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AllergyWatch®

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

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SLIT for Grass Allergy: Safe, Effective, and Available

SUBLINGUAL immunotherapy (SLIT) offers important advantages in the treatment of allergic rhinitis, with or without conjunctivitis (AR/C). Previous trials have shown good effectiveness and tolerability with the timothy grass SLIT tablet MK-7423, but there are few data in children. The investigators report a large randomized trial of grass SLIT in North American children and adults with AR/C.

The trial enrolled 1,501 children and adults, aged 5 to 65 years, with AR/C at U.S. and Canadian centers. Eighty-five percent of patients were polysensitized, and 25% had asthma. They were assigned to receive active SLIT with once-daily MK-7243 (2,3300 BAU *Phleum pretense*, or placebo. After an initial dose at the study center, patients took daily SLIT doses at home. The two groups were compared on a total combined score (TCS) consisting of rhinoconjunctivitis daily symptom score plus daily medication score over the entire grass pollen season.

The active SLIT group had an overall 23% improvement in entire-season TCS, compared to the placebo group. Treatment with MK-7243 was also associated with improvements of 29% in peak-season total symptom score, 20% in entire-season daily symptom score, and 35% in entire-season daily medication score. There was also a 12% improvement in peak-season rhinoconjunctivitis quality-of-life score.

Active SLIT produced comparable improvement in children and adults. Most adverse events were transient local reactions of the mouth, throat, and ear; there were no serious treatment-related adverse events and no cases of anaphylaxis. Moderate systemic allergic reactions occurred in 3 patients, 2 of them in the MK-7243 group.

Results of the largest immunotherapy trial ever published support the safety and efficacy of grass SLIT ➤➤

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The following journals have been selected as the primary focus of review in the preparation of materials within "AllergyWatch®".

- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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for AR/C in children and adults. Significant improvement is achieved in a polysensitized population, even with use of a single-allergen tablet. The long-term disease-modifying effect remains to be determined.

COMMENT: *Sublingual immunotherapy has been available and practiced in Europe, and will soon be available for ragweed and grass in the United States. The authors demonstrate that grass tablet SLIT is safe and effective in patients with AR/C, including all grass sensitivities, for daily at-home administration. The study--the largest population to date of multiply sensitized adults and children in North America--reported only local reactions.*
C.C.R.

Maloney J, Bernstein DI, Nelson H, et al: Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial.
Ann Allergy Asthma Immunol. 2014;112:146-153. ♦♦

More Striking ImmunologicChanges with SCIT vs SLIT

SUBLINGUAL immunotherapy (SLIT) is emerging as an alternative to subcutaneous immunotherapy (SCIT) for IgE-mediated grass pollen allergy. Although the two approaches offer similar efficacy, they may work through different mechanisms. This trial compared immunologic parameters in grass-allergic patients receiving SLIT vs SCIT.

Forty patients with grass allergy were randomly assigned to receive grass-pollen SCIT or SLIT (15 patients each) or neither treatment (10 patients). Through 15 months' follow-up, patients underwent regular immunologic assessments, including serum specific IgE, IgG4, IgE-blocking factor, facilitated antigen presentation (FAP), and basophil activation test (BAT). Responses to nasal allergen challenge were assessed as well.

At 15 months, values for IgG4, IgE-blocking factor, and BAT were all significantly different in the two immunotherapy groups, compared to no treatment. These changes were apparent within 1 to 3 months. For most immunologic parameters, the magnitude of the changes was about twice as large with SCIT as with SLIT. The exception was specific IgE, which showed a threefold greater initial increase with SLIT compared to SCIT.

After pollen season, small but significant increases in IgE and BAT were apparent only in the no-treatment group. The early differences in immunologic measures between SCIT and SLIT narrowed over time, particularly for FAP inhibition.

Patients with grass allergy show significant immunologic changes in response to both SLIT and SCIT, including specific antibody levels and competition assays. For most measures, the magnitude of the effect is two to three times larger with SCIT compared to SLIT. Peak changes generally occur by 3 months of treatment; the differences between the two forms of immunotherapy appear to diminish over time.

COMMENT: *There is no longer any debate whether SLIT is an effective form of treatment for allergic rhinitis. However, there remains considerable debate regarding the relative magnitude of clinical improvement with SLIT vs SCIT. This prospective study included nasal allergen challenge and measured a variety of immunologic changes in patients treated with grass-pollen SCIT or SLIT. The magnitude of change in specific IgG4 and competition assays was generally significantly higher for subjects receiving SCIT. Symptoms in response to allergen challenge at 3 months improved much more with SCIT compared to SLIT, although it is unclear if this difference is relevant to long-term efficacy. Further studies should help determine whether in fact there is a difference in magnitude of efficacy between these forms of immunotherapy.*
S.A.T.

Aasbjerg K, Backer V, Lund G, et al: Immunological comparison of allergen immunotherapy tablet treatment and subcutaneous immunotherapy against grass allergy.
Clin Exp Allergy. 2014;44:417-428. ♦♦

FOCUS ON PHENOTYPES

In this issue of *AllergyWatch*, we highlight some of the emerging evidence relating to differing asthma phenotypes.
A.M.

'Frequent Exacerbator': A New Asthma Phenotype

Some asthma patients have a higher rate of exacerbations, which is not always related to the level of asthma symptoms. The phenotype of "frequent exacerbators" is well-recognized in patients with chronic obstructive pulmonary disease, but not asthma. This study evaluated the characteristics of the frequent exacerbator phenotype among patients with severe asthma.

The 1-year prospective follow-up study included 93 patients with severe asthma and 76 with mild to moderate asthma. Risk factors associated with a pattern of frequent exacerbations were identified by assessment of the patients' medical history, baseline clinical data, and biomarkers.

During follow-up, 104 exacerbations occurred in patients with severe asthma and 18 in those with mild to moderate asthma. Thirty patients who had two or more exacerbations--most with severe asthma --were classified as frequent exacerbators. These patients had a higher mean inhaled corticosteroid dose than nonfrequent exacerbators, 1,700 vs 800 μg; as well as a higher dose of oral steroids, 6.7 versus 1.7 μg.

Other characteristics of frequent exacerbators included worse asthma control score (2.3 vs 1.4), lower quality of life (48.5 vs 33.3 on the St George's Respiratory Questionnaire), higher sputum eosinophils (25.7% versus 8.2%), and more rapid decline in FEV_1/FVC ratio (-0.07 vs -0.01). On multivariate analysis, factors independently associated with the frequent exacerbator phenotype were history of smoking and exhaled nitric oxide level greater than 45 ppb: odds ratio 4.32 and 2.90, respectively.

The study identifies a group of asthma patients with a frequent exacerbator phenotype. Clinical characteristics and risk factors associated with frequent exacerbations, two or more per year, are identified. In particular, patients with a history of smoking and those with exhaled NO greater than 45 ppb should receive careful clinical monitoring.

COMMENT: *Uncontrolled severe asthma remains a large unmet need, despite impressive advances in management options. Poor adherence to recommended treatment plans, particularly high-dose inhaled corticosteroids, has been thought to be a particularly important factor. This study followed nearly 100 difficult asthmatic patients prospectively for 1 year. The subgroup at risk of more frequent exacerbations tended to use higher doses of inhaled corticosteroids and to have higher levels of exhaled nitric oxide, C-reactive protein, and sputum eosinophils. They were also more likely to be smokers. The authors argue that adherence to corticosteroid and other medications does not explain these results. The accompanying editorial by Corren (Clin Exp Allergy. 2014;44:152-153) summarizes potential future therapies.*
S.A.T.
Kupczyk M, ten Brinke A, Sterk PJ, et al: Frequent exacerbators--a distinct phenotype of severe asthma. **Clin Exp Allergy**. 2014;44:212-221. ♦♦

Four Phenotypes of Allergic Asthma in Children

PREVIOUS reports have described cases of childhood allergic asthma ranging from severe exacerbations with multiple allergies to mild respiratory disease with normal lung function and no systemic inflammation. This study looked for differing phenotypes based on allergic sensitization in a cohort of children with allergic asthma.

The investigators examined 18 parameters in 125 children with allergic asthma, average age 8.9 years. Factors of interest included age and sex, eczema and food allergy, asthma duration and severity, disease control, total IgE, allergic sensitization, exhaled nitric oxide, and lung function measures. Clusters of patients were identified and cross-tabulated with environmental factors, such as exposure to mold, pets, cockroaches, and household smoking.

The largest cluster, 57 children, had house dust mite sensitization and mild asthma. Nearly all of these patients were monosensitized, and three-fourths had mild asthma. A cluster of 12 children was defined as having pollen sensitization with severe exacerbations--all but one had both of these findings. In a cluster of 20 children with multiple allergies and severe asthma, 95% had moderate to severe asthma along with decreased forced expiratory flow rate at 25% to 75% of forced vital capacity. All children in this cluster had eczema. Other characteristics included higher IgE and exhaled nitric oxide levels and exposure to molds at home. A fourth cluster of 36 children had multiple allergic sensitizations and mild asthma.

This study identifies four phenotypes in a cohort of children with allergic asthma, associated with differences in exacerbation risk, allergic sensitizations, and environmental exposures. Evaluating phenotype may be of value not only for assessing the risk of exacerbations, but also for choosing the most appropriate maintenance therapy.

COMMENT: *Allergic asthma is just one of many phenotypes of asthma. The authors now describe four phenotypic clusters of childhood allergic asthma. Variations of sensitization and severity as well as occurrence of atopic dermatitis are discriminating factors. Specific treatments may evolve, such as sublingual immunotherapy for mite-sensitive mild allergic asthma and omalizumab for severe multi-sensitized asthma. Things could get exciting!*
S.F.W.
Just J, Saint-Pierre P, Gouvis-Echraghi R, et al: ➤➤

Childhood allergic asthma is not a single phenotype. **J Pediatr**. 2014;164:815-820. ♦♦

'Th2 Gene Mean' Assesses Asthma Endotype in Sputum Cells

THE gene signature of periostin, chloride calcium channel accessory 21*(CLCA1)*, and Serpin β2 *(SERPINB2)* in airway epithelial brushings can distinguish Th2-high and Th2-low endotypes of asthma. This study evaluated the possibility of performing asthma gene profiling in sputum cells.

The researchers analyzed stored sputum samples from 37 asthma patients and 15 healthy controls. Using real-time quantitative polymerase chain reaction, gene expression of periostin, *(CLCA1)*, and *(SERPINB2)* were profiled to assess the epithelial cell signature of interleukin-13 (IL-13) activation. Genes associated with airway Th2 inflammation, including *IL4*, *IL5*, and *IL13*, were evaluated as well.

Sputum cells from asthma patients showed higher expression of *CLCA1* and periostin, but not *SERPINB2*, compared to cells from controls. Asthma was associated with increased expression of *IL4*, *IL5*, and *IL13*, which were highly correlated within individual patients.

Expression levels of *IL4*, *IL5*, and *IL13* were combined into a single quantitative metric, the "Th2 gene mean." Based on this metric, 70% of patients were classified as having Th2-high asthma, associated with greater asthma severity and higher blood and sputum eosinophil levels. When initial Th2 gene mean levels were very high or very low, the values tended to remain stable. However, when initial levels were intermediate, the values fluctuated above or below the Th2-high threshold.

Gene expression levels of IL-4, IL-5, and IL-13 are readily measurable in sputum cells from asthma patients and controls. A "Th2 gene mean" metric consisting of these variables can classify asthma patients into Th2-high and Th2-low endotype groups. Measures of gene expression in sputum cells can identify patients with increased Th2 airway inflammation, which is associated with poor asthma control and more severe airflow obstruction.

COMMENT: *One of the latest developments in asthma therapy is identification of phenotypes to potentially target therapy. Identification of gene transcripts for IL-4, IL-5, and IL-13 expressed in airway epithelium can differentiate the patient as either Th2-high or Th2-low. Previous studies have used bronchial biopsies to obtain appropriate samples for analysis. These researchers used material from induced sputum samples to make the classification. They developed a "Th2 gene mean" value, which combines the expression levels of markers to classify patients as either Th2-high or Th2-low. The results are compelling but with some limitations, including modest within-sample and between-sample reproducibility, the use of sputum samples obtained from four different studies, and potential gene/cell changes with corticosteroid treatment. Nevertheless it is intriguing to conjecture that this type of non-invasive sample analysis could be used to target therapy for specific asthma phenotypes. Stay tuned. . . S.M.F.*

Peters MC, Mekonnen ZK, Yuan S, et al: Measures of gene expression in sputum cells can identify Th2-high and Th2-low subtypes of asthma. **J Allergy Clin Immunol**. 2014;133:388-394. ♦♦

Nasal Transcriptome Analysis in Children with Asthma

GENE expression studies in bronchial airway specimens can identify asthma patients with a "Th2-high" inflammatory pattern. However, this invasive technique has been of limited value in children. Nasal transcriptome analysis was assessed for use in identifying asthma subphenotypes in children.

A novel targeted RNA sequencing technology was used to study nasal airway brushings from 10 adolescents with atopic asthma and 10 healthy controls. The findings on nasal transcriptome analysis were compared with those of established bronchial and small-airway transcriptomes. The researchers also performed differential expression and clustering analyses using targeted RNA sequencing nasal expression analysis to profile 105 genes in 50 asthma patients and 50 controls.

Gene expression in the nasal and bronchial transcriptomes overlapped by about 90%, with strong correlation in gene expression. Previously reported asthmatic bronchial differential expression was strongly correlated with nasal expression. On clustering analysis, Th2-high and Th2-low groups of asthma patients could be identified by expression of 70 different genes, including *IL13*, *IL5*, and genes for periostin, calcium-activated chloride channel regulator 1, and serpin peptidase inhibitor, clade B.

Clinical findings associated with Th2-high asthma included atopy, odds ratio (OR) 10.3 compared to the Th2-low group; atopic asthma, OR 32.6; high blood eosinophil count, OR 9.1; and rhinitis, OR 0.83. Asthma patients with an exacerbation in the past year had a 3.9-fold increase in nasal *IL13* expression. Nasal transcript analysis identified several other genes as specific to asthma and independent of atopic status.

The gene expression profiles observed in nasal specimens are very similar to those reported in bronchial specimens. Nasal transcriptomics can identify patients with *IL13*-driven asthma and a Th2-skewed immune pattern. The nasal airway may be a useful, less-invasive alternative to the bronchial airways for transcriptional profiling studies.

COMMENT: *Using nasal mucosal brush samples for RNA extraction and transcriptome analysis, these researchers found that children with high-Th2 allergic asthma could be differentiated from nonallergic, low-Th2 controls with differential expression of a variety of genes including those regulating IL-13, IL-5, periostin, CLCA1, and SERPINB2. The interesting finding is that nasal tissue sampling results could predict Th2 asthma phenotypes and airway characteristics. This pro-* ➤➤

vides further evidence for the "unified airway" theory.
S.M.F.
Poole A, Urbanek C, Eng C, et al: Dissecting childhood asthma with nasal transcriptomics distinguishes subphenotypes of disease.
J Allergy Clin Immunol. 2014;133:670-678. ♦♦

What's the Prevalence of Bronchoconstriction in Recreational Athletes?

EXERCISE -induced bronchoconstriction (EIB) is more common among elite athletes than in the general population. Diagnosis of EIB relies on objective tests of pulmonary function, such as a positive eucapnic voluntary hyperpnea (EVH) challenge. This study used EVH challenge to assess the prevalence of EIB among recreationally active individuals.

The investigators performed EVH challenge in 136 healthy young adults, mean age 22 years, who participated in sports and fitness activities at least 3 hours per week. All were nonsmokers with no previous diagnosis of asthma or EIB. A positive test for EIB was defined as a fall in FEV_1 from baseline at 2 consecutive time points, reversible with an inhaled short-acting β_2-agonist.

The results of EVH challenge were positive in 13.2% of participants, with decreases in FEV_1 ranging from 12% to 50%. The EVH-positive subjects had lower levels of baseline pulmonary function variables: FEV_1 97.5% versus 104.9%, FEV_1/FVC ratio 79.5% versus 87.8%, $FEF_{25-75\%}$ 3.73 versus 4.73 L/s, and predicted PEF 89.4% versus 97.5%.

About 13% of recreationally active young adults with no history of asthma have a positive EVH challenge indicating EIB. Since self-reported symptoms alone can't make the diagnosis of EIB, objective testing may be useful in this group of patients. The authors note that 1 out of 5 study participants could not achieve the target maximal voluntary ventilation rate used in the study protocol.

COMMENT: *The authors demonstrate that 13.2% of recreationally active individuals with no previous history of asthma or EIB had a positive EVH challenge. The true percentage may be higher, as some individuals could not achieve the maximum ventilation needed for completing the test. Symptom and environmental questionnaires were not sensitive or specific enough to predict EIB, although questions positive for wheezing, cold, and high pollen exposure were correlated with positive EVH challenge. Recreationally active individuals may be candidates for objective bronchial provocation testing for EIB, since self-reported symptoms alone are not diagnostic.*
C.C.R.
Molphy J, Dickinson J, Hu J, et al: Prevalence of bronchoconstriction induced by eucapnic voluntary hyperpnoea in recreationally active individuals.
J Asthma. 2014;51:44-50. ♦♦

Increased Anxiety Risk in Patients with Mild Asthma

SEVERE asthma is associated with anxiety, leading to decreased quality of life, increased mortality, and greater health care utilization. This study looked for associations with anxiety in a group of patients with mild asthma.

The researchers analyzed 15,675 patients undergoing preventive medical examinations at one clinic over a 13-year period. As part of an extensive medical history and physical examination, patients completed an anxiety questionnaire and underwent laboratory and spirometric testing. Associations between asthma and anxiety were assessed by multiple logistic regression.

Nine percent of patients were diagnosed with asthma. Most of these patients rated themselves in good to excellent health, did not use an inhaler, and had an FEV_1/FVC ratio greater than 70%.

On controlling for covariates, anxiety was significantly associated with asthma: odds ratio 1.435. The strength of the association was similar to that for smoking, which is potentially associated with asthma severity. Anxiety was unrelated to other variables in the model, including FEV_1/FVC ratio or use of an inhaled corticosteroid, with or without a long-acting β agonist.

The results suggest a substantially increased risk of anxiety in a clinical population of patients with mild asthma. Patients with asthma may be a target population for anxiety screening, the researchers suggest. They call for further studies to assess the course, clinical correlates, and potential mechanisms of anxiety symptoms in asthma.

COMMENT: *Chronic stress has an impact on allergy and asthma, likely through neuro-endocrine-immune mechanisms. Asthma exacerbations are increasingly linked to depression and anxiety. The interaction between behavior and biology affects our patients' adherence to therapy, perceptions of their condition, quality of life, risk behaviors, and specific symptoms. (See the editorial by Marshall: Ann Allergy Asthma Immunol. 2014;112:275.) This study in a cohort of mild asthmatics demonstrates more than a 40% increase in the risk of anxiety, suggesting that all patients with asthma should be considered for anxiety screening.*
C.C.R.
Gada E, Khan DA, DeFina LF, Brown ES: The relationship between asthma and self-reported anxiety in a predominantly healthy adult population.
Ann Allergy Asthma Immunol. 2014;112:329-332. ♦♦

Large Improvement with Omalizumab for Severe Allergic Asthma in Children

OMALIZUMAB effectively reduces exacerbations in patients with moderate to severe allergic asthma. Real-life studies in adults have extended the findings of randomized trials. There are comparatively few data on the use and safety outcomes of omalizumab in children. ►►

The authors report an experience with add-on treatment with omalizumab in 104 pediatric patients, aged 6 to 18 years, with severe allergic asthma. The children were followed up at 12 pediatric pulmonary tertiary care centers for more than 1 year after the start of omalizumab treatment. Outcomes of interest included asthma control, exacerbations, inhaled corticosteroid dosage, lung function measures, and adverse events.

Two-thirds of the children were sensitized to at least 3 allergens. The mean IgE level was 1.125 kU/L, exacerbation rate 4.4 per year, and inhaled corticosteroid dose (fluticasone equivalent) 703 µg /d. At baseline, none of the patients had good asthma control, 18% had partial control, and 82% had poor control.

By 20 weeks, 53% of the children had good asthma control, 30% had partial control, and 17% had poor control. By 52 weeks, the figures were 67%, 25%, and 8%, respectively. Exacerbation rate decreased by 72% and hospitalization rate by 88.5% with omalizumab. Other findings included a 4.9% reduction in FEV_1 and a 30% decrease in inhaled corticosteroid dose.

Age younger than 12 years was the only factor associated with a good response to omalizumab. Six children had significant adverse events leading to discontinuation of omalizumab; treatment was successfully restarted in two cases.

This real-life experience shows large improvements in disease control with add-on omalizumab in children with severe allergic asthma. Exacerbation and hospitalization rates and other outcomes show improvements even greater than reported in clinical trials. Omalizumab produces good responses in a difficult-to-treat group of children with high IgE levels, multiple sensitizations, and/or food allergy.

COMMENT: *This study supports the ICATA study (N Engl J Med. 2011;364:1005-1015) showing the benefits of omalizumab add-on therapy for children with severe allergic asthma. Omalizumab is associated with a significant drop in fluticasone equivalents, from 703 to 592 µg/d, with 47% of the patients having greater than 50% reduction. The 70% drop in exacerbations is greater than in the ICATA data. The study supports omalizumab as an extremely important intervention in children as young as 6 years of age, and highlights the need for the FDA to approve this drug for younger children.*
B.E.C.

Deschildre A, Marguet C, Salleron J, et al: Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey.
Eur Respir J. 2013;42:1224-1233. ♦♦

Adverse Effects of Smoking during Pregnancy Persist into Teens

MATERNAL smoking during pregnancy (MSP) has known adverse health effects in children. It's still unclear whether the respiratory health effects of MSP persist into later childhood. If so, then altered immune function is one possible mechanism. This study sought evidence of persistent respiratory effects of maternal smoking during pregnancy in children followed up to adolescence.

The study included 1,129 adolescents followed up to age 14 as part of an Australian birth cohort study. The teens underwent spirometry along with assessments of bronchial responsiveness, respiratory symptoms, total and specific IgE and IgG4 levels, immune function, and inflammatory markers. These outcomes were related to maternal history of smoking during pregnancy.

Maternal smoking during pregnancy was recorded for 21.0% of subjects, and 8.1% were smoking at age 14. Among current smokers, maternal smoking during pregnancy was associated with reductions in lung function, including $FEF_{25-75\%}$ and FEV_1/FVC. There were also significant increases in risk of current asthma, odds ratio (OR) 1.84; current wheezing, OR 1.77; and exercise-induced wheezing, OR 2.29.

Maternal smoking during pregnancy was unrelated to bronchial hyperresponsiveness or atopy. The associations were similar after adjustment for measures of immune function or lung function. The increases in asthma and wheezing showed no modifying effect of sex, atopy, or maternal history of atopy or asthma.

The results suggest that some adverse respiratory health effects of MSP persist into adolescence, including increased rates of asthma and wheezing. The mechanisms involve more than reductions in lung function, and do not include altered immune function or increased atopy. Efforts to prevent asthma and other childhood respiratory conditions should include prevention of MSP.

COMMENT: *Reading the title, you would think this study gives strong support to the observation that MSP has adverse effects even through adolescence. However, several important points need to be recognized. Eight percent of the 14-year-olds were already smoking, and the study did not account for environmental tobacco smoke after birth. It is also interesting to note there was no effect on bronchial hyperresponsiveness, and the expected persistence of symptoms in females after puberty was not seen. See the accompanying editorial by Johnson et al (Am J Respir Crit Care Med. 2014;189:380-381).*
B.E.C.

Hollams EM, de Klerk NH, Holt PG, Sly PD: Persistent effects of maternal smoking during pregnancy on lung function and asthma in adolescents.
Am J Respir Crit Care Med. 2014;189:401-407. ♦♦

Should We Be Measuring eNO in Peanut Allergy?

SERUM-specific IgE against peanut allergen Ara h 2 may identify children likely to have a clinical reaction to peanut challenge. Exhaled nitric oxide (eNO), a noninvasive measure of allergic inflammation of the airways, is independently associated with food-specific IgE levels. This study evaluated an approach combining specific IgE measurement and eNO to predict allergic reactions to peanut challenge.

The study included 53 consecutive children referred for open-label peanut oral food challenge (OFC) by a pediatric allergist. All patients underwent skin-➤➤

prick testing using whole peanut extract and measurement of Ara h2-specific IgE in serum. Exhaled NO was measured in 44 cooperative children. Peanut OFC was then performed, with results interpreted in blinded fashion.

Twenty-three children had a clinical reaction to peanut OFC. On receiver operator characteristic curve analysis, Ara h2-specific IgE and eNO were each more accurate than peanut SPT in predicting the response to OFC. Area under the curve (AUC) was 0.84 for Ara h2 specific IgE and 0.83 for eNO. When the results of SPT, Ara h2-specific IgE, and eNO were combined, AUC for response to peanut challenge was 0.96. Exhaled NO was unrelated to serum nitrite levels.

Serum Ara h2-specific IgE is a potentially robust indicator of clinical peanut allergy in children. Especially in combination with eNO, prospective measurement of Ara h2-specific IgE might improve diagnostic accuracy in patients undergoing clinically indicated peanut OFC. Further study is needed to validate the clinical value of the proposed algorithm.

COMMENT: *We are all familiar with component testing to help us understand which epitopes are targeted by our patients' specific IgE. Serum IgE recognizing Ara h2 may help distinguish "clinically allergic" from "sensitized but tolerant" patients. This study found that higher levels of eNO help predict positive reactions to "open label" peanut oral challenges. The authors propose an algorithm using both Ara h2 and eNO. This finding is intriguing, but more controlled study is required before routine eNO measurement is recommended in peanut-allergic patients.*
S.A.T.

Preece K, Bhatia R, Belcher J, et al: The fraction of exhaled nitric oxide improves prediction of clinical allergic reaction to peanut challenge in children.
Clin Exp Allergy. 2014;44:371-380. ♦♦

Pediatric Food Allergy--Rising Prevalence and Racial Disparity

THE prevalence of food allergy is thought to be increasing worldwide. However, there have been no systematic analyses of US trends in food allergy, including changes over time and racial/ethnic differences. These issues were addressed in a meta-analysis of US studies of self-reported food allergy in children.

A systematic review of publically available data sets identified 27 different survey administrations providing data on food allergy prevalence from 1988 to 2011. The surveys represented a total of 452,237 US children.

Because of heterogeneity between studies, no summary estimate of the national prevalence of pediatric food allergy was possible. To evaluate the effects of study- and participant-level covariates, metaregression was performed in 20 surveys performed by the Centers for Disease Control and Prevention.

The data suggested marked temporal trends: estimated increase in prevalence of self-reported food allergy prevalence was 1.2 percentage points per decade. There was significant racial/ethnic variation, with the largest increase per decade among non-Hispanic black children: 2.1%, compared to 1.2% for Hispanic and 1.0% for non-Hispanic white children. In sensitivity analyses, the trends remained significant, with a racial/ethnic disparity at least as large as in the primary analysis.

The results support the perception that the prevalence of food allergy among US children has increased since the late 1980s. There is evidence of racial/ethnic differences, with the largest increases reported among non-Hispanic black children. The authors call for further studies to investigate the apparent increase in pediatric food allergy and the emerging racial/ethnic disparity.

COMMENT: *This large meta-analysis and metaregression of publications reporting food allergy prevalence finds large increases in food allergy prevalence from one decade to another. The highest increases in self-reported food allergy were among non-Hispanic black children. As these authors recommend, since the prevalence continues to increase, it's important to consider increased resources to address prevention and treatment of food allergy. Further studies are also needed to address the disparity in food allergy among non-Hispanic black children.*
V.H.-T.

Keet CA, Savage JH, Seopaul S, et al: Temporal trends and racial/ethnic disparity in self-reported pediatric food allergy in the United States.
Ann Allergy Asthma Immunol. 2014;112:222-229. ♦♦

Penicillin 'Allergy' Affects Hospital Costs and Outcomes

MANY patients report a history of penicillin "allergy," but most of them are not truly allergic. These inaccurate diagnoses could affect the amount and types of care provided. This study evaluated the impact of penicillin "allergy" in hospitalized patients.

In the retrospective study, 51,582 patients with reported penicillin "allergy" at hospital admission were matched for age and sex, date of admission, and discharge diagnosis category to 2 unique controls. At 20.1 months of follow-up, the penicillin "allergy" cases averaged 0.59 more hospital days than controls. The difference in hospital days was larger for female patients.

There were significant differences in antibiotic exposure, with cases more likely to be treated with fluoroquinolones, clindamycin, and vancomycin. The patients with penicillin "allergy" also had a higher prevalence of *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus*. Odds ratios were 1.234, 1.141, and 1.301, respectively, with most infections being hospital acquired.

Penicillin "allergy" recorded at admission is not a benign finding. Patients with this often-inaccurate diagnosis spend more time in the hospital and are exposed to more antibiotics previously linked to *C. difficile* and MRSA. The authors suggest that admission testing of patients with a history of penicillin "allergy" might reduce costs and improve clinical outcomes. ➤➤

COMMENT: *It has been estimated that approximately 10% of all patients report a history of penicillin allergic reactions and are subsequently labeled "allergic to penicillin." Most of these patients have negative results on allergy skin testing to penicillin proteins and can safely take penicillin. Using a case-controlled cohort analysis of 2 years of hospitalizations, these authors found that patients with penicillin "allergy" had longer hospitalizations, used antibiotics that were more expensive and associated with more side effects, and had a higher rate of hospital-acquired infections such as* C. difficile, *MRSA, and VRE. As allergists, we should take a more active role in helping to identify the true risk for reactions to antibiotics.*
S.M.F.

Macy E, Contreras R: Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study.
J Allergy Clin Immunol 2014;133:790-796. ♦♦

Anaphylaxis in the US Population: High Prevalence, Low Preparedness

ANAPHYLAXIS is well-recognized as a life-threatening condition, yet there are limited data on its population prevalence and characteristics. Studies focusing on specific triggers have reached varying conclusions. This study reports two nationwide surveys of the prevalence and characteristics of anaphylaxis among US adults.

In a random-digit-dial "public survey," the lifetime prevalence of anaphylaxis was assessed in a population of 1,000 US adults. In addition, a "patient survey" of 1,059 adults provided data on history of reactions to medications, foods, insect stings, or latex--or idiopathic reactions--in household members over the previous 10 years. Both surveys asked about anaphylaxis symptoms, treatments, knowledge, and behaviors.

In the public survey. 7.7% of adults reported a previous anaphylactic reaction. In analyses using more stringent criteria, estimated rates were 5.1% for probable anaphylaxis and 1.6% for very likely anaphylaxis.

In the patient survey, 32.5% of respondents reported a history of anaphylaxis in a family member. Treatment was sought within 15 minutes of anaphylaxis symptoms by 42% of patients. Thirty-four percent of patients reported going to the hospital, 27% self-treated with antihistamines, 10% called 911, 11% self-administered epinephrine, and 6.4% reported no treatment.

Most respondents reporting anaphylaxis said they had had at least two previous episodes, with 19% reporting at least five episodes. However, 52% did not have a prescription for self-injectable epinephrine and 60% did not currently have an epinephrine injector.

The prevalence of anaphylaxis in the US population is at least 1.6%, and probably around 5%. The patient survey highlights deficiencies in treatment of past anaphylaxis episodes and lack of preparedness to treat future episodes. The results "indicate a pressing need for improved public health initiatives regarding anaphylaxis recognition and treatment."

COMMENT: *Data from two large surveys were used for this report. It concludes that the prevalence of anaphylaxis is probably greater than 1.6%. Patients report that their episodes are triggered by foods in 38% of cases, insect stings in 41%, and unknown in 39%. The main concern is that 27% of patients self-treated with antihistamines while only 11% self-administered epinephrine, which is the treatment of choice. Even among patients who had at least two prior anaphylaxis episodes, 52% report not receiving an epinephrine autoinjector and 60% didn't have it available. The findings show a large gap in patient and public knowledge of appropriate treatment for anaphylaxis. The role of the allergist is clear: teach, teach, teach!*
S.M.F.

Wood RA, Camargo CA Jr, Lieberman P, et al: Anaphylaxis in America: The prevalence and characteristics of anaphylaxis in the United States.
J Allergy Clin Immunol. 2014;133:461-467. ♦♦

Measurements of Small-Airway Dysfunction In Asthma--Do They Matter?

THE contribution of small-airway obstruction to the clinical expression of asthma remains unclear. Several indicators of small-airway obstruction have been proposed, although they are likely not completely specific to the small airways. Various markers of small-airway obstruction were evaluated for association with key clinical outcomes in asthma.

The study included 64 adults with asthma, representing a range of severity on the Global Initiative for Asthma treatment steps; and 18 healthy controls. Both groups were assessed by spirometry along with impulse oscillometry, multiple breath inert gas washout, body plethysmography, and single-breath determination of carbon monoxide uptake. Asthma patients were evaluated on the six-point Asthma Control Questionnaire (ACQ-6) and standardized Asthma Quality of Life Questionnaire (AQLQ[S]).

Asthma severity, disease control, and quality of life were unrelated to putative measures of small-airway obstruction: resistance at 5 Hz minus resistance at 20 Hz (R5-R20) and reactance area. However, severe asthma was associated with elevated markers of total (R5) and mean airway resistance of large and small airways (R20). The R5 value for patients with severe asthma was 0.47, compared to 0.37 for those with mild-to-moderate asthma. Values for R20 were 0.39 vs 0.31, respectively.

R20 was a strong independent contributor to ACQ-6 score, along with FEV_1 % predicted. For AQLQ(S) score, the strongest contributors were R20 and FVC % predicted. R20 was also independently related to a history of one or more exacerbations within the previous year.

Various markers of small airway obstruction do not appear to reflect the clinical expression of asthma. However, measurement of the large and small airway resistance marker R20 on impulse oscillometry appears to be independently associated with asthma control ➤➤

and quality of life. Prospective studies are needed to confirm this finding and its clinical significance.

COMMENT: *Small airway obstruction plays a well-recognized role in the physiology of asthma. This study evaluated a well-characterized group of adult asthma patients with varying severity and correlated asthma control and quality of life with pulmonary physiology. Somewhat surprisingly, physiologic measurements of small airway obstruction did not correlate with asthma control, quality of life, or being exacerbation-prone. The strongest independent predictor for asthma control, quality of life and exacerbations was the variable R20, which measures the mean level of large and small airway resistance. It appears that this variable deserves further study.*

The researchers intentionally evaluated post-bronchodilator findings to minimize the contribution of large airway tone. That may explain differences from prior studies showing an association with small airways and clinical outcomes in asthma. The authors point out that, since small and large airways are not independent from one another, the distinction between markers of small and large airway obstruction may be somewhat artifactual.

D.A.K.

Gonem S, Natarajan S, Desai D, et al: Clinical significance of small airway obstruction markers in patients with asthma.

Clin Exp Allergy. 2014;44:499-507. ♦♦

Beta-Blockers in Asthma: Selectivity Matters, or Does It?

BECAUSE of the potential for acute bronchoconstriction, otherwise-indicated treatment with β-blockers is often avoided in patients with asthma. However, the effects of selective versus nonselective β-blockers are unclear, as are the possible differences between individual drugs. An updated meta-analysis of the evidence on adverse respiratory effects of acute β-blocker exposure in patients with asthma is presented.

A systematic review identified 32 randomized, blinded, placebo-controlled trials evaluating changes in respiratory function and β_2 agonist efficacy after acute β-blockade. Sixteen studies evaluated selective β-blockers, six evaluated nonselective β-blockers, and six evaluated both classes.

On meta-analysis of pooled data, the study doses of acute selective β-blockers produced a mean 6.9% decrease in FEV_1, with an accompanying 10.2% reduction in β_2 agonist response. Selective β-blockers led to an FEV_1 reduction of at least 20% in 1 out of 8 patients and symptoms in 1 out of 33.

For acute nonselective β-blockers, there was a mean 10.2% reduction in FEV_1 and a 20.0% reduction in β_2 agonist response. Decreases in FEV_1 of 20% or greater occurred in 1 out of 9 patients and symptoms in 1 out of 13. On analysis of heterogeneity, these changes did not occur with celiprolol or labetalol. For selective β-blockers, there was evidence of a dose-response relationship.

The adverse respiratory effects of selective β-blockers in asthma are smaller than with nonselective β-blockers, but are significant for both classes. Using the smallest possible dose and using drugs with higher β_1-selectivity may help to limit the risks from acute exposure. When β-blocker-induced bronchospasm occurs, the response to β_2-agonists is blunted to a greater extent by nonselective vs selective β-blockers.

COMMENT: *Prior meta-analyses of selective β-blockers have been largely reassuring in regards to their impact on asthma. This more recent meta-analysis evaluated both selective and nonselective β-blockers in terms of mean change in FEV_1 as well as the frequency of falls in FEV_1 of 20% or greater. Although selective β-blockers had only modest mean decreases in FEV_1 (less than with non-selective β-blockers), 1 in 8 still had falls of 20% or greater. Mean baseline FEV_1 did not influence the change in FEV_1. There also appeared to be a dose-response effect, and certain β-blockers (celiprolol and labetalol) did not cause a statistically significant change in FEV_1. Beta-blockers are commonly indicated for cardiovascular disease. Although most asthma patients will tolerate selective β-blockers, these drugs are not risk-free. Their use should be based on individual risk assessment.*

D.A.K.

Morales DR, Jackson C, Lipworth BJ, et al: Adverse respiratory effect of acute β-blocker exposure in asthma: a systematic review and meta-analysis of randomized controlled trials.

Chest. 2014;145:779-786. ♦♦

Does Nebulized Beclomethasone Prevent Viral Wheezing in Young Children?

THERE is ongoing debate over the effectiveness of inhaled steroids in preventing viral wheezing in preschool-aged children. Nevertheless, nebulized beclomethasone is commonly prescribed for children with upper respiratory tract infections (URTIs). This placebo-controlled trial evaluated the use of nebulized beclomethasone to prevent recurrent viral wheezing in young children.

The trial included 525 children with a history of viral wheezing in Italy, where beclomethasone is widely prescribed for pediatric URTIs. The children, aged 1 to 5 years, were seen by 40 pediatricians for URTI. Patients were randomly assigned to 10 days of treatment with nebulized beclomethasone, 400 μg twice daily, or placebo. The physician-diagnosed incidence of viral wheezing during the 10-day period was compared between groups; parents completed subjective assessments as well.

The pediatricians diagnosed wheezing in 9% of children, with no significant difference between the nebulized beclomethasone versus placebo groups. More than 60% of parents in both groups rated the assigned treatment as helpful. Just under half of children still had URTI symptoms after 10 days, with no difference between groups. Adverse events were also similar ►►

with beclomethasone versus placebo.

In young children with URTI, nebulized beclomethasone does not reduce the rate of viral wheezing, compared to placebo. There is also no difference in persistence of symptoms through the 10-day treatment period. Nearly two-thirds of parents rate nebulized treatment helpful, whether with beclomethasone or placebo.

COMMENT: *In this randomized trial of 521 Italian children with URTI, use of nebulized beclomethasone was not significantly different from placebo in preventing occurrence of wheezing during 10 days of treatment. Interestingly, the treatment was considered helpful by most parents in either group--even though there was no difference in the persistence of URTI symptoms or in parental perception of asthma-like symptom severity! As often happens in studies of wheezing episodes, the incidence of wheezing was lower than expected, making the study underpowered. Also, the adherence was imperfect--only 60% completed all days of therapy. Hmm. . . Should nebulized placebo be the prescription of choice for these children?*
C.D.

Clavenna A, Sequi M, Cartabia M, et al: Effectiveness of nebulized beclomethasone in preventing viral wheezing: an RCT.
Pediatrics. 2014;133:e505-e512. ♦♦

Do Allergies Protect Against Lung Cancer?

THERE are conflicting reports regarding the potential association between history of allergic diseases and lung cancer. Opposing theories--the antigenic hypothesis and the immune surveillance hypothesis--propose a potential increase or decrease in cancer risk, respectively. This question was addressed in a Canadian population-based study.

The researchers analyzed interview data from 1,169 Montreal-area residents with incident lung cancer and 1,486 controls. Logistic regression models were used to assess the relative risk of lung cancer in participants with versus without asthma, eczema, or hay fever. Analyses were adjusted for demographic and lifestyle factors, including smoking.

A decreased rate of lung cancer associated with asthma became significant on analysis of participants who reported use of asthma medications: odds ratio (OR) 0.64. A similar association was noted for participants who reported using medication for eczema: OR 0.63. Hay fever showed the strongest protective effect against lung cancer: OR 0.37. Odds ratios did not vary significantly by age at onset, latency period, or smoking level.

Asthma, eczema, and hay fever all appear to have a protective effect against the development of lung cancer. The strength of the effect varies between diseases, and becomes more pronounced when associated medication use is considered. The findings suggest that the immune surveillance hypothesis could be a shared underlying mechanism of the association between history of allergic diseases and lung cancer.

COMMENT: *Studies have varied in reports of lung cancer in patients with allergy. Increased risk of lung cancer has been reported among patients with asthma in some studies. Overall, in this study, no association was seen in patients with asthma alone, while lower risk was seen in patients with only hay fever. The authors found that patients with at least two allergic diseases were at lower risk of lung cancer. Asthma, hay fever, and eczema were inversely associated with lung cancer. Interestingly enough, allergic disease may protect patients from lung cancer.*
V.H.-T.

El-Zein M, Parent M-E, Siemiatycki J, Rousseau M-C: History of allergic diseases and lung cancer risk.
Ann Allergy Asthma Immunol. 2014;112:230-236. ♦♦

CLINICAL TIDBITS

Clusterin May Predict Asthma Severity

OXIDATIVE stress may play a role in asthma-related chronic airway inflammation. The secretory glycoprotein clusterin is a biosensor of oxidative stress with antioxidant properties. This study examined clusterin expression in asthma patients, including its response to inhaled corticosteroids.

The researchers measured clusterin levels in serum, induced sputum, and peripheral blood mononuclear cells in 142 adult patients with asthma. Patients with severe asthma had elevated levels of serum clusterin, which were inversely correlated with pulmonary function. Peripheral blood mononuclear cells from asthma patients showed greatly increased expression of hyperoxidized peroxiredoxins, which was correlated with clusterin expression. Sputum clusterin expression was also increased in asthma.

Thirty-seven treatment-naive patients underwent serum clusterin measurement before and after initial inhaled corticosteroid therapy. Mean serum clusterin decreased from 82.1 μg/mL before treatment to 76.3 μg/mL afterward.

Patients with asthma show increased expression of clusterin, showing high levels of oxidative stress. With further study, clusterin could be a useful biomarker of asthma severity and airway inflammation status.

COMMENT: *Oxidative stress occurs from inflammation and leads to inflammation. The glycoprotein clusterin is a biosensor of oxidative stress. The authors measured clusterin in serum, induced sputum, and peripheral blood mononuclear cells, before and after treatment with inhaled corticosteroids. Serum clusterin levels were significantly higher in patients with severe asthma. Serum clusterin decreased after use of inhaled corticosteroids in patients with asthma who were treatment naive. Since different subtypes of asthma exist, the use of clusterin levels needs to be studied in each subtype. As the authors comment, this may be a new promising and noninvasive biomarker of asthma severity.* ►►

V.H.-T.
Kwon H-S, Kim T-B, Lee YS, et al: Clusterin expression level correlates with increased oxidative stress in asthmatics.
Ann Allergy Asthma Immunol. 2014;112:217-221. ♦♦

Can Terbutaline Prevent Respiratory Failure in Pediatric Asthma?

PREVENTING deterioration to acute respiratory failure is an important goal of emergency treatment for acute severe asthma. Recommendations include the use of systemic, selective β-agonists such as terbutaline. This study evaluated the effects of early intravenous terbutaline on the risk of acute respiratory failure in severe pediatric asthma.

The retrospective study included 85 children with severe asthma seen at the authors' emergency department (ED), who received early intravenous terbutaline; and 120 children from an outside ED in whom terbutaline was started later. Mean duration of intravenous terbutaline before pediatric ICU admission was 2.91 vs 0.69 hours, respectively.

Mechanical ventilation was required in 16% of patients from the authors' ED, compared to 60% of those from outlying EDs. The period of terbutaline treatment before pediatric ICU admission was 2.61 hours for spontaneously breathing patients, 2.04 hours for those receiving noninvasive ventilation, and 0.97 hours for those requiring mechanical ventilation.

For children with severe asthma, early intravenous terbutaline may reduce the rate of acute respiratory failure and mechanical ventilation. Further study is needed to confirm the benefits of early terbutaline infusion for severe pediatric asthma.

COMMENT: *Medications such as terbutaline have been shown to be safe in the treatment of asthmatic patients. Since pediatric mortality from asthma has been increasing over the recent decades, safe and effective treatment options are essential. This study found that early administration of terbutaline in the ED may improve outcomes via decreased need for ventilatory support. This may provide another treatment option for children with severe asthma. Further prospective studies would be important to compare IV terbutaline with other options in pediatric patients with severe asthma.*
V.H.-T.
Doymaz S, Schneider J, Sagy M: Early administration of terbutaline in severe pediatric asthma may reduce incidence of acute respiratory failure.
Ann Allergy Asthma Immunol. 2014;112:207-210. ♦♦

Is Dexamethasone an Alternative to Prednisone for Acute Asthma?

SEVERAL small trials have evaluated the hypothesis that dexamethasone is an equivalent therapy to prednisone or prednisolone for asthma exacerbations in children. The benefits of intramuscular or oral dexamethasone versus oral prednisolone or prednisone were evaluated in a meta-analysis.

The researchers identified six randomized trials comparing dexamethasone with 5 days of prednisolone for treatment of acute asthma exacerbations in patients aged 18 years or younger. On meta-analysis of pooled data, relapse rates were similar between groups at all times: 5 days, 10 to 14 days, and 30 days. Dexamethasone was associated with lower rates of vomiting, both in the emergency department and at home: relative risk 0.29 and 0.32, respectively. The route of dexamethasone administration was oral (single or double dose) in three studies and intramuscular (single dose) in three.

Oral or intramuscular dexamethasone, given in one or two doses, is a "viable alternative" to 5 days of treatment with prednisone/prednisolone for children with acute asthma exacerbations. Further studies of the two routes of administration, different oral formulation, and in ambulatory settings are warranted.

COMMENT: *This meta-analysis evaluated whether single- or two-dose regimens of intramuscular or oral dexamethasone were equivalent or superior to a 5-day course of oral prednisone or prednisolone. With respect to relative risk of relapse, there was no difference between the two groups at any time point. Children from the six trials studied who received dexamethasone were less likely to experience vomiting in either the emergency department or at home. It remains to be determined if these findings can be extrapolated to ambulatory care.*
C.D.
Keeney GE, Gray MP, Morrison AK, et al: Dexamethasone for acute asthma exacerbations in children: a meta-analysis.
Pediatrics. 2014;133:493-499. ♦♦

Racism: A New Risk Factor for Adult-Onset Asthma

CHRONIC stress from racism has been linked to several adverse health outcomes in black Americans. Data from a prospective follow-up study were used to analyze the association between experiences of racism and asthma incidence among black women.

The analysis included data on 38,142 black women completing biennial follow-up questionnaires. Of these, 1,068 reported incident asthma. The researchers examined associations of asthma with an "everyday racism" score, reflecting daily life experiences with racism; and a "lifetime racism" score, reflecting racism at work, and housing, and by police.

On multivariable analysis, both racism scores were associated with asthma risk. For women in the highest versus lowest categories in 1977, incidence rate ratios were 1.45 for the everyday racism score and 1.44 for the lifetime racism score. For women experiencing the same levels of racism in 2009, the IRRs were 2.12 and 1.66, respectively.

The results suggest that black women's experi- ➤➤

ences of everyday and lifetime racism are associated with an increased risk of developing asthma. The study adds to previous evidence of the adverse health effects of racism in society. Interventions to alleviate racism-related stress could play a role in asthma prevention strategies, especially in minority communities.

COMMENT: *Several risk factors have been suggested for the development of adult-onset asthma, including obesity, occupational exposures, smoking, and various life stressors. This article from the Black Women's Health Study found a 45% increase in asthma risk among black women who perceived high levels of racism, compared to those with perceived low levels of racism. This risk increased over time in those who continued to experience high levels of racism. Although the epidemiologic data do not prove causality, they add to the literature on the adverse health effects of racism and suggest a new potentially modifiable target risk factor to reduce asthma.*
D.A.K.

Coogan PF, Yu J, O'Connor GT, et al: Experiences of racism and the incidence of adult-onset asthma in the Black Women's Health Study.
Chest. 2014;145:480-485. ♦♦

Reacting to Placebos in Food Challenges: Who, What And How Often?

PATIENTS undergoing double-blind, placebo-controlled food challenges (DBPCFCs) receive the allergenic and placebo foods on separate days and are monitored for clinical reactions. This study evaluated the frequency and characteristics of positive responses to placebo challenges.

The retrospective study included a total of 740 placebo challenges in children with suspected food allergy between 1998 and 2007. There were 21 false-positive responses to placebo, a rate of 2.8%. All children with reactions to placebo had a history of atopic eczema (AE); the rate was somewhat higher among children aged 1.5 years or younger. Children with positive placebo challenges had higher total IgE levels.

Skin symptoms were more common than airway symptoms. The most frequent symptom was worsening of AE, followed by urticaria, redness, itching, and angioedema. Late reaction worsening of AE occurred in 57% of positive placebo challenges versus 14% of positive verum challenges.

Positive responses to placebo occur in close to 3% of children undergoing DBPCFC. The false-positive reactions most commonly consist of worsening of AE, highlighting the importance of DBPCFCs in this condition.

COMMENT: *Double-blind, placebo-controlled food challenges are used as a gold-standard in the diagnosis of food allergy. Analysis of placebo-reactors is scant in the literature. This study evaluated reactions to placebos during 740 DBPCFCs. Placebo reactions were uncommon (2.8%), occurred more frequently in younger vs older children, and typically manifested as worsening of atopic dermatitis. Therefore, in infants who have worsening of atopic dermatitis after an open or single-blind food challenge, a DBPCFC should certainly be considered to confirm such a reaction.*
D.A.K.

Ahrens B, Niggemann B, Wahn U, Beyer K: Positive reactions to placebo in children undergoing double-blind, placebo-controlled food challenge.
Clin Exp Allergy. 2014;44:572-578. ♦♦

REVIEWS OF NOTE

COMMENT: *Although written for non-specialists, this review resonates with recent editorials in our literature. (See Beigelman et al: J Allergy Clin Immunol 2014;133:1016-1077 and Weinberger: J Allergy Clin Immunol 2014;133:1014-1015.) These articles summarize the sometimes-contentious arguments regarding use of inhaled steroids, oral steroids, nebulizers and action plans for treatment of preschool wheezers. What is agreed on is the need for better therapies.*
S.F.W.

Bush A, Grigg J, Saglani S: Managing wheeze in preschool children.
BMJ. 2014;348:g15. ♦♦

COMMENT: *This is a very important guideline for the evaluation and treatment of severe asthma.*
B.E.C.

Fan Chung K, Wenzel SE. Brozek JL, et al: International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma.
Eur Respir J. 2014;43:343-373. ♦♦

COMMENT: *This well-written update on occupational asthma--ie, asthma due to conditions attributable to work exposures--is a must-read for those interested in a quick and comprehensive overview of the topic.*
C.D.

Tarlo SM, Lemiere C: Occupational asthma.
N Engl J Med. 2014;370:640-649. ♦♦

COMMENT: *Here's an excellent review of the fundamentals of lung auscultation. The authors use current concepts of lung acoustics and technology to characterize and demonstrate the lung sounds in an online interactive graphic.*
C.D.

Bohadana A, Izbicki G, Kraman SS: Fundamentals of lung auscultation.
N Engl J Med. 2014;370:744-751. ♦♦