 1.8; and age 4 years or younger, OR 2.3.

Both oxygen saturation of 92% or less and fever in the ED were associated with x-ray findings leading to alteration in treatment: OR 4.2 and 3.8, respectively. The x-ray results never led to treatment alteration in a patient with triage oxygen saturation above 96%.

In this children's hospital experience, only 10% ➤➤

of chest radiographs ordered in pediatric inpatients with asthma led to a change in the treatment plan. The authors call for quality improvement and educational interventions to reduce unnecessary chest x-rays.

**COMMENT:** *In this study, most chest x-rays ordered in pediatric inpatients with asthma exacerbations did not provide clinical information that affected treatment. The practicing allergist should be cognizant that chest x-rays are unnecessary in mild to moderate asthma exacerbations. However, they are merited in severe asthma or where there is concern for pneumonia, pneumomediastinum, or pneumothorax.*
*C.C.R.*
*Narayanan S, Magruder T, Walley SC, et al: Relevance of chest radiography in pediatric inpatients with asthma.*
**J Asthma**. 2014;51:751-755. ♦♦

## CT Findings in CVID: Clinical and Immunologic Correlates

IN patients with common variable immunodeficiency (CVID), the presence of interstitial lung disease (ILD) is associated with reduced survival. It remains unclear whether CVID-associated lung disease is the result of chronic infection or a manifestation of pulmonary lymphoid hyperplasia. This study evaluated clinical and immunologic correlations with the chest CT findings in patients with CVID.

The retrospective analysis included 61 patients with CVID at a New York hospital: 34 women and 27 men, aged 14 to 89 years. The CT findings were classified as ground-glass opacities in 18 patients, pulmonary nodules (5 or more) in 34 patients, bronchiectasis only in 9 patients, and no lung disease in 13 patients. Clinical and laboratory features associated with these radiologic patterns were analyzed.

The presence of bronchiectasis was strongly linked to CD4+ T-cell counts of less than 700 cells/μL, as well as a history of pneumonia and older age. Pulmonary nodules were associated with elevated CD4+:CD8+ T-cell ratios, history of autoimmune hematologic conditions, elevated IgM, and younger age, along with a more robust immune response. For ground-glass opacity, the correlations were similar to those for pulmonary nodules, with the addition of elevated monocyte counts and hepatic disease.

The CT findings of bronchiectasis or ILD--including ground-glass opacity and extensive pulmonary nodules--were correlated with selected clinical and laboratory characteristics. These results suggest divergent processes of CVID lung disease, with bronchiectasis more strongly associated with infection and T-cell lymphopenia and ILD more strongly linked with autoimmunity and lymphoproliferation.

Common chest CT patterns in patients with CVID are associated with differing patterns of clinical and immunologic findings. The study suggests "divergent processes" of CVID-associated lung disease: bronchiectasis appears to be more strongly associated with infection and T-cell lymphopenia, while ILD seems to reflect autoimmunity and lymphoproliferation.

**COMMENT:** *These authors demonstrate that the CT scan findings of bronchiectasis and pulmonary nodules are significantly correlated with specific clinical and immunologic findings. As noted in a related editorial by Harville (Ann Allergy Asthma Immunol. 2014;113:336-337), these correlations may allow segregation of populations and prognosis, as well as targeted therapy. Bronchiectasis is more common in older populations with recurrent pneumonia and pulmonary nodules, while ground-glass opacities suggest a younger population with a more robust immune response and coexisting autoimmune hematologic disease.*
*C.C.R.*
*Maglione PJ, Overbey JR, Radigan L, et al: Pulmonary radiologic findings in common variable immunodeficiency: clinical and immunological correlations.*
**Ann Allergy Asthma Immunol**. 2014;113:452-459. ♦♦

## Breast-feeding Affects Nasopharyngeal Bacteria

BREAST-feeding has a protective effect against respiratory tract infections in infancy. The mechanism of this benefit remains unclear, but may involve immune stimulatory and antimicrobial factors in breast milk. There are conflicting data on the effects of breast-feeding on bacterial colonization of the respiratory tract. This study compared the nasopharyngeal microbiota of breast-fed versus formula-fed infants.

The study included 101 healthy infants who were exclusively breast-fed and 101 formula-fed infants. Nasopharyngeal samples obtained at 6 weeks and 6 months of age were studied by 16S-based GLS-FLX-titanium-pyrosequencing. This deep sequencing technique provided complete information on the nasopharyngeal microbial communities, including noncultivable as well as cultivatable bacteria.

Six-week samples showed significant differences in the nasopharyngeal microbiota between breast-fed and formula-fed children. Exclusive breast-feeding was associated with increased presence and abundance of the lactic acid bacterium *Dolosigranulum*, relative effect size (RES) 2.61, as well as *Corynebacterium*, RES 1.98. Breast-fed infants also had decreased abundance of *Staphylococcus*, RES 0.48; as well as *Prevotella*, RES 0.25, *Veillonella*, and other anaerobic bacteria.

*Corynebacterium* and *Dolosigranulum* were predominant, comprising more than half of the nasopharyngeal microbial profile, in 44.6% of breast-fed infants versus 18.8% of formula-fed infants: relative risk, 2.37. The greater the abundance of *Dolosigranulum*, the lower the rate of wheezing symptoms and mild respiratory tract infections. In 6-month samples, the differences in nasopharyngeal microbiota were no longer observed.

Breast-feeding is associated with significant differences in composition of the nasopharyngeal microbiota in 6-week-old infants. These differences might help to explain the protective effects of breast-feeding on respiratory infections and wheezing in young infants. Further study is needed, including the involvement of *Dolosigranulum* and *Corynebacterium* spp. ►►

**COMMENT:** *This study shows that breast-feeding affects the microbiota of the upper respiratory tract. The increased presence and dominance of lactic acid bacteria might contribute to the protective effect of breast-feeding against respiratory infections. This effect was seen only at 6 weeks and not at 6 months of age. There is not a clear definition of "exclusive breast-feeding," when no other foods would have been allowed. The data should be viewed as preliminary, but may give further insight of protective effect of breast-feeding on the development of asthma. (Also see accompanying editorial by Herrington et al: Am J Respir Critical Care Med. 2014;190:246-248.)*
*B.E.C.*
*Biesbroek G, Bosch AATM, Wang X, et al: The impact of breastfeeding on nasopharyngeal microbial communities in infants.*
**Am J Respir Crit Care Med**. 2014;190:298-308. ♦♦

## Interferon-β May Reduce Viral Asthma Exacerbations

RESPIRATORY viruses are the main cause of asthma exacerbations. Some form of antiviral therapy that could prevent exacerbations due to upper respiratory tract infection (URTI) would be of great value, particularly in patients with severe asthma. Inhaled interferon-β (IFN-β) was evaluated as a treatment for URTI-associated asthma exacerbations.

The investigators enrolled 319 patients with asthma, British Thoracic Society (BTS) steps 2 to 5, who were receiving treatment with inhaled corticosteroids. All had a history of asthma exacerbations associated with colds or URTIs. In response to daily text messages, 147 patients were seen within 24 hours of developing cold symptoms.

At that time, patients were randomly assigned to 14 days of treatment with recombinant IFN-β1a (SNG001), 6 mIU via nebulizer, or placebo. The ability of IFN-β to prevent or reduce cold-related asthma symptoms was assessed, along with measures of viral infections and antiviral responses.

Ninety-one percent of randomized patients went on to develop a defined cold. On modified intention-to-treat analysis, there was no clinically significant worsening of asthma symptoms, based on the Asthma Control Questionnaire. Treatment with IFN-β did not significantly affect asthma symptoms, although morning peak expiratory flow recovery was improved. The IFN-β group also required less additional treatment, with evidence of increased innate immunity based on blood and sputum biomarkers.

An exploratory subgroup analysis focused on patients with BTS step 4 to 5 asthma: 27 in the IFN-β group and 31 in the placebo group. The results showed worsening of asthma symptoms in the placebo group, which was prevented by IFN-β treatment.

The findings support a possible benefit of nebulized IFN-β in the treatment of cold-induced asthma exacerbations. Treatment is associated with a positive effect on morning lung function and enhanced innate immunity. A clinically significant reduction in asthma symptoms is apparent in IFN-β-treated patients with more difficult-to-treat asthma.

**COMMENT:** *Patients on ICS were monitored for the onset of symptoms associated with viral respiratory tract infection and were treated with either 14 days of inhaled IFN-β or placebo. In patients with more severe disease, BTS step 4 or 5, IFN-β was associated with decreased symptoms and increased peak flow rates. This may be a result of up-regulation of innate immunity and improved viral clearance. Inhaled IFN-β may evolve as an important adjunct to the care of patients with more severe asthma during times of exacerbation. (Also see accompanying editorial by Jackson: Am J Respir Crit Care Med. 2014;190:123-124.)*
*B.E.C.*
*Djukanovic R, Harrison T, Johnston SL, et al: The effect of inhaled IFN-β on worsening of asthma symptoms caused by viral infections: a randomized trial.*
**Am J Respir Crit Care Med**. 2014;190:145-154. ♦♦

## African Americans Have Higher Rate of Nocturnal Asthma

NOCTURNAL asthma is a common condition associated with increased disease severity, morbidity, and mortality. Epidemiologic studies of this condition are limited, particularly in minority populations. Racial/ethnic differences in the frequency of nocturnal asthma were assessed, along with characteristics associated with this presentation.

The study included a multiethnic cohort from the "Study for Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity" (SAPPHIRE). Participants completed a detailed survey including information on nocturnal asthma symptoms. Sixty-five percent of the study cohort was African American. Compared to European Americans, African American participants had a higher body mass index, were more likely to have a history of childhood asthma, and had more lung function abnormalities.

African American participants were about three times more likely to report nocturnal asthma, compared to European Americans: odds ratio (OR) 2.95. The difference remained significant after adjustment for potential explanatory factors, including controller medication use: OR 2.56.

In a subset of African American participants, those with a higher estimated proportion of African ancestry had a higher risk of nocturnal asthma. Lung function differences explained a small but significant proportion of the link between genetic ancestry and nocturnal asthma.

African American race is associated with a higher rate of self-reported nocturnal asthma. Within this racial group, African ancestry is independently associated with nocturnal asthma. The mechanisms of these racial and genetic associations are unclear, but appear to be largely unrelated to differences in lung function.

**COMMENT:** *African Americans have more than a 2.5-fold increased risk of nocturnal asthma. The* ➤➤

*increased body mass index in this cohort could predispose to other comorbidities such as obstructive sleep apnea, leading to increased risk of significant nocturnal symptoms. The mechanism of this association is unknown; it does not appear to be linked to the degree of lung function abnormalities.*
*B.E.C.*
*Levin AM, Wang Y, Wells KE, et al: Nocturnal asthma and the importance of race/ethnicity and genetic ancestry.*
**Am J Respir Crit Care Med**. 2014;190:266-273. ♦♦

## Interactive Effect of Early RSV Infection and Smoking on Asthma Risk

INFANTS with lower respiratory illness (LRI) caused by respiratory syncytial virus (RSV) are at increased risk of asthma-like symptoms during childhood, although this risk is diminished by adolescence. Smoking is an important risk factor for asthma in adulthood. This study evaluated the potential interaction between RSV-LRI and smoking on the risk of adult asthma.

The study included 1,246 infants enrolled at birth (1980-84) in the Tucson Children's Respiratory Study, with prospective follow-up to age 29. Through age 3, episodes of RSV-LRI were assessed with virologic confirmation. Throughout their twenties, participants responded to questionnaires regarding current asthma and smoking. At age 26, peak flow variability was assessed. The association of early childhood RSV-LRI and later active smoking with adult asthma risk was evaluated.

Adult asthma and peak flow variability were not directly related to history of RSV-LRI or active smoking. However, a significant interaction between RSV-LRI and active smoking was associated with both current asthma and peak flow variability when the subjects were in their twenties. For those with episodes of RSV-LRI during the first 3 years of life, active smoking was associated with a 70% increase in the risk of current asthma. For this group, the amplitude percentage mean peak flow variability was 10.0%, compared to 6.4% in nonsmokers. For subjects who did not have early RSV-LRI, later smoking did not affect the risk of asthma risk or peak flow variability.

For children with early-life episodes of RSV-LRI, active smoking later in life is associated with an increased risk of asthma by age 30. In contrast, in the absence of early-life RSV-LRI, smoking does not appear to affect the risk of asthma in young adulthood. Further study is needed to assess the causal nature of the interaction, and whether history of RSV-LRI influences the risk of chronic airflow limitation in smokers.

**COMMENT:** *These data support a decreasing effect over time in non-hospitalized RSV infections on the development of asthma by adolescents. Among young adults who had RSV infection early in life, exposure to secondhand smoke increases the risk of having asthma by 1.7-fold. These data reinforce the need for smoking cessation education as an adjunct to prevent later-onset asthma.*
*B.E.C.*
*Voraphani N, Stern DA, Wright AL, et al: Risk of current asthma among adult smokers with respiratory syncytial virus illnesses in early life.*
**Am J Respir Crit Care Med**. 2014;190:392-398. ♦♦

## Efficacy and Steroid-Sparing Effect of Mepolizumab in Severe Eosinophilic Asthma

SOME form of safe, glucocorticoid-sparing treatment for patients with severe asthma is needed. The anti-interleukin-5 (IL-5) antibody mepolizumab reduces exacerbations in patients with severe eosinophilic asthma, including those taking oral glucocorticoids. A randomized trial evaluated the mepolizumab's effects on oral glucocorticoid requirement and disease control in this group of patients.

The "Steroid Reduction with Mepolizumab Study" (SIRIUS) included 135 patients with severe eosinophilic asthma. All had been taking maintenance systemic glucocorticoids for at least 6 months previously, with a blood eosinophil level of 300 cells/μL or greater before the study (or 150 cells/μL or greater during the screening phase). Patients were assigned to treatment with mepolizumab, 100 mg sc, or placebo, every 4 weeks for 20 weeks. The main efficacy outcome was reduction in daily oral glucocorticoid dose.

At week 20 to 24, the mepolizumab group had a median 50% reduction in oral glucocorticoid dose, compared to no reduction in the placebo group. The overall odds ratio for reduction in oral glucocorticoid dose category was 2.39. Mepolizumab was also associated with a reduced exacerbation rate, rate ratio 0.689, and improvement in asthma symptoms and asthma control scores.

The SIRIUS results support previous studies showing benefits of anti-IL-5 therapy with mepolizumab for patients with severe eosinophilic asthma. The authors note improved outcomes even after oral glucocorticoids were reduced as much as possible before the start of study treatment. For some patients, mepolizumab can further reduce the need for systemic glucocorticoids.

**COMMENT:** *Mepolizumab, an anti-IL-5 humanized monoclonal antibody, was studied in a 24-week randomized controlled trial involving 135 patients with severe eosinophilic asthma. There was an impressive reduction in steroid dose in the mepolizumab group--median 50% from baseline, compared to no change in the placebo group. Furthermore, the patients in the mepolizumab group had a reduction in exacerbations and improvement in asthma control. Since this was a relatively short study, it was not possible to determine if complete withdrawal of oral steroids was possible. The MENSA trial, published in the same issue, showed a reduced exacerbation rate in patients receiving intravenous or subcutaneous mepolizumab (Ortega HG, et al: N Engl J Med. 2014;371:1198-1207).*

*As pointed out in a discerning editorial by Nair* ➤➤

*(N Engl J Med. 2014;371:1249-1251), these studies incidentally helped generate a handy approach to bedside identification of patients with the eosinophilic phenotype who are likely to respond to mepolizumab: namely, blood eosinophil count of more than 300 cells/μL, despite concurrent treatment with high-dose glucocorticoids. Also notable was the observation that patients receiving placebo had a 50% reduction in exacerbations compared to baseline. That is a not-surprising validation of the belief that lack of adherence to good clinical practice and to prescribed therapy is the most common cause of poor asthma control!*
*C.D.*
*Bel EH, et al: Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma.*
**N Engl J Med**. 2014;371:1189-1197. ♦♦

## 'Can I Prevent My Child from Developing Celiac Disease?'

CELIAC disease develops in about 10 percent of infants with an affected first-degree relative. Recent studies suggest a possible "window of opportunity" to prevent celiac disease by introducing gluten into the infant's diet between 4 and 6 months of age. This approach was tested in a multicenter European trial.

The Prevent Coeliac Disease (PreventCD) project included 944 children at high risk of celiac disease, based on family history and HLA genotype. One group was assigned to early introduction of immunologically active gluten: 100 mg/d between 16 to 24 weeks. Control infants received placebo. The frequency of celiac disease was compared between groups at age 3.

There was no significant difference in this primary outcome: 5.9% with early gluten introduction and 4.5% with placebo. The two groups were also similar in terms of their rates of elevated anti-transglutaminase type 2 and antigliadin antibody levels: 7.0% and 5.7%, respectively. There was no significant effect of breast-feeding on the development of celiac disease, including infants who were breast-fed exclusively or at the time of gluten introduction.

In high-risk infants, introducing small amounts of immunologically active gluten between 16 and 24 weeks of age does not reduce the risk of celiac disease at age 3. The study also finds no protective effect of breast-feeding. The investigators conclude, "Our results do not provide evidence to support…any specific feeding recommendation with respect to the timing of gluten introduction for infants at risk for celiac disease."

GLUTEN appears to trigger the development of celiac disease in genetically predisposed individuals, but the interplay between genetic and environmental factors remains unclear. Despite a lack of strong evidence, many countries follow a practice of introducing gluten at 6 months. Two different times of gluten introduction were compared in a randomized trial.

The multicenter "Risk of Celiac Disease and Age at Gluten Introduction" (CELIPREV) trial included 832 infants at familial risk of celiac disease (at least one affected first-degree relative). Infants were assigned to introduction of dietary gluten at 6 or 12 months of age. HLA genotyping was performed at 15 months, and serologic screening for celiac disease at intervals from 15 months to 10 years. The main outcomes of interest were celiac disease autoimmunity and overt celiac disease at age 5.

At 36 months, 707 children remained in the study; of these, 533 had standard- or high-risk HLA genotypes. At age 2, infants assigned to gluten introduction at 6 months had higher rates of celiac disease autoimmunity, 16% versus 7%; and overt celiac disease, 12% versus 5%. By age 5, the differences were nonsignificant: 21% and 20% of children had celiac disease autoimmunity, respectively, while 16% of both groups had overt celiac disease.

At age 10, high-risk HLA was associated with increased rates of both outcomes, compared to standard-risk HLA: 38% versus 19% for autoimmunity and 26% versus 16% for overt disease. There was no effect of breast-feeding or other variables.

The results show no reduction in development of celiac disease in high-risk infants assigned to introduction of gluten at age 6 versus 12 months. Disease onset may be delayed with later introduction of gluten. High-risk HLA genotype is an important risk factor.

**COMMENT:** *Two recent, large-scale studies attempted to answer the question we commonly hear from parents: "How can I protect my child from the development of celiac disease?" In the PreventCD trial, children were randomly assigned to the introduction of gluten at 4 to 6 months of age. In the CELIPREV trial, gluten was introduced at 6 or 12 months of age.*

*As noted astutely by Ludvigsson and Green in the accompanying editorial (N Engl J Med. 2014;371:1341-1343), although there were differences between the two studies, their key (and disappointing) findings align and will likely have a significant impact on clinical practice. The timing of introduction of gluten in high-risk children does not appear to influence the development of celiac disease. There is no evidence that the duration or maintenance of breast-feeding when gluten is introduced influences the risk of celiac disease later in life. The only risk factor for celiac disease identified in these studies is the HLA genotype.*
*C.D.*
*Vriezinga SL, Auricchio R, Bravi E, et al: Randomized feeding intervention in infants at high risk for celiac disease.* **N Engl J Med**. 2014;371:1304-1315.
*Lionetti E, Castelleneta S, Francavilla R, et al: Introduction of gluten, HLA status, and the risk of celiac disease in children.*
**N Engl J Med**. 2014;371:1295-1303. ♦♦

## Early Allergen Plus Bacterial Exposure Reduces Allergy Risk in Urban Children

WHEEZING is an important cause of morbidity in infants, and is a common precursor of asthma. Children living in poor urban neighborhoods may ➤➤

be exposed to several conditions that promote allergic sensitization and wheezing. Data from an inner-city birth cohort study were used to evaluate environmental factors associated with recurrent wheezing.

The Urban Environment and Childhood Asthma (URECA) study included a high-risk cohort of children in Baltimore, Boston, New York, and St Louis. Exposure to indoor allergens, such as cockroach and mouse, was measured in household dust samples. In a subgroup of children, the bacterial content of dust samples was evaluated as well. These environmental exposures were analyzed for association with allergic sensitization and recurrent wheezing when the children were 3 years old.

Cumulative allergen exposure at age 3 was associated with aeroallergen sensitization, which in turn was associated with recurrent wheezing. Recurrent wheezing was less frequent for children exposed to cockroach, mouse, and cat allergen during the first year: odds ratio 0.60, 0.65, and 0.75, respectively. The bacterial content of house dust during the first year--and particularly lower levels of exposure to specific Firmicutes and Bacteroidetes--was associated with atopy and atopic wheezing. Children free of atopy and wheezing were the most likely to have high exposure to allergens and to these specific bacteria during the first week of life.

For US inner-city children, increased exposure to specific indoor allergens and to certain bacteria in house dust is associated with decreased rates of recurrent wheezing and allergic sensitization. Associations with these concomitant early-life exposures might provide clues to new strategies for preventing childhood wheezing and allergic disease.

**COMMENT:** *The URECA study follows a birth cohort of inner-city children in four urban areas. This study is unique since it not only monitored reports of wheezing illnesses, but also checked for specific allergic sensitivity in the children and also measured both allergen and bacteria in the house dust. Children exposed to high levels of cockroach, mouse, or cat allergens were less likely to have recurrent wheeze. However, those also exposed to increased bacteria were even less likely to have atopy, with or without wheezing illnesses. The authors conclude that concomitant exposure to both allergen and bacteria may help prevent allergies and wheezing in children. We need a better understanding of the bacteria-human interactions in the development of allergic diseases, particularly in the urban setting.*
*S.M.F.*

*Lynch SV, Wood RA, Boushey H, et al: Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children.*
**J Allergy Clin Immunol**. 2014;134:593-601. ♦♦

## How Little Peanut Does It Take to Cause a Reaction?

INFORMATION on threshold levels of peanut and other allergens has important implications for food labeling. Determining the minimum eliciting dose (ED) by oral food challenge provides a means for estimating the clinical threshold--the smallest dose of peanut to which that individual might react in real life. A modified food challenge protocol was used to assess the ED in children with peanut allergy, including associations with biologic markers.

The study included 63 children with confirmed peanut allergy, most of whom had reacted to accidental peanut ingestion. The modified peanut challenge procedure included 2 hours between dose steps, with the goal of better reflecting a real-life ED response. Children received up to 8 semi-log increasing titration steps of roasted peanut, from 3 up to 4,500 mg of peanut protein, until an objective allergic reaction occurred. Symptom severity was graded from I to IV, and correlated with biologic markers measured before challenge.

Forty-five of the children had objective symptoms of an allergic reaction after more than 30 minutes, with a median latency of 55 minutes to clinical reaction. The ED5 was calculated at 1.95 mg of peanut protein, based on a log-normal dose-distribution model. Inverse correlations were observed between the ED and peanut- and Ara h 2-specific IgE levels, skin prick responses, basophil activation, and Th2 cytokine production by peripheral blood mononuclear cells. None of these markers, nor the ED, was significantly correlated with symptom severity.

The modified food challenge procedure evaluated in this study, with most patients reacting after more than 30 minutes, may provide more real-life estimates of the threshold level for peanut allergy. Although the ED is significantly correlated with various markers of allergic sensitization and immune reactions, none of these markers reflect the severity of the allergic reaction. The authors discuss the implications for patient care as well as for food labeling.

**COMMENT:** *"Can my peanut-allergic child eat something from a factory that processes peanuts?" The threshold amount triggering an allergic reaction, also called the eliciting dose, was determined in a group of highly sensitive peanut-allergic children with a protocol that extended the time between challenge doses from the usual 15 to 30 minutes to 2 hours. The ED was lower than usually reported and was inversely correlated with the patient's peanut sensitivity, measured by specific IgE to Ara h2, skin test, basophil activation, and cytokine production. Interestingly, symptom severity did not correlate with any of these markers. Although it is not practical to follow this extended interval protocol in practice, these types of research studies are important to help us understand real-world challenges. Since product labeling is still not optimal, it is prudent to advise our patients to be cautious.*
*S.M.F.*

*Blumchen K, Beder A, Beschorner J, et al: Modified oral food challenge used with sensitization biomarkers provides more real-life clinical thresholds for peanut allergy.*
**J Allergy Clin Immunol**. 2014;134:390-398. ♦♦

## Fungal Involvement in Th2-Associated Airway Disease

FUNGI are known to be associated with Th2 cell-related airway inflammation and Th2-associated chronic airway diseases, including asthma, chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP), and allergic fungal rhinosinusitis (AFRS). Fungi are capable of growing in the airway, and clinical trials have shown positive results with oral antifungals in severe asth- ►►

ma patients with fungal sensitization. However, it remains unclear whether fungi are directly or indirectly involved in these diseases.

The researchers obtained sinus lavage fluid and blood samples from 118 patients undergoing sinus surgery. The sample included 37 patients with CRSwNP, 21 with CRS without nasal polyps, 26 with AFRS, and 15 controls without CRS or asthma. The presence of fungi was assessed on culture of sinus lavage fluids. The study also included an enzyme-linked immunocell spot assay in which PBMCs were restimulated with fungal antigens to assess total memory fungus-specific IL-4-secreting cells. Levels of fungus-specific IgE levels in plasma were measured by enzyme-linked immunosorbent assay.

Filamentous fungi were cultured in 74% of patients with Th2-associated airway disease, ie, asthma, CRSwNP, or AFRS; compared to control patients with non-Th2-associated disease. The presence of Th2-associated diseases was predicted by the findings of fungus-specific IL-4 enzyme-linked immunocell spot, sensitivity 73% and specificity 100%; and specific IgE measurement, 50% and 77%, respectively.

At sinus surgery, many patients with Th2-associated chronic airways diseases are found to have fungi growing directly in the airways, along with evidence of specific immunity to these organisms. The findings support the theory that fungi participate directly in the pathology of these diseases. Some patients with Th2-associated airway diseases may benefit from airway fungal eradication.

**COMMENT:** *What is the role of environmental fungi on the development of allergic airway diseases? Using sinus lavage fluid and blood samples from sinus surgery patients, these researchers used a new T cell-based specific enzyme-linked immunocell spot assay for memory fungus-specific IL-4-secreting cells as well as the usual specific IgE antibody measures in both allergic and nonallergic controls. Interestingly, patients with Th2 airway diseases including asthma, CRSwNP, or AFRS more frequently had filamentous fungi compared to nonallergic controls. These findings suggest that sinus fungal growth contributes to expression of allergic conditions. The authors suggest that eradicating filamentous fungi in such patients could improve patient management.*
*S.M.F.*

*Porter PC, Lim DJ, Maskatia ZK, et al: Airway surface mycosis in chronic Th2-associated airway disease.*
**J Allergy Clin Immunol**. 2014;134:325-331. ♦♦

## Basophil Activation Test Is Useful in 'Equivocal' Peanut Allergy

MOST children who are clinically sensitized to peanut do not have clinical peanut allergy. Oral food challenge (OFC) is the standard test in these equivocal cases, but it is a time-consuming procedure that is not without risk. The basophil activation test (BAT) was evaluated as a diagnostic marker of peanut allergy versus tolerance in peanut-sensitized children.

The study included two groups of peanut-sensitized children: 43 with peanut allergy and 36 with peanut tolerance. Twenty-five children without peanut sensitization or peanut allergy were studied as controls. All underwent BAT using flow cytometry. The diagnostic performance of BAT for identifying peanut allergy was assessed, then validated in an independent sample of 65 children.

In children with peanut allergy, there was peanut dose-dependent upregulation of CD63 and CD203c on BAT, compared to no significant response in peanut-sensitized but tolerant and non-peanut-sensitized controls. Using optimal BAT cutoffs, diagnostic accuracy was 97%, with positive predictive value of 95% and negative predictive value of 98%.

Based on the BAT results, the number of OFCs could be reduced by two-thirds. The test was especially valuable for patients in whom peanut allergy could not be diagnosed by skin-prick testing and measurement of specific IgE to peanut and Ara h 2. With a two-step protocol reserving BAT for patients with equivocal findings on skin-prick tests and specific IgE measurement, the number of OFCs required was reduced by 97%.

The BAT is a useful test for identifying peanut allergy versus tolerance in peanut-sensitized children. Its value appears highest when standard allergy tests have been unable to diagnose peanut allergy, with the potential to avoid the need for OFC.

**COMMENT:** *Although approximately 10% of children have sensitivity to peanut, only 1.4% are clinically allergic. Oral food challenge has been the gold standard for many of patients in the 'gray area' of IgE sensitivity but no true clinical reaction. Prospectively studying peanut-allergic, peanut-sensitized but tolerant and non-peanut-sensitized children, these researchers found that a two-step approach using BAT when allergy skin tests or specific IgE were equivocal reduced the need for OFC by 97%. The authors suggest that BAT can be cost effective, but the problem is that BAT is technically difficult and not generally available. So at this time, we still need to use OFC in those patients with equivocal skin tests and specific IgE.*
*S.M.F.*

*Santos AF, Douiri A, Bécares N, et al: Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children.*
**J Allergy Clin Immunol**. 2014;134:645-652. ♦♦

## Mastocytosis-- More Common Than We Think

IDIOPATHIC or unexplained anaphylaxis shows significant overlap with the signs and symptoms of clonal mast cell disorders (CMD), suggesting a possible association between these two rare conditions. Some patients with idiopathic anaphylaxis may have underlying mast cell disorders. This study looked for some aberrant population of mast cells in patients with unexplained anaphylaxis, with evaluation of possible predictive markers.

The study included 16 women and 14 men, median age 53 years, with unexplained anaphylaxis and no ►►

evidence of cutaneous mastocytosis. All had no identifiable cause of anaphylaxis on complete allergy workup. Patients underwent measurement of serum tryptase (sBT) and total IgE, along with bone marrow examination for diagnosis of systemic mastocytosis or monoclonal mast cell activation syndromes.

A diagnosis of CMD was made in 47% of patients with unexplained anaphylaxis: 9 men and 5 women. The diagnosis was systemic mastocytosis (SM) in 10 patients and monoclonal mast cell activation syndrome (MMAS) in 4. Four patients in the SM group had mast cell aggregates in bone marrow. All patients with SM had an elevated sBT level (over 11.4 ng/mL), compared to only 2 of those with MMAS and four with unexplained anaphylaxis but no CMD diagnosis. Patients with CMD had lower total IgE levels.

Nearly half of this series of patients with unexplained anaphylaxis have immunophenotypically aberrant mast cells with clonal markers in bone marrow, consistent with clonal mast cell disorders. For patients with idiopathic anaphylaxis who have an elevated sBT level and cardiovascular symptoms such as syncope, the possibility of CMD should be considered.

**COMMENT:** *Allergists frequently see patients with idiopathic anaphylaxis. These authors from the Mastocytosis Center Karolinska evaluated 30 patients with unexplained anaphylaxis and no signs of mastocytosis. Remarkably, 47% were diagnosed with mastocytosis or a monoclonal mast cell activation syndrome. Not surprisingly, serum tryptase was a fairly good predictor of mast cell disease. As in other reports, flushing was more often associated with mast cell disease, whereas urticaria and angioedema were seen with idiopathic anaphylaxis. This referral cohort is likely not representative of all patients with idiopathic anaphylaxis, as evidenced by a very high percentage (93%) who had syncope. Nevertheless, in a patient with flushing and syncope, mast cell disease should be high on the differential when no obvious allergen can be determined.*
*D.A.K.*

*Gülen T, Häglund H, Sander B, et al: The presence of mast cell clonality in patients with unexplained anaphylaxis.*
**Clin Exp Allergy**. 2014;44:1179-1187. ♦♦

## Can Peripheral Blood Determine the Type of Inflammation in the Lung?

ASTHMA patients have differing inflammatory airway phenotypes, which affect the clinical presentation and response to treatment. Although induced sputum analysis can be performed for evaluation of asthma phenotype, some more accessible test would be clinically useful. This study evaluated the use of circulating blood ratios and/or their derived ratios to predict sputum eosinophils or neutrophils in uncontrolled asthma.

The researchers analyzed 164 patients with asthma that remained uncontrolled despite maintenance inhaled corticosteroid therapy. Sputum induction was performed to assess the asthma inflammatory phenotype; blood cell counts and inflammatory cell ratios were analyzed for association with the sputum parameters.

Blood eosinophil level was significantly and positively associated with sputum eosinophil count. There was also a significant but weak association between the blood and sputum neutrophil percentages. On receiver-operating characteristic analysis, the presence of eosinophilic asthma was best predicted by the blood eosinophil percentage count: area under the curve (AUC) 0.907. At a cutoff point of 2.7%, blood eosinophil percentage was 92.2% sensitive and 75.8% specific for the eosinophilic asthma phenotype. Absolute blood eosinophil count was also a significant predictor, with an AUC of 0.898 at a cutoff of 0.26 × $10^9$/L.

Patients with eosinophilic asthma also had increased blood eosinophil/lymphocyte and eosinophil/neutrophil ratios, while those with neutrophilic asthma had an increased neutrophil/lymphocyte ratio. The latter ratio, along with blood neutrophil percentage, had lower accuracy for neutrophilic asthma.

Blood eosinophil percentage and count, along with the eosinophil/lymphocyte and eosinophil/neutrophil ratios, are accurate predictors of the eosinophilic phenotype in patients with persistent uncontrolled asthma despite treatment. Blood neutrophil analysis is less predictive for neutrophilic asthma. The authors conclude, "This study shows the promise of a simple and accessible blood test, when used in the appropriate clinical setting."

**COMMENT:** *Various inflammatory phenotypes have been recognized in asthma--including eosinophilic, neutrophilic, and paucigranulocytic asthma--based on airway inflammation in sputum or bronchoalveolar lavage fluid. These authors evaluated 164 subjects with uncontrolled asthma despite inhaled corticosteroids. Blood eosinophilia (by percentage or absolute count) was shown to be highly predictive for airway eosinophilia assessed by sputum. In contrast, blood neutrophilia had a weak association. The clinical relevance of this finding will be important in the future if mepolizumab (anti-IL-5) gets FDA approval to treat the eosinophilic subgroup of patients.*
*D.A.K.*

*Zhang X-Y, Simpson JL, Powell H, et al: Full blood count parameters for the detection of asthma inflammatory phenotypes.*
**Clin Exp Allergy**. 2014;44:1137-1145. ♦♦

## N-Acetylcysteine in COPD: Dose and Risk Matter

A recent trial in a heterogeneous group of patients with chronic obstructive pulmonary disease (COPD) found that high-dose N-acetylcysteine (NAC), 600 mg bid, reduced the exacerbation rate while improving small airway function. The investigators performed a post hoc analysis to identify those groups of patients most likely to benefit from high-dose NAC.

In the trial, 120 Chinese patients with stable COPD were randomly assigned to treatment with high- ►►

dose NAC or placebo, added to usual medications. The current analysis compared outcomes for 89 high-risk patients, with a history of 2 or more exacerbations per year and/or $FEV_1$ of 50% or less. The remaining 31 patients were considered low-risk, with neither of these characteristics and no recent hospitalization for COPD exacerbation.

One hundred eight patients completed the study. At 8 months, exacerbation frequency among high-risk patients was 0.85 in the high-dose NAC group versus 1.59 in the placebo group. Twelve-month rates were 1.08 and 2.22, respectively. High-dose NAC was associated with a longer time to first exacerbation and with a higher rate of freedom from exacerbation at 1 year: 51.3% versus 24.4%.

For low-risk patients, exacerbation rates were not significantly different for the NAC versus placebo groups. There were no major adverse effects of either treatment.

The results suggest that 1 year of treatment with NAC 600 mg bid reduces exacerbation rate in high-risk patients with COPD, but not in low-risk patients. The authors note their results are discordant with a previous large trial showing no benefit of NAC 600 mg daily. The findings also disagree with studies reporting that mucolytics are beneficial only for patients not using inhaled corticosteroids.

**COMMENT:** *N-acetylcysteine is a mucolytic with antioxidant and anti-inflammatory effects. Studies of its effect on COPD have been mixed, with lower (600 mg/d) doses shown to be ineffective. These authors previously reported in a randomized controlled trial that NAC 600 mg twice daily reduced COPD exacerbations. The current study was a post-hoc analysis undertaken to determine which patients are most likely to respond. High-risk COPD patients with $FEV_1$ less than 50% or two or more exacerbations per year had a reduction in exacerbations with NAC, whereas low-risk COPD patients had no improvement. While it would have been better if this determination was done a priori, NAC was well-tolerated and may be of value for high-risk COPD patients.*
*D.A.K.*

*Tse HN, Raiteri L, Wong KY, et al: Benefits of high-dose N-acetylcysteine to exacerbation-prone patients with COPD.*
**Chest**. 2014;146:611-623. ♦♦

## CLINICAL TIDBIT

## Can Adults Identify Stinging Insects?

INSECT identification plays an important role in diagnosis, treatment, and prevention for patients with Hymenoptera venom allergy. This study evaluated the public's accuracy in identifying different types of stinging insects.

Six hundred forty adults completed a questionnaire evaluating their ability to identify pictures of a honeybees, yellow jacket, bald-face hornet, and paper wasp, as well as hornets' and wasps' nests. The average percentage of correct responses was 3.2 out of 6; only 1.6% of respondents had no correct responses. Identification rates ranged from 91.3% for honeybee to 50.9% for paper wasp. About 90% of respondents reported being stung by any of the insects (including unidentified insects). Men and people who had been stung by at least four insects had more correct responses.

Adults don't perform well in identifying different types of stinging insects, except for honeybee. The authors discuss the implications for testing and management of patients with reactions to Hymenoptera.

**COMMENT:** *As past studies have been done in patients with food allergy, this study investigated the ability of adults to identify stinging insects or their nests. In this population of adults, only 3% identified all six stinging insects. The honeybee was most frequently correctly identified. Almost all participants had been stung at least one time. Men and those stung by at least four insects were most likely to correctly identify the insects. Current guidelines recommend testing all flying Hymenoptera in patients with history of reaction, and this was supported by the new findings. The authors suggest that using insect identification pictures or boxes may be helpful for at-risk patients. This reminds us that patient education continues to be our responsibility as health care providers.*
*V.H.-T.*

*Baker TW, Forester JP, Johnson ML, et al: The HIT study: Hymenoptera Identification Test--how accurate are people at identifying stinging insects?*
**Ann Allergy Asthma Immunol**. 2014;113:267-270. ♦♦

## REVIEWS OF NOTE

**COMMENT:** *The gut microflora has received considerable attention. In this first in a series of two articles about "Infections in chronic lung diseases," the role of the microbiome in exacerbations of chronic lung diseases such as chronic obstructive pulmonary disease, asthma, bronchiectasis and cystic fibrosis is explored. This review is important for understanding the concept of dysbiosis and subsequent inflammation.*
*S.F.W.*

*Dickson RP, Martinez FJ, Huffnagle GB: The role of the microbiome in exacerbations of chronic lung diseases.*
**Lancet**. 2014;384:691-702. ♦♦

**COMMENT:** *This is an excellent review of the use of antifungal strategies in the management of antifungal bronchopulmonary aspergillosis. We sure have come a long way!*
*B.E.C.*

*Moreira AS, Silva D, Ferreira AR, Delgado R: Antifungal treatment in allergic bronchopulmonary aspergillosis with and without cystic fibrosis: a systematic review.*
**Clin Exp Allergy**. 2014;44:1210-1227. ♦♦

**COMMENT:** *This is an excellent review of the disparities of asthma prevalence in the Hispanic population.*
*B.E.C.*

*Rosser FJ, Forno E, Cooper P, Celedón JC: Asthma in Hispanics: an 8-year update.*
**Am J Respir Crit Care Med**. 2014;189:1316-1327. ♦♦