AllergyWatch®

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

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Climate Change Linked to Increased Pollen Sensitization

VARIATIONS in climate will affect the pollen load, and thus the rate of allergic sensitization. Long-term observations in a specific geographic area are necessary to show how climate changes affect the quality and amount of airborne pollens. The researchers analyzed 27-year data on climate, major allergenic pollens, and allergic sensitization from one region of Italy.

The study included information on pollen counts, season durations, and pollen sensitization in western Liguria, a coastal region of northwest Italy, from 1981 to 2007. Sensitization data included skin prick tests for five major airborne pollens: birch, cypress, olive, grass, and *Parietaria*.

For three of the five pollens, the duration of the pollen season increased progressively during the study period, mainly reflecting earlier start dates. The largest increase, 85 days, was noted for *Parietaria*; olive and cypress season increased by 18 days each. Except for grasses, all pollens showed a progressive increase in pollen load, by approximately 25%. The percentage of patents sensitized to these non-grass pollens also increased, despite no change in sensitization to house dust mite. The changes in pollen load and sensitization were correlated with increases in direct radiation, temperature, and number of days with temperatures over 30° C.

Warming and other climate changes over the past three decades are accompanied by an increased load of non-grass pollens. These changes are correlated with increased rates of allergic sensitization. Ongoing climate change may thus lead to increased global pollen loads and sensitization rates.

COMMENT: *Allergists/immunologists provide a knowledge link between the biology of the complex human immune system and the complex ecosystem. Environmental change, which is debated by various contingents with variable conclusions as to cause and effect, is occurring with a warming trend. This paper provides additional evidence that this warming is*➤➤

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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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likely to result in the greater occurrence of allergic symptoms.
D.K.L.

Ariano R, Canonica GW, Passalcqua G: Possible role of climate changes in variations in pollen seasons and allergic sensitizations during 27 years.
Ann Allergy Asthma Immunol. 2010;104:215-222. ♦♦

No Increase in Serious Asthma Events with Formoterol

CURRENT guidelines call for addition of a long-acting β_2-adrenergic agonist (LABA) in patients with persistent asthma that is not well-controlled with an inhaled corticosteroid (ICS) alone. However, there are concerns about the safety of long-term LABA use. A large database of asthma clinical trials was analyzed to compare the safety of formoterol-containing versus non-LABA treatments for asthma.

The analysis included data on 23,510 patients enrolled in randomized, active- or placebo-controlled trials, sponsored by AstraZeneca, that included formoterol-containing and non-LABA comparator treatments. Serious adverse events--including all-cause and asthma-related deaths, asthma-related intubation, and asthma-related hospitalization--were adjudicated in blinded fashion.

A total of 13,542 patients aged 4 years or older were assigned to formoterol and 9,968 to non-LABA treatments. About 90% of patients in both groups received ICS as part of their study treatment or as an allowed medication.

There were 3 deaths among patients assigned to formoterol and 4 among patients assigned to non-LABA treatments. All-cause mortality was nonsignificantly lower for patients assigned to formoterol: 0.53 versus 0.82 per 1,000 patient-treatment years, respectively. There were no asthma-related deaths and only 1 asthma-related intubation.

Formoterol was associated with a nonsignificant reduction in asthma-related hospitalizations: 12.1 versus 16.4 per 1,000 patient-treatment years. The treatment discontinuation rate was significantly lower in the formoterol-treated group: 12.7% versus 15.4%, relative risk 0.79. Higher daily formoterol doses were not associated with any increase in asthma-related hospitalizations, compared to non-LABA treatment.

This large analysis of formoterol safety data finds no evidence of deaths or serious asthma-related adverse events in patients assigned to formoterol, relative to non-LABA treatments. Because of the rarity of asthma-related deaths or intubations, an increased risk of these events cannot be ruled out. However, together with data showing clinical benefits, the findings support current recommendations for the use of ICS/LABA combination therapy for patients with persistent asthma.

COMMENT: *This meta-analysis addresses the safety of the LABA formoterol compared to non-LABA treatment in over 23,000 subjects from 42 trials. There was no evidence of an increased risk for serious events, including hospitalization and death, in the formoterol groups. The Food and Drug Administration analysis questioning the safety of LABAs included only 5% as many subjects as in this much larger analysis.*
R.J.M.

Nelson H, Bonuccelli C, Radner F, et al: Safety of formoterol in patients with asthma: combined analysis of data from double-blind, randomized controlled trials.
J Allergy Clin Immunol. 2010;125:390-396. ♦♦

FDA Announces New Label Changes for LABAs

THERE is a long-history of debate over the safe use of long-acting β_2-agonists for the treatment of asthma. The U.S. Food and Drug ➤➤

Administration (FDA) presents specific label changes for LABAs, including the rationale for its conclusions.

Based on a comprehensive review of the evidence, the FDA concludes that the benefits of LABAs for asthma treatment outweigh the risks, when used appropriately. However, because of the risk of serious adverse events, LABAs should be used only in patients whose asthma cannot be controlled with controller medications, such as inhaled corticosteroids (ICS).

The new label stipulates that LABAs should only be used along with a concurrent controller medication. Once asthma control is achieved, LABA treatment should be stopped, if possible, and the patient continued on a controller medication. If asthma can be adequately controlled with low- or medium-dose ICS, exposure to LABAs should be avoided. Because of problems with compliance, combination products containing ICS and a LABA should be used in children and adolescents.

Important questions remain, including whether concomitant ICS use lessens the increase in asthma-related death. The FDA outlines actions it will take to ensure that patients and providers are aware of the new recommendations, and to assess whether prescribing patterns are changing accordingly. More research is needed to confirm whether adding LABAs to ICS increases the risk of serious adverse events. The FDA will require manufacturers to perform clinical trials comparing ICS alone with ICS plus LABAs.

COMMENT: *This FDA statement regarding the safety of LABAs considers the increased risk of death from asthma to be fact unless disproven by newer studies. In the absence of evidence that LABAs increase survival or reduce severe asthma exacerbations, and with uncertainty about whether ICS mitigate the risk, the FDA believes "soft" restrictions on the use of LABAs are warranted. Of course, the steroid-sparing benefits of LABAs, which weren't mentioned in the statement, also should be taken into account. Practitioners can still decide on the risk-benefit ratio for their individual patients, but should consider ICS monotherapy to be the safer alternative for many, but not necessarily all, patients.*
R.J.M.

Chowdhury BA, Dal Pan G: The FDA and safe use of long-acting beta-agonists in the treatment of asthma.
N Engl J Med. 2010;362:1169-1171. ♦♦

Added to Budesonide, Formoterol Affects Airway Remodeling

ADDING a long-acting β_2-agonist (LABA) to inhaled corticosteroid (ICS) improves asthma symptom control while reducing the exacerbation rate, compared to ICS alone. However, it is unclear whether this clinical benefit results from a synergistic effect or from the bronchodilator effect of LABAs. This study evaluated the effects of inhaled budesonide and formoterol on airway hyperresponsiveness, inflammation, and remodeling.

The randomized, double-blind, crossover study included 14 patients with mild atopic asthma and a dual response to inhaled allergen challenge. In random order, patients underwent 11 days of treatment with inhaled budesonide 200 µg twice daily (Pulmicort Turbuhaler), inhaled budesonide 200 µg plus formoterol 6 µg twice daily (Symbicort Turbuhaler), and placebo Turbuhaler. Early and late asthmatic responses, airway responsiveness, sputum eosinophilia, airway submucosal fibroblast numbers, and smooth muscle area were assessed.

The budesonide/formoterol combination attenuated the early asthmatic response by 48.0% and the late asthmatic response by 42.8%, compared to placebo. Airway responsiveness to allergen was also reduced. The combination was associated with reduced allergen-induced sputum eosinophilia, compared to budesonide alone. The addition of formoterol also attenuated the allergen-induced changes in submucosal tissue myofibroblast numbers and percentage smooth muscle area.

The budesonide/formoterol combination appears to affect airway inflammation and remodeling, as reflected by its effects on allergen-induced changes in sputum eosinophilia, airway myofibroblasts, and smooth muscle area. Formoterol's functional antagonistic effect likely explains the effects of combination therapy on early asthmatic responses and airway hyperresponsiveness. The findings suggest a smooth muscle origin of myofibroblasts.

COMMENT: *The safety of combination ICS/LABA has been questioned, and clinicians defend its importance. This study shows that the beneficial effects of adding formoterol to budesonide are due to more than bronchodilation. Formoterol inhibited inflammatory cells and myofibroblasts in the airway more than with budesonide alone, suggesting that formoterol has a beneficial effect on remodeling.*
R.J.M.

Kelly M, O'Connor TM, Leigh R, et al: Effects of budesonide and formoterol on allergen-induced airway responses, inflammation, and airway remodeling in asthma.
J Allergy Clin Immunol. 2010;125:349-356. ♦♦

How Many Sensitized Children Have Clinical Peanut Allergy?

THE clinical diagnosis of peanut allergy is usually based on the clinical history, confirmed by positive results on specific IgE measurement or skin prick testing. However, some children who test positive for peanut sensitization do not have clinical peanut allergy. Oral challenge tests were used to assess the rate of clinical peanut allergy among children with positive tests for peanut sensitization.

From a U.K. population-based birth cohort of 933 children, the investigators identified 110 with peanut sensitization at age 8, based on skin tests and specific IgE measurement. Open challenge testing was performed in 45 children and double-blind placebo-controlled challenge in 34. Another 12 children were considered to have evidence of peanut allergy without challenge, based on a convincing history of reactions, ➤➤

specific IgE of 15 kUa/L or greater, and/or skin test reaction of 8 mm or larger.

Of the 79 children who underwent peanut challenge, 7 were considered to have peanut allergy, based on the presence of two or more objective signs. Overall, peanut allergy was diagnosed in 19 of 85 sensitized children with an unequivocal outcome, for an estimated prevalence of 22.4%.

A new component-resolved diagnostics test using microarray technology was used to assess differences in component recognition between 29 children with peanut allergy and 52 peanut-tolerant children. The strongest predictor of clinical peanut allergy was the component Ara h 2.

Clinical peanut allergy is present in less than 1 in 4 children with test results showing peanut sensitization. In this British sample, although about 10% of children are sensitized to peanut, the rate of peanut allergy is less than 2%. The IgE response to major peanut allergen Ara h 2 appears to be a useful predictor of clinical peanut allergy.

COMMENT: *With few exceptions in clinical medicine, a test result does not make a diagnosis; it depends on clinical information to confirm it. So it is with skin and blood tests for allergy. In this study, oral challenges in children with a "positive" conventional skin test or specific IgE blood test (greater than 0.2 kUa/L) to peanut showed that only 22% of these children were clinically allergic to peanut. Thus, the tests had a false positive rate of 78%. Component peanut allergen testing shows why this might be so. Specific IgE to the epitope Ara h 2 discriminated best between the allergic and the merely sensitized children. Previous studies suggested a 95% predictive value for whole-peanut specific IgE of greater than 15 kUa/L. But in this study, one child tolerant to oral challenge had a specific IgE of 44 kUa/L, and one who was allergic had a value of 0.20 kUa/L. It takes more than a test to make a diagnosis of peanut allergy.*
R.J.M.

Nicolauo N, Poorafshar M, Murray C, et al: Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics.
J Allergy Clin Immunol. 2010;125:191-197. ♦♦

Low Rate of Remission in Children with Asthma

QUESTIONS remain as to how many children with asthma will "outgrow" their disease. The prognostic implications of long-term controller therapy are also unclear. Childhood Asthma Management Program (CAMP) data were used to assess rates and predictors of remitting, periodic, and persistent asthma.

The analysis included 909 children with mild to moderate persistent asthma who were enrolled in the randomized, multicenter CAMP trial. In that study, children were assigned to continuous therapy with budesonide, nedocromil, or placebo, followed by a 4-year observational follow-up period. Based on asthma activity during the observation period, children were divided into three outcome groups: remitting (no asthma activity in the past year), persistent (asthma activity in every quarter) or periodic (meeting criteria for neither remitting nor persistent asthma).

Only 6% of children met the criteria for remitting asthma, while 55% had persistent asthma and 39% had periodic asthma. All three groups had significant improvements in airway hyperresponsiveness, eosinophilia, and asthma morbidity. Outcomes did not differ based on treatment assignment. Baseline characteristics associated with remitting asthma, as opposed to persistent asthma were: absence of allergen sensitization and exposure to indoor allergens, odds ratio (OR) 3.23; milder asthma, OR 2.03; older age, OR 1.23; less airway hyperresponsiveness, OR 1.39; higher prebronchodilator FEV_1 percent predicted, OR 1.05; and lower forced vital capacity percent predicted, OR 0.96.

Only 6% of children enrolled in CAMP have asthma remission at follow-up in adolescence. Long-term anti-inflammatory controller therapy does not affect the chances of remitting, persistent, or periodic asthma. Efforts to modify sensitization and exposure to indoor allergens might help to improve the chances of asthma remission.

COMMENT: *Clinicians who see children with asthma confront the parents' inevitable questions: "Will my child outgrow the asthma? What can we do to increase that possibility?" This longitudinal study of children with mild-to-moderate persistent asthma from 5 to 12 years of age gives us some insight. Complete remission by adolescence is infrequent--only about 6%. Treatment with anti-inflammatory medicine does not improve the prognosis but does reduce asthma morbidity. Allergy to, and exposure to, indoor allergens worsens the prognosis. (Tell them to get rid of the pets.)*
R.J.M.

Covar RA, Strunk R, Zeiger RS, et al: Predictors of remitting, periodic, and persistent childhood asthma.
J Allergy Clin Immunol. 2010;125:359-366. ♦♦

Benefit from Probiotic Use in Presumptive Cow's Milk-Induced Colitis

WHEN blood appears in the stool of otherwise healthy infants, with or without mucus or diarrhea, the diagnosis of cow's milk allergic colitis (CMAC) may be suspected. The probiotic strain *Lactobacillus rhamnosus* GG reportedly has preventive and therapeutic benefits, especially in infants with atopic dermatitis and sensitization and cow's milk. The effects of this probiotic were evaluated in infants with presumptive CMAC.

Two groups of infants were studied. Group A included 30 infants with hematochezia and a presumptive diagnosis of CMAC, fed with a casein-based formula or breast milk. Group B included 32 healthy infants of the same sex and weight. Fecal calprotectin--a neutrophil-derived protein that is a marker of intestinal ➤➤

inflammation--was measured in both groups. In group A, measurement was repeated 4 weeks after milk elimination.

In addition, formula-fed infants in group A were randomly assigned to extensively hydrolyzed casein formula (EHCF), with or without *L. rhamnosus* GG. The effects on fecal calprotectin and hematochezia were assessed.

Mean fecal calprotectin level was 325.89 µg/g of stool in infants with hematochezia, compared to 131.97 µg/g in the healthy infants. Four weeks after milk elimination, fecal calprotectin level in the infants with presumptive CMAC had decreased by half, but was still higher than in the healthy infants: 157.5 vs 93.72 µg/g.

The decrease in fecal calprotectin was greater in infants assigned to EHCF plus GG, compared to EHCF without GG: -214.5 vs -112.7 µg/g, respectively. None of the infants receiving EHCF plus GG had blood in stool after 4 weeks, compared to 35.7% of those not receiving GG.

The results demonstrate an increase in fecal calprotectin among infants with hematochezia and presumptive allergic colitis. Given along with EHCF, treatment with *L. rhamnosus* GG is associated with elimination of hematochezia and reduction in fecal calprotectin. The mechanism of this effect could be related to enhanced barrier function of the intestinal mucosa.

COMMENT: *In the past decade, probiotics have become a focus of medical research, with investigation centered on the potential for disease modification. Use of probiotics as a preventive measure in pediatric atopic dermatitis has been studied, with largely negative results and occasional complications.*

Probiotic use has also been evaluated in a variety of gastrointestinal diseases, in both adults and children. Prior study of probiotic use in breast-fed infants with cow's milk-induced colitis (where cow's milk was eliminated from the mother's diet) found no improvement in outcome. While the current study is small, administration of EHCF plus the probiotic L. rhamnosus *GG for presumed cow's milk colitis yielded dramatic improvement over extensively hydrolyzed formula alone. Replication of these results in a larger study would be most convincing!*
K.R.M.

Baldassarre ME, Laforgia N, Fanelli M, et al: Lactobacillus *GG improves recovery in infants with blood in the stools and presumptive allergic colitis compared with extensively hydrolyzed formula alone.*
J Pediatr. 2010;156:397-401. ♦♦

Carbon Monoxide Affects Lung Function in Adult Asthmatics

THERE is significant evidence linking exposure to air pollution to reduced lung function in asthmatic in children, less so in adults. Most studies of this issue have focused on peak expiratory flow (PEF) as an indicator of lung function. This study assessed the effects of exposure to air pollutants on PEF and FEV_1 in adult asthma patients.

Over a 2-year period, 19 Italian adults with asthma were followed up for five 30-day periods. Patients used a pocket electronic meter to measure their PEF and FEV in the morning and evening. Associations with pollutant exposure were assessed by comparison with pollution monitoring data.

Higher carbon monoxide levels were associated with lower morning and evening PEF values, with similar associations across lag times of 0 to 3 days. For each 1 mg/m^{-3} increase in CO, there was a -2.6 to -2.8% drop in PEF. The associations were still significant, and somewhat strengthened, after controlling for particles with a 50% cutoff aerodynamic diameter of 10 µm, nitrogen dioxide, and sulfur dioxide, in both single- and multiple-pollutant models.

Similar but nonsignificant patterns were noted for FEV_1; there was also a nonsignificant inverse relationship between evening PEF and sulfur dioxide. Neither PEF nor FEV_1 was related to small particles or nitrogen dioxide level.

In adult patients with asthma, lung function decreases in association with exposure to gaseous pollutants. These detrimental effects are noted at carbon monoxide and sulfur dioxide levels below current European standards. Pollution appears to have a greater effect on PEF than on FEV_1.

COMMENT: *This study supports the association of drop in lung function in adult asthmatics with exposure to gaseous air pollutants, especially carbon monoxide. This is important, as the study was done in a population having 80% moderate or more severe asthma. The patients were taking medium- to high-dose inhaled steroid. These results add further to the evidence that our currently available intervention strategies are not effective to mitigate the sequence of air pollution.*
B.E.C.

Canova C, Torresan S, Simonato L, et al: Carbon monoxide pollution is associated with decreased lung function in asthmatic adults.
Eur Respir J. 2010;35:266-272. ♦♦

In Ontario, 1 in 3 Residents Will Develop Asthma

ESTIMATES of lifetime risk have been established for chronic diseases such as cancer, diabetes, and coronary heart disease, but not for asthma. This information could have important implications for asthma prevention and management, research planning, and other purposes. Administrative health data were used to estimate the lifetime risk of asthma in the population of Ontario, Canada.

All individuals in Ontario, aged 0 to 79, were followed up for 11 years until they died, turned 80, or received a physician's diagnosis of asthma. The overall lifetime risk of asthma was calculated as 33.9%: higher for females (35.0%) than males (32.99%). However, the risk was higher for males through early childhood. Asthma incidence was highest in children aged 0 to 9--16.2 per 1,000 person-years---then decreased until ages 20 to 29, remaining stable thereafter. Lifetime risk ➤➤

was higher for residents of urban areas, 34.5% vs 30.1%; and for people in the lowest vs highest quintile of income, 35.0% vs 32.2%.

Just over one-third of Ontario residents will develop asthma at some time in their lives. Asthma differs from other chronic diseases like cancer and diabetes, in which risk is minimal early in life but increases exponentially beginning in later adulthood. The results may inform efforts to reduce the public health burden and productivity and economic losses attributable to asthma.

COMMENT: *This study helps better understand the lifetime risk of physician-diagnosed asthma. The absolute risk dropped dramatically from approximately one-third in the first few years of life to less than 3% at age 75. This gives us a better understanding and describes the frequency of asthma diagnoses at different age ranges.*
B.E.C.
To T, Wang C, Guan J, et al: What is the lifetime risk of physician-diagnosed asthma in Ontario, Canada?
Am J Respir Crit Care Med. 2010;181:33-343. ♦♦

Severe Asthma Patients Fall into Five Phenotype 'Clusters'

CURRENT guidelines for defining severe asthma do not reflect the clinical heterogeneity observed in asthma patients. Previous reports from the National Heart Lung and Blood Institute's Severe Asthma Research Program (SARP) suggest some patients with severe asthma have a later-onset phenotype with less atopy and frequent sinus and pulmonary infections. Cluster analysis was performed to further evaluate phenotypes of severe asthma.

Hierarchical cluster analysis was performed using data from 726 patients enrolled in SARP. The analysis used data on 34 core variables, reduced from an initial dataset of 628 phenotypic variables.

Five clusters of severe asthma were identified. Cluster 1 included 110 patients with early-onset atopic asthma and normal lung function. More than 80% of these patients were using no more than three controller medications and used few health care resources. The 321 patients in cluster 2 also had early-onset atopic asthma and preserved lung function, but needed more medications--about 30% were using more than three drugs.

Cluster 3 included 59 patients, mostly older obese women, with late-onset asthma, moderately reduced FEV_1, and frequent use of oral corticosteroids to manage exacerbations. Clusters 4 and 5 included 120 and 116 patients, respectively, characterized by severe airflow obstruction and bronchodilator responsiveness. These groups varied in terms of achievement of normal lung function, age at asthma onset, atopy, and need for oral corticosteroids.

Five distinct phenotypes of severe asthma are identified, all consistent with American Thoracic Society criteria for severe asthma. This clinical heterogeneity underscores the need for new approaches to disease classification. The authors are investigating ways of using the cluster analysis to improve disease control via personalized asthma management.

COMMENT: *This landmark study describes five clinical phenotypes of asthma. It is particularly important in that the clusters were defined based upon the patients' age at onset and FEV_1. It also adds further confirmation that the younger-onset asthmatic is more likely to have an allergic diathesis. This supports the need for allergy evaluation and intervention. Patients in the later-onset, more severely affected clusters did not have optimal response to currently available pharmacologic strategies.*
B.E.C.
Moore WC, Meyers DA, Wenzel SE, et al: Identification of asthma phenotypes using cluster analysis in the severe asthma research program.
Am J Respir Crit Care Med. 2010;181:315-323. ♦♦

Asthma Patients Have Increased Rate of Psychologic Distress

PREVIOUS studies have suggested that asthma patients have more frequent mental distress, and that depression and decreased health-related quality of life (HRQOL) are associated with poor asthma management. National Health Interview Survey Data were used to assess the prevalence of serious psychologic distress (SPD) among patients with asthma.

Using data on 186,738 adult respondents to from the 2001-07 NIHS, the investigators calculated weighted average prevalence estimates of current asthma and SPD. The odds of SPD among participants with and without asthma were analyzed in terms of demographic, behavioral, and health-related factors.

Average annual prevalences were 7.0% for current asthma and 3.0% for SPD. The prevalence of SPD was significantly elevated for patients with current asthma: 7.5%, compared to 2.6% for nonasthmatics. Whether or not asthma was present, SPD was associated with reduced HRQOL. The predictive factors for asthma and SPD were similar to those for SPD alone. Among asthma patients, factors associated with an increased risk of SPD were lower socioeconomic status, smoking or alcohol use, and higher number of chronic comorbid conditions.

The rate of SPD among asthma patients is more than twice as high as in the general population, and nearly three times as high as in people without asthma. Patients with asthma should receive mental health screening. There is also a need for interventions addressing lifestyle factors associated with increased psychologic distress and worse asthma outcomes.

COMMENT: *The obvious finding in this national survey of over 200,000 individuals was a higher risk of serious psychological distress (SPD) in adults with asthma. In addition, patients with asthma had lower health-related quality of life. Whether asthma provokes* ➤➤

SPD or SPD provokes more severe asthma is debatable. What isn't, is that we are obliged to address SPD in our asthmatic population.
S.F.W.
Oraka E, King ME, Callahan DB: Asthma and serious psychological distress: prevalence and risk factors among us adults, 2001-2007.
Chest. 2010;137:609-616 ♦♦

Beta-Lactam Testing Has High Negative Predictive Value

DRUG provocation tests play an important role in diagnosing hypersensitivity reactions to beta-lactam antibiotics. There is a need to clarify the negative predictive value of these tests--ie, the likelihood that a patient who tests negative will not have a reaction to subsequent beta-lactam exposure. This issue was addressed in a series of 457 patients undergoing beta-lactam provocation testing for suspected drug allergy/hypersensitivity.

The patients were tested at four European allergy units between 2003 and 2007. Follow-up data, including subsequent beta-lactam exposure and any reactions, were available of 365 patients (79.9%). Patients with subsequent reactions were offered a new allergy workup.

Just 118 patients (25.8%) were re-exposed to the beta-lactam antibiotic to which they had a negative provocation test. In this group, the rate of nonimmediate reactions (after 1 hour) was 7.6%. Of the 9 reactions, 5 were urticaria, 3 were exanthems, and 1 was an unidentified skin reaction; none was severe. Of 4 patients who consented to repeat challenge, 2 had no further reaction. Thus beta-lactam provocation testing had a negative predictive value of 94.1% (111 of 118 patients).

Only about 6% of patients with a negative result on beta-lactam provocation testing will react to beta-lactam re-exposure. This study finds no serious reactions among patients with false-negative results. The results suggest that beta-lactams can safely be prescribed to patients with negative results on provocation testing.

COMMENT: *Penicillin skin tests have been reported to have excellent negative predictive value for assessing the risk of life-threatening immediate reactions. However, there are relatively few data to reassure prescribing physicians regarding the risk of other types of reactions. This European multicenter study contacted patients who had previously had negative workups to find out how they did with subsequent beta-lactam exposure. All patients had both negative specific IgE testing and a negative oral challenge to the implicated drug. Of those who were re-exposed over time, only about 6% reported reactions: none of the reactions were immediate and none were more severe than the reaction responsible for the initial workup. Given the high frequency of unnecessary beta-lactam antibiotic avoidance, these results should support the practice of testing, oral challenge, and appropriate future reintroduction of these drugs.*
S.A.T.
Demoly P, Romano A, Botelho C, et al: Determining the negative predictive value of provocation tests with beta-lactams.
Allergy. 2010;65:327-332. ♦♦

Immunotherapy Improves Innate Immunity Too!

DENDRITIC cells express toll-like receptors (TLRs) and other innate immune receptors. A previous study found that dendritic cells from allergic patients have impaired production of interferon-α (IFN-α) in response to TLR9-dependent innate immune stimulation. This study evaluated the effects of subcutaneous immunotherapy (SCIT) on innate immune responses in dendritic cells.

Blood samples were obtained from 7 patients with dust mite allergy before and after a standard SCIT dose including mite and other aeroallergens. Peripheral blood mononuclear cells (PBMCs) and plasmacytoid dendritic cells (pDCs) were isolated, and responses to various adaptive and innate immune receptor stimuli were assessed.

After SCIT, there was a threefold increase in PBMC production of IFN-α in response to stimulation with the TLR9 receptor agonist CpG. Consistent with the fact that dendritic cells are the main cell type producing IFN-α in response to CpG, there was a fivefold increase in CPG-stimulated IFN-α production by pDCs after SCIT.

Although interleukin-6 production was unaffected, SCIT led to a tenfold increase in IgG4 blocking antibody. There was no other factor besides SCIT that could explain the increase in IFN-α production, such as an increase in pDC frequency or TLR9 expression.

Administration of SCIT leads to increased dendritic cell TLR9-mediated innate immune function in patients with dust mite allergy. In addition to reducing IgE-mediated responses, SCIT may also restore dendritic cell responses to innate immune receptor stimuli. This could have important implications for the development of new approaches to allergen immunotherapy.

COMMENT: *The past few years have seen an explosion of information regarding our understanding of the innate immune system. I would have thought that allergen immunotherapy--a prime example of manipulating adaptive immunity (or perhaps "maladaptive" immunity)--would not have any effect on innate immunity. For example, immunotherapy's effects on lymphocytes have been well-characterized over the years. However, as this manuscript shows, immunotherapy also improves TLR9-mediated immunity in dendritic cells. No wonder pharmacotherapies for allergic disease are hard-pressed to match the efficacy of immunotherapy.*
S.A.T.
Tversky JR, Bineman AP, Chichester KL, et al: Subcutaneous allergen immunotherapy restores human dendritic cell innate immune function.
Clin Exp Allergy. 2010;40:94-102. ♦♦

Cat Exposure Early in Life Is a Good Thing--Maybe Not!

SOME evidence suggests that early life exposure to indoor allergens and microbial products may affect the later risk of asthma and allergic sensitization. These exposures need to be assessed in the context of other factors known to affect asthma risk. This was done using data from a Norwegian birth cohort study with follow-up to age 10.

The study included 260 children living in Oslo who were enrolled in the Environment and Childhood Asthma study. At birth, the children underwent measurement of lung function using tidal flow volume loops. When they were 2 years old, home dust samples were collected for measurement of mite, dog, and cat allergens and of the microbial products endotoxin and β(1,3)-glucans. Asthma and allergic sensitization were assessed when the children were 10 years old.

At age 2 years, 6.5% of the children had a cat at home and 5.5% had a dog. Just 4 of the 260 dust samples had detectable levels of mite allergen. Asthma risk at age 10 was significantly increased for children with higher exposure to cat allergen at age 2. Odds ratios per 10 μg/g increase in cat allergen levels were 1.20 for asthma and 1.22 for bronchial hyperresponsiveness. Neither asthma nor allergic sensitization risk was significantly affected by exposure to endotoxin or β(1,3)-glucans at age 2. Early-life exposure to allergens or microbial products was unrelated to lung function at age 10 or to relative change in lung function from birth.

In this group of Norwegian children, high exposure to cat allergen in early childhood is linked to increased risk of asthma and bronchial hyperresponsiveness by age 10. Cat exposure does not affect allergic sensitization risk, and neither outcome is affected by exposure to dog or microbial products. The authors point out the low rates of pet ownership and dust mite exposure in their study population.

COMMENT: *In this prospective Norwegian study, the likelihood of having asthma at age 10 was proportional to level of cat allergen in the home at age 2. This finding may not apply to populations in North America, since in Norway there are very low levels of dust mite and fewer people have indoor pets. However, it does support the hypothesis that many cat-sensitized individuals who choose to continue to live with a cat will eventually develop asthma.*
S.A.T.

Bertelsen RJ, Carlsen KCL, Granum B, et al: Childhood asthma and early life exposure to indoor allergens, endotoxin and β(1,3)-glucans.
Clin Exp Allergy. 2010;40:307-316. ♦♦

Dust Mites More Likely Than Grass Pollens to Cause Late-Phase Asthma Reactions

SOME patients with allergic asthma have late asthmatic reactions, which may be a more important predictor of clinical asthma than the early reaction. The mechanism of the late-phase reaction is not fully understood, but may be allergen dependent. The presence and magnitude of late asthmatic reactions to different allergens were assessed.

The study included 6 patients with mild asthma and dual sensitization to house dust mite and grass pollen. Two weeks apart, the subjects underwent inhaled challenges with these two allergens, matched to produce a similar magnitude of early asthmatic reaction. The late asthmatic reactions were assessed by monitoring lung function for 8 hours after challenge. Bronchial reactivity and airway inflammation were assessed through 24 hours.

During the early phase, the mean reduction in FEV_1 was 28.0% after house dust mite challenge and 25.8% after grass pollen challenge. In contrast, the late-phase reaction was greater in response to house dust mite challenge: 22.8%, compared to 13.0% after grass pollen challenge. House dust mite challenge was also associated with an increase in sputum eosinophil percentage--from 5.4% to 22.1%--that did not occur after grass pollen challenge. There was no late difference in bronchial reactivity.

This small study suggests a stronger late asthmatic reaction to house dust mite challenge than to grass pollen challenge in asthma patients sensitized to both allergens. The results have implications not only for understanding the allergen-induced airway responses to asthma, but also for the conduct of allergen challenge studies, most of which are performed using single allergens.

COMMENT: *Late responses to allergens are characterized by inflammatory cell recruitment to the allergen exposed tissues. The mechanisms of this response are not well understood. In this double-blind crossover study, dust mite and grass inhalation allergen challenges were performed in sensitized patients with allergic asthma. The immediate responses to dust mite and grass were similar. However, compared to grass pollen, dust mite inhalation resulted in a significantly greater fall in FEV_1 24 hours after challenge. This suggests that the late-phase allergic reaction may have allergen specificity.*
S.A.T.

Hatzivlassiou M, Grainge C, Kehagia V, et al: The allergen specificity of the late asthmatic reaction.
Allergy. 2010;65:355-358. ♦♦

Preterm Birth after Chorioamnionitis Linked to Increased Asthma Risk

CHORIOAMNIONITIS is an important cause of maternal, fetal, and neonatal morbidity and has been linked to fetal lung injury. Few studies have looked at the possible association between chorioamnionitis and childhood asthma. This issue was addressed in a large series of births, including the effects of preterm birth and race/ethnicity.

The retrospective analysis included 397,852 singleton live births occurring at Kaiser Permanente Southern California hospitals from 1991 through 2007. ➤➤

Clinically diagnosed chorioamnionitis was assessed as a risk factor for physician-diagnosed asthma before 8 years of age. The possible modifying effects of gestational age at birth and race/ethnicity were evaluated as well.

The incidence of asthma among children born in pregnancies complicated by chorioamnionitis was 100.7 per 1,000 person-years in preterm births and 39.6 per 1,000 person-years in full-term births: incidence rate ratio 2.9. Factors associated with an increased risk of asthma diagnosis before age 8 included maternal age 35 years or older, African American race, maternal education of 13 years or more, maternal asthma, chorioamnionitis during pregnancy, and male sex. On multivariate analysis, hazard ratios for asthma in children born after pregnancies complicated by chorioamnionitis were 1.23 for birth at 23 to 28 weeks' gestation, 1.51 for birth at 29 to 33 weeks' gestation, and 1.20 for birth at 34 to 36 weeks' gestation (compared to pregnancies without chorioamnionitis). The hazard ratio for asthma in a child born after preterm pregnancy complicated by chorioamnionitis was 1.66 for white women, 1.98 for African American women, and 1.70 for Hispanic women.

Children born after preterm pregnancies complicated by chorioamnionitis are at increased risk of childhood asthma. The effect appears strongest in African Americans. The increased asthma risk likely reflects inflammation-mediated fetal lung injury and/or a heightened immune response to subsequent pathogen exposures.

COMMENT: *Chorioamnionitis, characterized by inflammation of the maternal-fetal interface, complicates 8% of pregnancies but is present in over half of preterm births. Using retrospective data from a cohort of over 500,000 births, this report suggests that there is an independent association between chorioamnionitis and preterm delivery with the development of childhood asthma. The authors suggest that intrauterine exposure to inflammation may affect the developing lung in the newborn.*
S.M.F.

Getahun D, Strickland D, Zeiger RS, et al: Effect of chorioamnionitis on early childhood asthma.
Arch Pediatr Adolesc Med. 2010;164:187-192. ♦♦

Integrated Data on Atopy and Infections Could Predict Childhood Wheezing Risk

ALLERGIC sensitization in early life is an important risk factor for childhood asthma, particularly when early sensitization is accompanied by severe lower respiratory tract infection. The development of strategies to prevent asthma will require the ability to identify high-risk children at an early stage. Early childhood clinical and laboratory predictors of persistent atopy and wheezing at age 5 were evaluated.

The prospective cohort study included 198 children, aged 2 years at baseline, with a family history of atopy. In addition to regular clinical follow-up and laboratory tests for factors related to asthma and atopy, the children were monitored for episodes of acute respiratory illness. The data were analyzed to identify factors associated with the risk of persistent atopy and wheezing at age 5.

In children without atopy, allergen-specific IgE levels continuously cycled in the low range throughout follow-up. Atopic children showed a similar cycling pattern in infancy but gradually developed a stable pattern of increasing antibody production and Th2-polarized cellular immunity. This pattern was characterized by stable expression of interleukin-4 receptor in allergen-specific Th2 memory responses, which had not been present in infancy.

Early sensitization with early infection was strongly associated with risk of persistent wheezing. On logistic regression analysis, children who reached mite-specific IgE titers of greater than 0.20 kU/L by age 2 had a 12.7% risk of persistent wheezing. For those who went on to have numerous severe respiratory infections, this risk increased up to 87.2%.

Integrated analysis of early childhood factors related to allergic sensitization and respiratory infections may aid in assessing the risk of persistent wheezing by school age. Larger studies in unselected populations will be needed to refine this approach, which could enable effective use of preventive therapies.

COMMENT: *This report presents data collected from a cohort of children with a family history of allergies through age 5 years. Higher levels of house dust mite-specific IgE along with lower respiratory infections before 2 years significantly increased the likelihood that these children would have persistent wheezing and allergy to dust mite at 5 years. The immunologic data collected throughout the study suggest that there is an active interplay between Th1 and Th2 signals in preschoolers. The authors also suggest that "inhalation tolerance" may develop in those children who do not become sensitized.*
S.M.F.

Holt P, Rowe J, Kusel M, et al: Toward improved prediction of risk for atopy and asthma among preschoolers: a prospective cohort study.
J Allergy Clin Immunol. 2010;125:653-659. ♦♦

Intravenous Montelukast Not Effective for Acute Asthma in Children

DESPITE emergency department treatment, up to 30% of patients with acute asthma exacerbations require hospitalization. Studies in adults have shown that adding montelukast to standard therapy can improve lung function and reduce the hospital admission rate. This study evaluated the use of intravenous montelukast in children with acute asthma.

Children aged 6 to 14 years with acute asthma, seen at 36 hospitals worldwide, were eligible for the randomized, double-blind trial. Those who had an FEV_1 of 75% predicted or less after 2 hours of standard therapy were assigned to receive additional therapy with intravenous montelukast, 5.25 mg, or placebo. Changes in pulmonary function and decisions regarding hospital-➤➤

ization were compared between groups.

The time-weighted change in FEV_1 over 60 minutes was similar between groups: 0.08 L with intravenous montelukast and 0.07 L with placebo. The rate of treatment failure--defined as hospitalization or no decision regarding admission within 2 hours after assigned treatment--was similar as well. Black patients were more likely to have treatment failure on montelukast, compared to other racial/ethnic groups. There was no difference in the modified pulmonary index score after 60 minutes.

For children with acute asthma exacerbations who do not respond to standard treatment, the addition of intravenous montelukast does not improve lung function, asthma symptoms, or hospital admission rate. The reasons for the difference from adult studies are unclear; the authors note the "numerous and substantial" baseline differences between treatment groups.

COMMENT: *The lack of a response when a variety of data suggests that a response should occur engenders more questions. Is asthma in children different from adults? Was the study powered sufficiently to answer the question? Was the dose optimal? Does the triggering event of an asthma exacerbation affect the response to treatment? No immediate answers. but questions are important in advancing our understanding. In the meantime, I would not be as enthusiastic about using montelukast during an acute exacerbation in pediatric asthma, but I would consider it for adult asthma.*
D.K.L.

Morris CR, Becker AB, Piñeiro A, et al: A randomized, placebo-controlled study of intravenous montelukast in children with acute asthma.
Ann Allergy Asthma Immunol. 2010;104:161-171. ♦♦

No Increase in Cardiovascular Risk with Clopidogrel Plus PPI

MANY patients taking clopidogrel also receive proton-pump inhibitors (PPIs) to reduce the risk of gastroduodenal bleeding. There is concern that PPIs may reduce the efficacy of clopidogrel. Concurrent use of PPIs and clopidogrel was evaluated as a risk factor for gastroduodenal bleeding and coronary heart disease events.

Tennessee Medicaid data were used to identify 20,596 patients hospitalized for coronary heart disease, of whom 7,593 were also receiving PPIs. Rates of hospitalizations for gastrointestinal bleeding and serious cardiovascular disease--fatal or nonfatal myocardial infarction and sudden cardiac death, stroke, or other cardiovascular death--were compared between groups.

Sixty-two percent of patients receiving PPIs were taking pantoprazole while 9% were taking omeprazole. Patients taking PPIs along with clopidogrel were at lower risk of hospitalization for gastrointestinal bleeding: hazard ratio 0.50. Among those at highest risk of bleeding, the absolute reduction in hospitalization for gastroduodenal bleeding for PPI users was 28.5 per 1,000 person-years. Concurrent use of a PPI was not associated with increased risk of serious cardiovascular disease. This was also true on subgroup analysis of patients undergoing percutaneous coronary intervention with stent placement during the index hospitalization. The 95% confidence intervals included a clinically significant increase in risk, however.

In patients with coronary heart disease, use of PPIs in addition to clopidogrel appears to reduce the risk of hospitalization for gastroduodenal bleeding. Although there is no significant change in the risk of serious cardiovascular disease, an increase in risk cannot be excluded.

COMMENT: *This paper is reassuring concerning the use of PPIs, particularly pantoprazole, along with clopidogrel. However, other data are not as comforting. Allergists/immunologists frequently recommend PPIs, often at higher than typical dosing, to treat airway symptoms possibly related to gastroesophageal reflux. We should be aware of the risks or potential risks of PPIs including reduced absorption of iron, calcium, and vitamin B12; increased bacterial content of the stomach, with potential heightened risk of pneumonia with aspiration; and decreased effectiveness of clopidogrel, particularly when combined with omeprazole.*
D.K.L.

Ray WA, Murray KT, Griffin MR, et al: Outcomes with concurrent use of clopidogrel and proton-pump inhibitors.
Ann Intern Med. 2010;152:337-345. ♦♦

Formoterol Similar to SABAs for Acute Asthma

RECENT studies suggest that formoterol fumarate could be useful in the treatment of acute asthma, with efficacy comparable to that of short-acting β_2-agonists (SABAs). Published data on inhaled formoterol versus SABAs for the treatment of acute asthma were pooled for meta-analysis.

A systematic review of the literature identified 9 randomized trials of inhaled formoterol versus SABAs for emergency department treatment of acute asthma. On meta-analysis, there were no significant differences in spirometric measures between treatments at any of the time points considered: 30 to 40 minutes after first dose, at the end of treatment, or 60 to 90 minutes after the last dose. This was also true after exclusion of two studies that were sources of statistical heterogeneity. Secondary outcomes--final serum potassium level, heart rate, QT interval corrected for heart rate, and total withdrawals were also similar between groups.

High-dose formoterol administered via dry-powder inhaler provides rapid and effective bronchodilation in patients with acute asthma treated in the emergency department. Safety and efficacy outcomes are similar to those of high-dose salbutamol or terbutaline via metered-dose inhaler or nebulizer.

COMMENT: *Formoterol provides long-lasting bronchodilation and rapid onset of action, raising the* ➤➤

possibility of this drug being used both for long-term control and rescue therapy. The confusion between control and rescue is compounded by the increased concern, at least in the United States, about the safety of long-acting β-agonists. Why would a physician choose to use formoterol for acute asthma therapy? I am not sure, but it may be effective and safe based upon data from approximately 580 subjects. This is an insufficient number of subjects to detect infrequent adverse events. The debate continues.
D.K.L.
Rodrigo GJ, Neffen H, Colodenco FD, Castro-Rodriguez JA: Formoterol for acute asthma in the emergency department: a systematic review with meta-analysis.
Ann Allergy Asthma Immunol. 2010;104:247-252. ♦♦

Summer Mailing Doesn't Affect Allergen Extract Potency

SEVERAL factors, including temperature, can affect the stability of allergen extracts. This study evaluated the effects of mailing during the summer months on the potency of a standardized allergen extract.

The investigators mailed standardized timothy grass extracts, with potencies of 10,000 and 100,000 BAU/mL, between Texas and Arizona in August, 2007. A portable temperature monitor included in the packages recorded temperatures over 20° C for 11 days during mailing, and over 30∞ C for 6 hours.

However, enzyme-linked immunosorbent assay inhibition results showed no significant change in in vitro extract potency after mailing. Some degradation occurred, especially in the more dilute extract. However, all potency measurements were within current Food and Drug Administration lot release and stability limits. Assessment of in vivo skin test reactivity in 3 patients also showed no significant effect.

Exposure to high temperatures during mailing does not appear to affect the potency of standardized timothy grass extracts. Further studies would be needed to determine the effects of mailing on more dilute extract concentrations and mixtures of multiple pollen extracts.

COMMENT: *These real-world data provide reassurance that mailing of maintenance or highly concentrated allergen vaccines does not appreciably affect potency, despite exposure to temperatures greater than recommended. As the authors point out in their discussion, more dilute vaccines or vaccine mixtures are probably much more susceptible to degradation during mailing.*
D.K.L.
Moore M, Tucker M, Grier T, Quinn J: Effects of summer mailing on in vivo and in vitro relative potencies of standardized timothy grass extract.
Ann Allergy Asthma Immunol. 2010;104:147-151. ♦♦

Omalizumab Blocks Cytokine Responses to IgE in Airway Cells

AIRWAY smooth muscle cells (ASMCs) express low- and high-affinity IgE receptors, which are responsive to IgE stimulation. Few studies have looked at how airway wall cells response to newer anti-IgE therapies. This study examined the effects of omalizumab on ASMC responsiveness to IgE.

The in vitro study used ASMCs isolated from patients with asthma or chronic obstructive pulmonary disease, as well as from healthy controls. The cells underwent IgE stimulation in the presence and absence of omalizumab.

In response to IgE stimulation, the ASMCs showed increases in cytokine mRNA synthesis and protein secretion. Secretion of interleukin (IL)-6, IL-8, and tumor necrosis factor-α were significantly increased within 6 hours, while IL-4 secretion was increased at 24 hours. Omalizumab inhibited these responses in dose-dependent fashion, but had no effect on expression of low- and high-affinity IgE receptors in ASMCs.

Human ASMCs show increased expression of proinflammatory cytokines in response to IgE stimulation. These responses are inhibited in the presence of omalizumab. This effect of anti-IgE therapy is seen in tissue-forming as well as inflammatory cells.

COMMENT: *Omalizumab and IgE may affect a variety of cells other than the traditional basophil and mast cell. This paper highlights the potential of bronchial smooth muscle cells to contribute to IgE-dependent inflammation.*
D.K.L.
Roth M, Tamm M: The effects of omalizumab on IgE-induced cytokine synthesis by asthmatic airway smooth muscle cells.
Ann Allergy Asthma Immunol. 2010;104:152-160. ♦♦

CLINICAL TIDBITS

Baby Out With the Bathwater?

EMOLLIENT creams or ointments, applied directly to the skin, are a safe and effective treatment for atopic eczema. The use of bath emollients is also widely recommended, especially for children.

The authors performed a literature review to identify research evidence on the use of bath emollients for atopic eczema. They found no randomized controlled trials of this issue, nor any longstanding clinical experience showing that the benefits of bath emollients match that of directly applied emollients. There was also little evidence to support the concept of "complete emollient therapy," which may lead patients to assume that bath emollients offer separate benefits.

The common recommendation to use bath emollients for atopic eczema has little or no supporting evidence. There appears to be no ongoing research into this issue; the authors suggest some areas for further study.

COMMENT: *It's amazing how recommendations get passed down from attendings to residents and subsequently into practice. The authors note that there are no (and there probably won't be any) randomized clinical trials to explore this issue. They conclude that* ➤➤

spending $25 million on bath emollients in the United Kingdom doesn't seem warranted if parents will apply creams or ointments directly. The answer is no.
S.F.W.
Tarr A, Iheanacho I: Should we use bath emollients for atopic eczema?
BMJ. 2009;339:b4273. ♦♦

Smoking's Effect on NO Differs by Asthma Type

SMOKING has been linked to reduced exhaled nitric oxide (eNO) levels, which may affect the diagnostic use of eNO measurement in smokers. The effects of smoking on eNO in patients with atopic versus nonatopic asthma are unknown.

Two groups of Finnish army conscripts with current asthma were studied: 46 smokers (30 with atopic asthma) and 70 nonsmokers (54 with atopic asthma). None had received previous steroid treatment. The smokers with asthma had higher eNO levels than healthy controls, both smokers and nonsmokers. Smoking was associated with lower eNO in patients with atopic asthma, but not in those with nonatopic asthma. However, smokers with nonatopic asthma still had higher eNO levels than healthy controls.

The asthma-related increase in eNO is lessened by smoking in patients with atopic asthma, but not those with nonatopic asthma. Thus the mechanisms of nitric oxide formation may differ in the two types of asthma. Both groups of asthmatic smokers have higher eNO levels than healthy controls, however.

COMMENT: *Many studies have evaluated eNO as a potentially useful noninvasive marker in the diagnosis of asthma and for guiding anti-inflammatory treatment and assessing eosinophilic airway inflammation. Smoking is known to reduce eNO by several mechanisms, which are discussed in this article. In this study smokers with asthma showed higher eNO than healthy smokers and nonsmokers; in atopic asthmatics, eNO was lower in smokers than nonsmokers. In nonatopic asthmatics no such difference was noted, and even among nonatopic asthmatic smokers, eNO was significantly higher than among healthy controls. The authors suggest that eNO can be used for diagnosis in young adult smokers.*
M.F.
Rouhos A, Ekroos H, Karjalainen, J et al: Smoking attenuates increase in exhaled
nitric oxide in atopic but not in nonatopic young adults with asthma.
Int Arch Allergy Immunol. 2010;152:226-232. ♦♦

REVIEWS OF NOTE

COMMENT: *There is a high placebo response to treatments for the most common allergic conditions: asthma and allergic rhinitis. In fact, at one meeting I attended, one of the investigators announced that he'd rather administer the placebo instead of the active drug. There are multiple environmental situations in our offices that augment a placebo response to the treatments we administer. This article reviews the conditions that influence placebo response. It's not just in the patient's mind!*
S.F.W.
Finniss DG, Kaptchuk TJ, Miller F, Benedetti F: Biological, clinical, and ethical advances of placebo effects.
Lancet. 2010;375:686-696. ♦♦

COMMENT: *Written by two of our allergy/immunology colleagues for pediatricians, this review of cough in the pediatric population focuses on the more common etiologies of this problem. The article includes algorithms and tables useful for evaluation of cough, and suggests referral be considered to an allergy or pulmonary specialist in complicated cases.*
K.R.M.
Goldsobel AB, Chipps BE: Cough in the pediatric population.
J Pediatr. 2010;156:352-358. ♦♦

COMMENT: *This review summarizes the world's literature devoted to a simple asthma management approach: the use of a single inhaler for both maintenance and rescue. I am skeptical this will ever gain approval in the United States. Yet the approach is applied, albeit incorrectly, by many of my patients who vary their dose of inhaled controller according to how they are feeling.*
D.K.L.
Oppenheimer JJ, Peters SP: Is the maintenance and reliever approach the answer?
Ann Allergy Asthma Immunol. 2010;104:112-117. ♦♦

COMMENT: *This is a succinct and useful review. The paper is particularly relevant with the variety of new therapies for hereditary angioedema.*
D.K.L.
Kaplan AP, Joseph K: The bradykinin-forming cascade and its role in hereditary angioedema.
Ann Allergy Asthma Immunol. 2010;104:193-204. ♦♦

COMMENT: *Severe asthma, however it is defined, is a major challenge for allergists/immunologists. In my experience, the significance of allergic triggers in these subjects is difficult to determine. This is a review from experienced, knowledgeable clinicians addressing the potential of novel immunotherapies for severe asthma. I for one say, "Bring them on," as I need something better.*
D.K.L.
Levine SJ, Wenzel SE: Narrative review: the role of Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes.
Ann Intern Med. 2010;152:232-237. ♦♦