# AllergyWatch®

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

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

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## Useful Pearls on AD

ATOPIC dermatitis (AD) is a clinically challenging andfrequent problem, affecting nearly 17% of U.S. schoolchildren. This article reviews some of the diagnostic and treatment challenges faced by clinicians managing patients with AD.

Patients with AD are at risk of recurrent skin infections, caused mainly by *Staphylococcus aureus*. A short course of systemic antibiotics is appropriate treatment for these infections--topical antibiotics may be used for milder cases. However, to prevent colonization with resistant bacteria, it is important to avoid prolonged treatment with antibiotics. Bathing with antibacterial cleansers such as Lever 2000 may help to reduce colonization. Recent studies have documented sensitization to *Malassezia* spp and other fungi in patients with AD. The response to antifungal therapy appears to be correlated with the patient's level of fungal-specific IgE.

Questions have been raised regarding the role of antihistamines in treating the distressing symptom of pruritus. Other mediators, such as neuropeptides and cytokines, appear more important than histamine in causing pruritus. Some patients with AD have positive skin test responses to a number of allergens, or have positive ImmunoCAP assay results to food allergens. Although the negative predictive value of skin prick tests for food is high, the positive predictive value is not. Food challenge studies may be needed.

Topical calcineurin inhibitors have emerged as a potentially useful alternative to topical steroids for patients with AD. Despite the FDA's "black box" warning, there is no evidence showing a causal association between these medications and the development of cancers. So far, long-term surveillance studies in infants receiving pimecrolimus and tacrolimus have yielded reassuring results.

More research is needed to clarify the clinical role of omalizumab. Despite its limitations, this form of anti-IgE therapy may be useful in patients with AD and accompanying food allergy. Patients with AD may receive contradictory advice regarding bathing. ➤➤

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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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Bathing rehydrates the skin, which is beneficial. However, immediate application of an emollient or topical medication is recommended to prevent evaporation.

Common clinical questions and answers in the management of patients with AD are reviewed. The article includes some suggested approaches in the patient with very recalcitrant AD--however, the authors underscore the need for expert consultation.

**COMMENT:** *Atopic dermatitis can present one of the greatest management challenges to the clinical allergist. This article asks and answers seven of the most mundane, yet intriguing, questions about its management. This is the prototypical article for presenting useful clinical pearls.*
*R. J. M.*

*Boguniewicz M, Schmid-Grendelmeier, Leung DYM: Atopic Dermatitis.*
**J Allergy Clin Immunol**. 2006;118:40-43. ♦♦

## Can Asthma Be Prevented?

EARLY-life exposure to allergens such as house dust mite (HDM) may promote the development of asthma in high-risk children. Some studies have suggested that dietary factors may play a role, including reports of reduced asthma symptoms in children with high consumption of omega-3 fatty acids in fish. An HDM avoidance intervention and dietary fatty acid modification were evaluated for their effects on asthma and atopy rates in high-risk children.

The Australian study included 616 infants with a family history of asthma (parents or siblings with asthma or wheezing). At birth, the infants were randomized to active or control HDM avoidance conditions. They were also separately randomized to a dietary intervention, designed to increase the proportion of omega-3 long-chain unsaturated fatty while reducing the content of omega-6 fatty acids, or to a diet low in omega-3 fatty acids. Clinical assessments for asthma and eczema and skin prick tests for atopy were performed when the children were 5 years old.

The HDM avoidance group had a 61% reduction in the concentration of HDM allergen level in dust samples collected from the child's bed. However, HDM reduction yielded no significant reduction in rates of asthma, wheezing, or atopy at age 5. Children in the HDM avoidance group were actually more likely to develop eczema, 26% vs 19%. The dietary intervention led to a lower ratio of omega-6 to omega-3 fatty acids in plasma samples: 5.8 vs 7.4. However, the intervention made no difference in clinical or allergic outcomes.

Neither HDM avoidance nor dietary fatty acid modification significantly affected the risk of developing asthma in high-risk children. The interventions also had no effect on eczema or atopy. The interventions evaluated in this study cannot be recommended for use in preventing asthma and allergic disease in young children.

**COMMENT:** *It is known that early childhood allergy to house dust mites is positively correlated with the development of asthma. On the other hand, diets high in omega-3 fatty acids have been negatively correlated with asthma. But once again science proves its advantage over intuition. This prospective study of 616 high-risk children from birth to 5 years of age showed that measures to decrease house dust mite exposures and increase omega-3 fatty acids did not prevent asthma, eczema, or atopy. Back to the drawing board.*
*R. J. M.*

*Marks GB, Mihrshahi S, Kemp AS, et al, for the Childhood Asthma Prevention Study team: Prevention of asthma during the first 5 years of life: a randomized controlled trial.*
**J Allergy**. 2006;118:53-61. ♦♦

## What's Good About the Farming Lifestyle?

PREVIOUS studies have reported reduced rates of allergic disease among the children of farmers, compared with nonfarm children living in rural areas. The protective aspects of farm life remain unclear--suggested factors include contact with livestock or drinking unpasteurized milk. This study sought to identify factors associated with reduced rates of allergic disorders among English schoolchildren.

In the initial phase of the study, the parents of 4,767 children living in Shropshire, U.K., responded to a questionnaire seeking detailed information on their child's allergic status, diet, and exposure to the farm environment. Subsequently, skin prick tests and measurement of dust endotoxin levels were performed in a subsample of 879 children.

As in previous studies, farm children had lower rates of asthma, adjusted odds ratio (OR) 0.67; and seasonal allergic rhinitis, OR 0.50, than control children. There was no significant difference in current eczema or atopy. Compared with controls, farm-exposed children had the lowest rates of sensitization to domestic pets, house dust, and horse dust, with no increase in sensitization to allergens commonly found in the farm environment.

Consumption of unpasteurized milk was associated with significant reduction in eczema, OR 0.59, and greater protection against atopy, OR 0.24. This effect was significant in farm and nonfarm children alike. Children who drank unpasteurized milk had a 59% reduction in total IgE along with increased production of whole blood stimulated interferon-gamma.

Consumption of unpasteurized milk may have a protective effect, against childhood allergic disease, rather than farm exposure per se. Even infrequent consumption of unpasteurized milk appears to have a significant protective effect which is little changed by adjustment for other factors. The effect on objective laboratory results argues in favor of a genuine effect of unpasteurized milk on allergy risk.

**COMMENT:** *This two-stage cross-sectional study reconfirms that farm children have a lower incidence of asthma and allergic rhinitis, but not eczema, compared to nonfarm children. Those children who drank unpasteurized milk had a lower incidence of eczema and a reduction in their risk of atopy but not of asthma, regardless of their farm status. Unpasteurized milk is no longer recommended for infants, but the authors speculate that the microbes found in the unpasteurized milk may have a protective effect similar to probiotics.*
*S. M. F.*
*Perkin M, Strachan DP: Which aspects of the farming lifestyle explain the inverse association with childhood allergy?*
**J Allergy Clin Immunol**. 2006;117:1374-1381. ♦♦

## Air Pollution Promotes Eosinophilia

A growing body of evidence suggests that indoor and outdoor air pollution has adverse effects on respiratory health. The role of pollutants in allergic asthma and rhinitis is unclear. The relationship between exposure to particulate pollutants and nasal inflammation was investigated in children.

The study included 85 Paris schoolchildren, 41 with allergic asthma. Over 48 hours, the children's personal exposure to particulate matter less than 2.5 µm in diameter (PM2.5) was measured using special active sampling equipment. Nasal lavage samples were obtained for measurement of cellular and soluble inflammatory mediators.

The asthmatic and nonasthmatic children were exposed to similar levels of PM2.5. However, significant associations with inflammatory markers and mediators were noted only in the asthmatic group. Personal PM2.5 exposure was significantly correlated to eosinophil percentage as well as to levels of albumin, urea, and α1-antitrypsin. The associations remained significant after adjustment for exposure to house dust mite, pollen, cat, and secondhand smoke.

High exposure to fine-particle pollutants is associated with nasal inflammation in asthmatic children and adolescents, suggesting an effect on the manifestations of allergic disease. Pollutant exposure is also related to mediators of inflammation in nasal lavage fluid. None of these associations is found in healthy children.

**COMMENT:** *The children in this small but well-controlled study carried backpacks for 2 days to collect samples of the particulates in the air. Allergy skin tests and collection of nasal lavage fluid for cellular and immunologic markers were also analyzed. The study not only shows that asthmatic children with the allergic phenotype have a stronger immunologic response to nasal exposure to particulates, but also supports the unified airway concept.*
*S. M. F.*
*Nikasinovic L, Just J, Sahraoui F, et al: Nasal inflammation and personal exposure to fine particles PM2.5 in asthmatic children.*
**J Allergy Clin Immunol**. 2006;117:1382-1388. ♦♦

## Leukotrienes Are Insensitive to ICS

INHALED corticosteroids (ICS), the foundation of asthma treatment, reduce bronchial hyperresponsiveness and inflammatory markers. The cysteinyl-leukotrienes (LTs), including $LTD_4$ and $LTE_4$, mediate the central components of asthma, such as bronchoconstriction and inflammatory cell infiltration. This study evaluated the effects of ICS treatment on bronchial responsiveness to $LTD_4$.

The randomized, placebo-controlled, crossover study included 13 patients with stable mild atopic asthma. Patients received 2 weeks of treatment with inhaled fluticasone propionate, 500 µg twice daily, and 2 weeks of placebo treatment. Before and after each treat-➤➤

ment, the patients underwent inhalation challenges with methacholine and $LTD_4$ on consecutive days. The investigators compared treatment effects on exhaled nitric oxide, an indicator of ICS responsiveness; and urinary $LTE_4$, a marker of cysteinyl-leukotriene biosynthesis.

Methacholine responsiveness decreased significantly with fluticasone treatment, with a 2.6-fold shift in the $PD_{20}$ $FEV_1$, as well as a drop in exhaled nitric oxide. However, fluticasone had no effect on the bronchial response to $LTD_4$ challenge, nor on urinary $LTE_4$ levels.

Inhaled fluticasone treatment has no effect on bronchial responsiveness to $LTD_4$, despite significant effects on bronchial responsiveness to methacholine and exhaled nitric oxide. These findings support the theory that the cysteinyl-leukotrienes have unique effects on the airway.

**COMMENT:** *The effects of inhaled fluticasone on $LTD_4$ and methacholine responsiveness in mild asthmatics were studied in this small, carefully controlled investigation. Although fluticasone did reduce exhaled nitric oxide and airway hyperreactivity to methacholine, it had no significant effect on $LTD_4$ airway responsiveness or urinary $LTE_4$ production. This study suggests that leukotrienes have a unique action on the airways, which may support the additive therapeutic efficacy of combining inhaled corticosteroids with leukotriene antagonists.*

*S. M. F.*

*Gyllfors P, Dahlén S-E, Kumlin M, et al: Bronchial responsiveness to leukotriene D4 ($LTD_4$) is resistant to inhaled fluticasone proprionate.*

**J Allergy Clin Immunol**. 2006;118:78-83. ♦♦

## Too Much or Too Little Hormone?

CHILDHOOD asthma is more common in boys, but adult asthma is more prevalent in women. This gender difference has been attributed to hormonal factors, although the exact explanation is unknown. Reproductive factors, including oral contraceptive use, were evaluated as risk factors for adult-onset asthma in women.

The study included a random sample of 681 women, aged 29 to 32 years, from a large population survey of Tasmanian schoolchildren, initiated in 1968. At 25 years' follow-up, the women were asked for detailed information on reproductive history. Reproductive variables associated with current asthma, defined as patient-reported asthma or wheezy breathing within the past year, were assessed.

At follow-up, current asthma was reported by 13% of women who did not have asthma at age 7 and 29% of those asthmatic as children. When surveyed in adulthood, 71% of the women had given birth and 78% had used oral contraceptives for more than 3 years. Among women without childhood asthma, the prevalence of current asthma increased from 8% for those who had had one child to 29% for those who had had four or more children. Asthma prevalence decreased with duration of oral contraceptive use: from 20% for those who had taken oral contraceptives for less than 4 years to 6% for those with at least 12 years' use.

On multivariate analysis, the difference in asthma prevalence with one vs no births was nonsignificant. None of the reproductive variables was significant among women who had had childhood asthma.

In women with no history of childhood asthma, the risk of current asthma increases with increased parity and decreases with oral contraceptive use. The findings support the hypothesis that the occurrence of adult-onset asthma may be related to female hormones, both endogenous and exogenous. Changes in cytokine responses during pregnancy may lead to the development of asthma in women.

**COMMENT:** *The female predominance in asthma that begins after early childhood has long been assumed to be related to hormonal differences between men and women. "The Tasmanian Survey" used in this study has the advantage of prospective design, following subjects for more than 20 years. Both increasing parity and decreased oral contraceptive use were associated with the tendency to develop asthma after childhood.*

*The authors propose that prolonged contraceptive use may result in "durable cumulative changes in the immune system, leading to asthma." Subsequent studies including immunologic characterization of study subjects are needed to clarify if this is true.*

*S. A. T.*

*Jenkins MA, Dharmage SC, Flander LB, et al: Parity and decreased use of oral contraceptives as predictors of asthma in young women.*

**Clin Exp Allergy**. 2006;36:609-613. ♦♦

## What Mediates Asthma in the Atopic Phenotype?

ALTHOUGH the link between childhood atopy and asthma is well known, wheezing may be atopic or nonatopic. Information on the characteristics of wheezing within atopic phenotypes could help to clarify the association between atopy and wheezing. Data from an English birth cohort were used to compare the characteristics of childhood wheezing between atopic phenotypes, as well as identify risk factors for the development of wheezing.

The birth cohort study included 1,456 children born on the Isle of Wight in 1989. Data on asthma, allergic disease, and associated risk factors were collected at regular intervals from birth to age 10. Atopic phenotypes were defined according to the results of skin prick tests performed in most children at ages 4 and 10. Wheezing characteristics and risk factors within these phenotypes were assessed.

Skin prick tests were performed at both 4 and 10 years in 823 children, allowing determination of atopic phenotype. Of 340 children who developed wheezing by age 10, 57.6% were never atopic, 25.6% had chronic childhood atopy, 13.2% had delayed childhood atopy, and 3.5% had early childhood atopy. Lifetime prevalence of wheezing differed by phenotype: 65% in chronic childhood atopics, 52% in delayed childhood atopics, 38% in early childhood atopics, and 37% in never ➤➤

atopics. For early childhood atopics, the rate of diagnosed asthma peaked at age 4, declining thereafter. Asthma rates varied little during the first 10 years for the delayed childhood atopics and never atopics, but increased steadily for chronic childhood atopics.

Risk factors for wheezing varied by phenotype. Among never atopics, risk was increased for boys, children with low birth weight or recurrent chest infections, those with nasal symptoms in infancy, and those whose parents smoked during the first 4 years of life. Family history of allergy was also a significant risk factor. Exclusive breast-feeding had a protective effect against atopic wheezing in early childhood. Risk factors for delayed atopic wheezing included maternal asthma, family history of urticaria, and having a pet dog.

The characteristics and risk factors for childhood wheezing differ by atopic phenotype. Although the chronic childhood atopic phenotype is associated with the highest prevalence and most clinically relevant wheezing, most childhood wheezing occurs in children with the never-atopic phenotype. Atopy is likely one of many factors affecting the airway that lead to the development of childhood asthma. Further study of these interrelated factors is needed.

**COMMENT:** *This large, well-defined birth cohort provides some interesting findings, some of which support other observations and some of which challenge prior data. Certainly the finding that a substantial number of older children with wheezing are not atopic is a bit surprising. The discussion of environmental, gender and genetic effects on wheezing, with or without atopy, is of particular interest. This cohort is probably limited in genetic variability due to the island location. Nevertheless, these data are valuable in advancing our understanding of wheezing in children.*
*D.K. L.*
*Kurukulaaratchy RJ, Matthews S, Arshad SH: Relationship between childhood atopy and wheeze: what mediates wheezing in atopic phenotypes?*
**Ann Allergy Asthma Immunol**. 2006;97:84-91. ♦♦

## More on Long-Acting β-Agonists in Asthma

LONG-acting β-agonists improve asthma symptoms, but there are concerns that regular use may be associated with worsening disease control. The true risks of severe, life-threatening, or fatal asthma exacerbations associated with these medications are unclear. A meta-analysis was performed to examine the risks of severe asthma exacerbations and asthma-related deaths in patients taking long-acting β-agonists.

The literature was searched for randomized, placebo-controlled trials of long-acting β-agonist use in asthma patients. All trials lasted 3 months or longer and permitted as-needed use of short-acting β-agonists. Outcomes of interest were severe exacerbations requiring hospitalization, life-threatening exacerbations requiring intubation and ventilation, and asthma-related deaths.

The analysis included 33,826 patients from 19 trials. Another 28 studies did not provide data on the relevant outcomes. Both severe and life-threatening exacerbations were increased with long-acting β-agonists: odds ratio (OR) 2.6 and 1.8, respectively. Salmeterol and formoterol were both associated with an increased risk of hospitalization: OR 1.7 and 3.2, respectively. Hospitalization risk was increased for children, OR 3.9; and adults, OR 2.0. The 6-month absolute increase in hospitalization was 0.7%.

Long-acting β-agonists were also associated with a significantly increased risk of asthma-related deaths, OR 3.5. Most of the deaths occurred in the Salmeterol Multicenter Asthma Research Trial. The pooled risk difference for this outcome, including trials with no deaths, was 0.07%.

This meta-analysis supports the increases risk of severe and life-threatening asthma exacerbations, as well as asthma-related deaths, in patients taking long-acting β-agonists. The risks of severe and fatal exacerbations are increased by 2- to 4-fold, although the impact on overall asthma-related deaths appears small. The findings have implications for the ongoing debate over the clinical use and continued availability of long-acting β-agonists.

**COMMENT:** *The discussion concerning risk/benefit ratio of long-acting β-agonists will not be resolved with another meta analysis. In my opinion, there is a signal of some risk with long-acting β-agonists in some patients, but this risk does not result in the suggested 4,000 deaths a year, as evidenced by the lack of an epidemiologic increase in asthma death rate with the increased use of fluticasone/salmeterol. Therefore, I am comfortable using long-acting β-agonists in a comprehensive approach to asthma. I do feel that long-acting β-agonists are sometimes used unnecessarily and consideration of risk is appropriate.*
*D. K. L.*
*Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE: Meta-analysis: effect of long-acting β-agonists on severe asthma exacerbations and asthma-related deaths.*
**Ann Intern Med**. 2006;144:904-912. ♦♦

## Role of Omalizumab in Asthma

IMMUNOGLOBULIN E is key to the pathophysiology of asthma, including allergen sensitization and the occurrence of symptoms on repeat exposure to allergen. Anti-IgE therapy with the recombinant humanized IgG1 monoclonal anti-IgE antibody omalizumab has been shown to reduce both early- and late-phase asthmatic reactions to allergen, but its role in clinical asthma management is unclear. A clinical scenario is used to illustrate issues surrounding the use of omalizumab for asthma treatment.

To date, four randomized trials have compared subcutaneous omalizumab with placebo for patients with asthma requiring inhaled corticosteroids. All four studies showed clinical benefits of omalizumab. Three studies in patients with moderate to severe persistent asthma found reductions in number of exacerbations per patient and percentage of patients with exacerbations. In a trial of patients with more severe asthma, frequency of exacerbations was unchanged, although ➤➤

inhaled corticosteroid dose was reduced with omalizumab.

Clinical indications for omalizumab include allergic asthmatic patients requiring high doses of inhaled corticosteroids and those with unstable disease leading to frequent exacerbations. Measurement of total serum IgE is needed to calculate omalizumab dose. Recommended dose is 0.016 mg/kg per international unit of IgE, given subcutaneously every 2 or 4 weeks. Omalizumab is expensive, with an average cost of $12,000 per year. Treatment response can take a while to achieve, although most responders do so within 12 weeks. Safety concerns include a possible increase in cancer risk; a few cases of anaphylaxis have been documented as well.

Clinical considerations in the use of omalizumab for asthma are reviewed. Issues to think about before recommending this form of anti-IgE therapy include the patient's compliance with current treatment and other possible treatment alternatives. More study is needed to clarify factors associated with the variable response to omalizumab.

**COMMENT:** *Anti-lgE therapy provides more questions than answers. This brief article, through the use of a clinical vignette, summarizes the possible role of this still-controversial treatment for asthma. The intriguing possibility that its concomitant use may allow higher doses of immunotherapy to be achieved is not mentioned.*
*R. J. M.*

*Strunk RC, Bloomberg GR: Omalizumab for asthma.*
**N EngI J Med**. 2006; 354:2690-2694. ♦♦

# TRIFECTA: MONITORING ASTHMA

## Sputum Cell Counts

SPUTUM cell counts are the definitive measure of airway inflammation. Recent studies have suggested using sputum cell counts to guide asthma treatment. The effects of this approach on asthma exacerbations were analyzed.

The multicenter, randomized trial included 107 adult patients with asthma. Patients were assigned to one of two treatment guidance strategies. In the clinical strategy, treatment was based on symptoms and spirometry. In the sputum strategy, corticosteroid therapy was adjusted to maintain the sputum cell count at 2% or less. After an initial 1-month phase to determine the minimum treatment necessary to maintain asthma control, patients continued on their assigned treatment for 2 years from baseline. The number, type, and severity of asthma exacerbations were compared.

In phase 1, time to maintain disease control and number and duration of exacerbations were similar with the two strategies. Most patients met criteria for moderate to severe asthma. During phase 2, a total of 126 exacerbations occurred in 63 patients. About 63% of the exacerbations occurred in patients managed by the clinical strategy, 37% in those managed by the sputum strategy. Eighty percent of exacerbations were mild; when sputum examination was performed before any treatment, most exacerbations were noneosinophilic.

The sputum strategy was associated with a 213-day increase in time to first exacerbation--490 days for patients deemed to require long-acting $\beta_2$-agonist treatment. The sputum strategy also provided a 49% reduction in relative risk ratio and a one-third reduction in exacerbations requiring prednisone therapy. Cumulative costicosteroid dosage was similar between the two groups.

Using sputum cell counts to guide asthma treatment can reduce exacerbations. Most of the benefit arises from a reduction in eosinophilic exacerbations in patients with moderate to severe asthma. For both eosinophilic and noneosinophilic exacerbations, severity is reduced without increasing corticosteroid dose. The frequency of noneosinophilic exacerbations is unaffected.

**COMMENT:** *The majority of exacerbations in optimally treated patients are mild and not associated with sputum eosinophilia. Not all exacerbations could be prevented by following current treatment guidelines. However, using sputum cell counts reduced the overall risk of exacerbations by 49%, reduced the number of severe exacerbations by 66%, and prolonged the time to first exacerbation. Patients who are most likely to benefit from monitoring sputum cell counts are those with moderate to severe asthma who are on multiple controller therapy.*
*B. E. C.*

*Jayaram L, Pizzichini MM, Cook RJ, et al: Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations.*
**Eur Respir J**. 2006;27:483-494. ♦♦

## Spirometry Plus eNO

NEW approaches are needed to identify asthma patients at high risk of exacerbations. Measurement of exhaled nitric oxide (eNO) is a simple, sensitive, though nonspecific test of airway inflammation. This prospective study assessed the ability of eNO plus spirometry to predict the risk of exacerbations in asthma patients.

The study included 44 adult patients with clinically stable asthma who had been taking fluticasone 250 µg/salmeterol 50 µg for at least 3 years. All underwent eNO measurement and lung function studies. These test results were evaluated for their ability to predict clinical asthma exacerbations over 18 months' follow-up.

Twenty-two patients had at least one exacerbation during follow-up, including 16 patients with two exacerbations and 6 who required hospitalization. Exacerbation risk was 65% for patients with a baseline $FEV_1$ of 76% predicted or less, compared with 15% of patients with an initial $FEV_1$ higher than 76%. On receiver operating characteristic curve analysis, a cutoff value of $FEV_1$ of 76% predicted had a sensitivity of 91%; specificity of 50%; and positive and negative predictive value of 65% and 85%, respectively.

Exhaled NO was also associated with exacerbation risk. Exacerbations occurred in 76% of patients with a baseline eNO of 28 ppb or higher, compared with ➤➤

33% of those with a lower eNO value. The combination of eNO 28 ppb or higher plus $FEV_1$ of 76% predicted or less identified a group of 13 patients with an 85% likelihood of future exacerbations. For 9 patients with a lower eNO and a higher $FEV_1$, the exacerbation rate was zero.

Combined data on baseline eNO and $FEV_1$ can help predict exacerbation risk in patients receiving treatment for asthma. The cutoffs used in this study identify a group of "stable" asthma patients at very high risk of exacerbations. More study is needed to validate these cutoffs and define the effective treatment response.

**COMMENT:** *Dr. Gelb and colleagues have evaluated the diagnostic utility of $FEV_1$ and eNO in predicting future asthma exacerbations in 44 nonsmoking asthmatics. The ability to measure both pulmonary function and eNO may have several advantages in clinical practice. It may be helpful to identify patients at risk for an exacerbation. In this group we would have the opportunity to attempt a pre-emptive strike and alter their therapeutic regimens. In addition, it would give us more objective evidence to present to the patient when stressing medication compliance. More studies would be helpful to clearly delineate the level of eNO that would serve as the cutoff point of asthma control in a clinical setting.*
*T. L. H.*
*Gelb AF, Taylor CF, Shinar CM, et al: Role of spirometry and exhaled nitric oxide to predict exacerbations in treated asthmatics.*
**Chest**. 2006;129:1492-1499. ♦♦

## High-Sensitivity CRP

SERUM C-reactive protein (CRP) is recognized as a marker of systemic inflammation. Newer high-sensitivity CRP (hs-CRP) assays can demonstrate low-grade inflammation in cardiovascular diseases and diabetes, but the results in asthma are unclear. The results and clinical implications of hs-CRP levels in patients with asthma were analyzed.

The study included 45 adult asthma patients, 22 steroid-naive and 23 currently using inhaled corticosteroids, along with 14 healthy controls. Measurements of serum hs-CRP were obtained and compared with clinical characteristics and sputum cell counts.

The steroid-naive asthma patients had a mean hs-CRP level of 1.33 mg/L--higher than in healthy controls (mean 0.2 mg/L) but not significantly different from steroid-treated asthma patients (mean 0.9 ng/mL). In the steroid-naive group, hs-CRP was negatively correlated with pulmonary function values and positively correlated with sputum eosinophil count. No significant correlations were noted in the steroid-treated patients.

High-sensitivity CRP may be an indirect marker of airway inflammation in asthma. In asthma patients not receiving corticosteroids, high serum hs-CRP is associated with decreased lung function and increased sputum eosinophilia. The clinical value of hs-CRP in asthma remains to be evaluated.

**COMMENT:** *Elevation of CRP by the high-sensitivity method is associated with airflow limitation obstruction and airway inflammation. This has been shown to be a surrogate marker in steroid-naive patients and may reflect airway inflammation, as measured by increased sputum eosinophil numbers and pulmonary function.*
*B. E. C.*
*Takemura M, Matsumoto H, Niimi A, et al: High sensitivity C-reactive protein in asthma.*
**Eur Respir J**. 2006;27:908-912. ♦♦

# CLINICAL TIDBITS

## Nasal NO Useful in Assessing CRS

EXHALED nitric oxide is a useful, noninvasive measure of airway inflammation in asthma. Nasal nitric oxide (nNO) was evaluated for use in monitoring the response to treatment in chronic rhinosinusitis (CRS). Ninety patients with CRS underwent nNO measurement before and after medical or surgical treatment. The baseline nNO levels were inversely correlated with abnormalities seen on CT scans. After treatment, the percentage increase in nNO was correlated with improvement in CRS symptom scores. Nasal NO was also related to changes in saccharin clearance time, endoscopic changes, and polyp grades. Nasal NO measurement may be a simple, noninvasive test to evaluate the response to medical or surgical treatment for CRS.

**COMMENT:** *Exhaled NO has been shown to be a useful way to measure airway inflammation in asthma. Since the assessment of patient response to various therapies of CRS has always been difficult, these investigators studied the effect of medical and surgical therapy of CRS on nasal NO levels to determine whether this parameter could be used as an objective indicator of efficacy. They observed that nasal NO provided a valuable, noninvasive measure of therapeutic response in CRS. This measure correlated well with the patient's perception of improvement as well as with endoscopic changes, polyp grades, and surgical scores. Additional studies will be required to confirm these interesting results. V.M.D. Struben et al have written an interesting review on nasal NO and nasal allergy (Allergy. 2006;61:665-670).*
*E. J. B.*
*Ragab SM, Lund VJ, Saleh HA, Scadding G: Nasal nitric oxide in objective evaluation of chronic rhinosinusitis therapy.*
**Allergy**. 2006;61:717-724. ♦♦

## What Is the Prognosis for VCD?

PATIENT education and speech therapy reportedly have a high success rate for patients with vocal cord dysfunction (VCD), but little is known about the long-term outcomes of this functional disorder. The authors attempted to contact 49 patients diagnosed with ➤➤

VCD over a 13-year period. Of these, 28 had exercise-induced VCD only, while 20 had spontaneously occurring VCD. Twenty-eight patients were successfully contacted. Eight of 11 patients with spontaneous VCD followed advice to seek speech therapy, and all learned to control their symptoms. Pretreatment with an anticholinergic inhaler was recommended for 6 patients with exercise-induced VCD, which successfully prevented symptoms. Except for two patients with coexisting spontaneous and exercise-induced VCD, all patients were symptom free at follow-up. Treatment recommendations vary for the differing phenotypes of VCD; in most cases, symptoms eventually resolve.

**COMMENT:** *Vocal cord dysfunction is a regular challenge I confront in clinic. This is a helpful paper as long-term data are not available in the literature. These authors suggest that inhaled anticholinergic therapy may be specific for exercise-induced VCD and that speech therapy is effective, though spontaneous resolution is common regardless of treatment. My experience agrees with the latter but I will have to try the former.*
*D. K. L.*
*Doshi DR, Weinberger MM: Long-term outcome of vocal cord dysfunction.*
**Ann Allergy Asthma Immunol**. 2006;96:794-799. ♦♦

## Variability in Asthma Severity in Children

PATIENTS with asthma do not necessarily remain in the same category of disease severity at all times, which may contribute to inadequate treatment. This study combined data from five 12-week randomized trials to assess variability in asthma severity over time. The analysis included 276 children with moderate to severe asthma, all previously treated with short-acting $\beta_2$ agonists only and then treated with placebo. On average, the children spent 56% of weeks meeting all criteria for moderate or severe persistent asthma. Based on asthma symptoms, they spent 48% of weeks in the intermittent category, 31% in the mild category, and 22% in the moderate to severe category. Based on albuterol use, the percentages were 57%, 27%, and 15%, respectively. Based on peak expiratory flow readings, more than one-third of children had 15 or more changes in asthma severity over 12 weeks. Changes in disease severity classification are common in children with asthma, especially those with inadequate disease control. Relying on one-time assessments may lead to underestimation of asthma severity.

**COMMENT:** *This unique study allowed the investigators to closely monitor the "natural history" of asthma severity in 4- to 11-year-old children. It is no surprise to me to see the great variability in the degree of asthma symptoms or signs that the children show at any one time. The authors feel that this observation may be responsible for missing the diagnosis of asthma in many children. While that may be true, perhaps the more important lesson we should take from these observations is that there is a need to regularly follow children with asthma throughout the year, in order to "catch" those times when more control is needed to keep them well!*
*J. A. A.*
*Chipps BE, Spahn JD, Sorkness CA, et al: Variability in asthma severity in pediatric subjects with asthma previously receiving short-acting $\beta_2$ agonists.*
**J Pediatrics**. 2006;148:517-521. ♦♦

## What's the Effect of Smoking on the Incidence of Asthma?

THE contribution of smoking to the occurrence of asthma remains a topic of debate. Data from a cohort study of German children were used to assess the effects of active and passive smoking on the incidence of asthma during adolescence. Active smokers had higher rates of incident wheezing, incidence rate ratio (IRR) 2.30; and of wheezing without a cold, IRR 2.76. Active smoking was also associated with a higher rate of diagnosed asthma, IRR 2.56. Risk increased with the duration and intensity of smoking. In smokers with atopy, risk of wheezing without a cold increased at lower baseline levels of plasma $\alpha_1$-antitrypsin. Active smoking increases the risk of asthma during adolescents, the new results suggest. There is no apparent effect of passive smoking on these respiratory outcomes.

**COMMENT:** *Even though cigarette smoking is a known risk factor for many chronic illnesses, including coronary heart disease and chronic obstructive pulmonary disease, its effect on the development of asthma remains controversial. There is little doubt that smoking can worsen asthma. This study focuses on a large cohort of adolescents followed over a 7-year period. The findings indicate that active smoking is an important risk factor for the incidence of wheeze and asthma in adolescence. The risk increases with the duration and intensity of the smoking habit.*
*E. J. B.*
*Genuneit J, Weinmayr G, Radon K, et al: Smoking and the incidence of asthma during adolescence: results of a large cohort study in Germany.*
**Thorax**. 2006;61:572-578. ♦♦

## Upper Airway Symptoms Appear First in Acid Anhydride Workers

OCCUPATIONAL exposure to organic acid anhydrides (OAA) is associated with high rates of sensitization, rhinitis, and asthma. This prospective study assessed rates of ocular and airway symptoms in all new employees at three plants handling OAA. The 146 workers studied had mean OAA exposure levels of 6 to 39 $\mu g/m^3$. Ocular symptoms occurred at a rate of 91 per 1,000 years of exposure to OAA. Other rates of symptoms of 1,000 years of exposure were 64 for nasal➤➤

symptoms, 46 for pharyngeal symptoms, and 31 for lower airway symptoms. Symptom rates were higher for smokers and workers with atopy. Even at low exposure, OAA is associated with high rates of ocular and respiratory symptoms. The authors suggest an OAA occupational threshold limit of less than 5 μg/m³.

**COMMENT:** *Organic acid anhydrides are frequently used as hardeners in epoxy resin systems. They are potent sensitizers even at low levels of exposure. This unique prospective study evaluated 146 subjects in three plants handling OAA. Even at relatively low levels of exposure (ie, less than 10 μg/m³), workers frequently developed ocular and airway symptoms. Smoking and atopy were both independent risk factors for sensitization, although the precise mechanism remains unknown.*
*E. J. B.*
*Nielsen J, Welinder H, Bensyrd I, et al: Ocular and airway symptoms related to organic acid anhydride (OAA) exposure--a prospective study.*
**Allergy**. 2006;61:743-749. ♦♦

## How Do Viral Infections Affect Skin Testing?

THE results of skin testing can be affected by many factors, such as treatment with antihistamines. This study examined the effects of respiratory syncytial virus (RSV) infection on skin test results. Skin testing with inhalant allergens was performed in 16 adults before and up to 21 days after experimental inoculation with RSV. Even subjects with no measurable skin test reactions at baseline showed increased wheal-and-flare areas in response to histamine and allergen skin tests after RSV exposure. New reactions to allergen were noted as well. The altered skin test results persisted for up to 21 days after RSV inoculation. Upregulation of pathways related to neurogenic inflammation may have played a role--this may help to explain some of the recognized complications of RSV infection. The findings show that viral infections may alter skin-test results.

**COMMENT:** *Respiratory syncytial virus infection remains a significant and common infection in atopic and normal children. The results of this study remind us that virally induced neurogenic inflammation may mediate many noninfectious manifestations of RSV. Perhaps we should delay skin testing for 4 to 6 weeks following a suspected viral respiratory infection in children undergoing an allergy evaluation.*
*A. M.*
*Skoner DP, Gentile DA, Angelini B, et al: Allergy skin test responses during experimental infection with respiratory syncytial virus.*
**Ann Allergy Asthma Immunol**. 2006;96:834-839. ♦♦

## Montelukast Doesn't Affect Linear Growth

THIS study was designed to determine whether the antileukotriene drug montelukast affected growth in children with asthma, compared with the inhaled corticosteroid beclomethasone. The multicenter trial randomly assigned 360 asthmatic children, age 6 to 9 years, to 56 weeks of treatment with montelukast 5 mg/d, beclomethasone 200 μg twice daily, or placebo. Linear growth velocity was not significantly different between the montelukast and placebo groups. For children assigned to beclomethasone, mean growth rate was 0.78 cm less than with placebo. Both active treatments reduced the percentage of days with β-agonist use, compared with placebo. Montelukast treatment does not adversely affect growth in children with asthma. In contrast, 1 year of treatment with the ICS beclomethasone is associated with a significant reduction in linear growth velocity.

**COMMENT:** *While the results are not surprising, this study needed to be done and provides us with reassuring data. The steroid responses also remind us to use the lowest effective dose of ICS in children.*
*A. M.*
*Becker AB, Kuznetsova O, Vermeulen J, et al: Linear growth in prepubertal asthmatic children treated with montelukast, beclomethasone or placebo: a 56-week randomized double-blind study.*
**Ann Allergy Asthma Immunol**. 2006;96:800-807. ♦♦

## Bacterial Biofilms in the Middle Ear

RECENT studies raise the possibility that chronic otitis media (OM) may be related to the presence of mucosal biofilms in the middle ear. Evidence of biofilms was sought in biopsy specimens of middle ear mucosa from 26 children undergoing tympanostomy treatment for otitis media with effusion and/or recurrent OM. Of 24 effusion specimens tested by polymerase chain reaction, all were positive for one or more OM pathogens. In contrast, just 6 of 27 effusions yielded positive culture results. Confocal laser scanning microscopy, performed with generic and species-specific probes, detected mucosal biofilms in 92% of biopsy specimens tested. No biofilms were found in a series of 8 biopsy specimens from children undergoing cochlear implant placement. Middle ear biofilms may contribute to the pathogenesis and chronic nature of OM in children.

**COMMENT:** *The concept of biofilms as an explanation of antigen source in chronic, respiratory mucosal disease is fascinating. Papers support that the same phenomenon occurs in the sinus mucosa. Maybe culture-negative cases of sinus or ear disease are due to bacteria. What about chronic asthma? However, we do not know what to do with these cases, since antibiotics are relatively ineffective against dormant bacteria in the biofilm. Clinicians should monitor this interesting literature.* ➤➤

*D. K. L.*
*Hall-Stoodley L, Hu FZ, Gieske A, et al: Direct detection of bacterial biofilms on the middle-ear mucosa of children with chronic otitis media.*
**JAMA**. 2006; 296:202-211. ♦♦

## Formoterol vs Salbutamol

EVEN with inhaled corticosteroids and rescue salbutamol, some patients have continued asthma symptoms. Formoterol was compared with salbutamol as rescue medication for asthma. In randomized, crossover fashion, 211 adult asthma patients received 3 weeks of treatment with as-needed formoterol 4.5 µg and salbutamol 100 µg via Turbuhaler. Patients had significantly better lung function and symptom control while receiving formoterol, compared with salbutamol. Formoterol was associated with lower daytime and nighttime symptom scores, higher peak expiratory flows, and higher $FEV_1$. More patients preferred formoterol, and believed it worked somewhat faster than salbutamol. As rescue medication for asthma, formoterol appears to offer several advantages over salbutamol.

**COMMENT:** *This study is timely, as Symbicort has been recently approved for use in the United States. The results reinforces the data previously published using combination formoterol and budesonide as maintenance and as-needed therapy. Patients preferred formoterol by more than 2 to 1, and it led to a significant increase in $FEV_1$. This continues to strengthen the case that formoterol may be used as an as-needed strategy when it is available in the lower (4.5 µg) dose in the United States.*
*B. E. C.*
*Cheung D, van Klink HCJ, Aalbers R, for the OZON Study Group: Improved lung function and symptom control with formoterol on demand in asthma.*
**Eur Respir J**. 2006;27:504-510. ♦♦

## More on Polymorphism and Asthma

A polymorphism of the tumor necrosis factor α (TNFα)-308 gene promoter has been suggested as a genetic factor affecting asthma susceptibility. A literature search identified 15 case-control studies addressing this issue--meta-analysis included 2,409 asthma patients and 3,266 controls. Using a random-effects model, the analysis found a significant association between asthma susceptibility and the TNF2 allele, odds ratio (OR) 1.37. For TNF2 homozygotes, the ORs were 2.01 compared with TNF1 homozygotes and 1.51 compared with TNF2/1 heterozygotes. TNF2/1 heterozygotes also had increased susceptibility compared with TNF 1/1 homozygotes, OR 1.47. The TNF2 allele of the TNFα gene promoter is associated with increased susceptibility to asthma. Larger studies are needed to clarify the functional effect of this genetic risk factor.

**COMMENT:** *We all understand that asthma is a complex condition that is determined by genetic and environmental factors. Candidate gene studies may provide useful insights into gene-disease associations, but have been criticized because of the frequent lack of replication. This meta-analysis addresses some of the inconsistencies in prior studies and concludes that the TNF2 allele confers a significant risk for developing asthma.*
*E. J. B.*
*Gao J, Shan G, Sun B, et al: Association between polymorphism of tumor necrosis factor α-308 gene promoter and asthma: a meta-analysis.*
**Thorax**. 2006;61:466-471. ♦♦

## Assessment of Latex Allergen Assays

A previous study found that only 0.6% of Veterans Administration health care workers with allergic symptoms related to latex gloves had a positive CAP assay. This study compared the results of the original UNICAP 100 assay for anti-latex allergen IgE with an enhanced CAP assay and an enzyme-linked immunosorbent assay (ELISA). The enhanced CAP and ELISA results were highly concordant with the results of the original CAP assay. Of 64 samples that were negative on the original CAP, 7 tested positive on the enhanced CAP, a rate of 11%. Just 3 of these results were class 2 or higher. The ELISA was positive in just 6 of the CAP-negative specimens, with 3 being marginally positive. Compared with the UNICAP 100 assay, the enhanced CAP and ELISA evaluated in this study identify a few additional cases of latex allergy.

**COMMENT:** *Latex allergy continues to be a diagnostic challenge to allergists. This study reminds us that in the absence of a standardized skin test reagent, we must rely on imperfect in vitro assays. While they are not perfect, in vitro assays in symptomatic individuals are still pretty good--and probably better when done in combination.*
*A. M.*
*Zeiss CR, Kurup VP, Elms N, Fink JN: Latex allergen IgE assays in the assessment of Veterans Affairs health care workers.*
**Ann Allergy Asthma Immunol**. 2006;96:840-843. ♦♦

## Improved Asthma Outcomes

AN emergency department (ED)-based intervention was tested for the ability to improve outcomes in asthmatic children at high risk for morbidity. The study included 488 asthmatic children seen in an urban children's ED. One group was offered a follow-up visit to a specialized asthma clinic located in the ED. The visit included an action plan with a 3-month prescription for controller medications, advice on environmental modifications, and referral back to the child's primary care physician (PCP). Controls received usual care. Seventy percent of children in the intervention group were seen in the asthma clinic. Children in the intervention group had fewer unscheduled visits for asthma care, rela-➤➤

tive risk 0.60. At 6 months, they were more likely to be using inhaled corticosteroids and to be free of limitations in quality of life. By taking advantage of the "teachable moment," ED interventions may improve outcomes for urban children with asthma.

**COMMENT:** *Recently, there have been more published studies in the pediatric literature involving the ED as a focus in the long-term management of urban asthma. This controlled study from Washington, D.C., involved a follow-up (one visit) asthma clinic located in the ED. Specifically excluded were children being actively seen by their PCP or an allergist or those receiving an asthma controller medication. The study group were given education and a 3-month prescription of an asthma controller medication and encouraged to go to their PCP. At 6 months, the study group had half the number of ED visits, compared with controls. However, one wonders if the controller medication prescription was the key to success, since there was no difference between the study group and controls in the number of patients returning to their PCP.*
*J. A. A.*
*Teach SJ, Crain EF, Quint DM, et al: Improved asthma outcomes in a high-morbidity pediatric population: results of an emergency department-based randomized clinical trial.*
**Arch Pediatr Adolesc Med**. 2006;160:535-541. ♦♦

## Bronchial Thermoplasty for Asthma

BRONCHIAL thermoplasty is a procedure using radiofrequency energy to reduce smooth muscle mass in the airway wall, with the goal of decreasing the potential for bronchoconstriction. An experience with bronchial thermoplasty in 16 adult patients with stable, mild to moderate asthma is reported. Side effects were similar to those occurring after bronchoscopy. Airway responsiveness improved in all patients--at 2 years' follow-up, mean $PC_{20}$ had increased by 2.64 doublings. In the months after the procedure, patient diaries indicated improvements in symptom-free days and evening peak flow measurements. Lung function values were stable. More study is needed to evaluate the risks and benefits of bronchial thermoplasty as a treatment for asthma.

**COMMENT:** *This study of 16 subjects with mild airflow limitation but significant bronchial hyperreactivity confirms the safety of thermoplasty over a 2-year period. This intriguing intervention will be proven to be an important strategy only after appropriately conducted randomized control trials.*
*B. E. C.*
*Cox G, Miller JD, McWilliams A, et al: Bronchial thermoplasty for asthma.*
**Am J Respir Crit Care Med**. 2006;173:965-969. ♦♦

## What Is Reactive Airway Disease?

ONE recent survey found that 11% of children had physician-diagnosed asthma with current symptoms, while an additional 17% had active wheezing but no diagnosis of asthma. Resource utilization and costs were compared for children with diagnosed asthma and those receiving asthma medications despite having no asthma diagnosis. Patients were identified from a managed care data base including more than 295,000 children--6.7% had an asthma diagnosis, while 4.4% had no asthma diagnosis but still received asthma medications. Both groups had higher total health care costs than control children, including more nonasthma emergency visits and more hospitalizations. Asthma costs were higher in the diagnosed group. Diagnosed children were more likely to receive controller medications and oral corticosteroids, while nondiagnosed children were more likely to receive short-acting $\beta_2$ agonists. Children receiving asthma medications despite having no asthma diagnosis have high morbidity and resource utilization. Physician hesitance to diagnose asthma may reflect lack of knowledge of the criteria or concerns about labeling a child "asthmatic."

**COMMENT:** *This study by Stempel and his associates clearly identifies a large pool of U.S. children who use asthma medications without a confirming diagnosis of asthma. I agree with the authors' assessment of the possible reasons why these children were not labeled as asthmatic by the physicians who prescribed the asthma drugs. Objective "proof" of asthma is not that easy, especially in children under age 5, teenagers who have symptoms only when exercising, or in a child who has bronchitis, sounds "congested," and is given an asthma medication empirically! A diagnosis of "reactive airway disease," instead of asthma, is all too frequent in children. Perhaps if more of these children were referred to specialists, a clearer picture of their medical condition would result.*
*J. A. A.*
*Stempel DA, Spahn JD, Stanford RH, et al: The economic impact of children dispensed asthma medications without an asthma diagnosis.*
**J Pediatr**. 2006;148:819-823. ♦♦

## REVIEWS OF NOTE

**COMMENT:** *This paper describes the observations of a remarkable clinician over a number of years and is a valuable addition to the anaphylaxis literature. The study of human anaphylaxis is unlikely with double-blind, controlled trials, so we must depend on superb case collections such as this. If you see patients, you should read this paper.*
*D. K. L.*
*Web LM, Lieberman P: Anaphylaxis: a review of 601 cases.*
**Ann Allergy Asthma Immunol**. 2006;97:39-43. ♦♦

**COMMENT:** *This review is a very complete summary of the current literature regarding the scientific basis of the home treatment of asthma exacerbations.*
*B. E. C.*
*Reddel HK, Barnes DJ, on behalf of the Exacerbation Advisory Panel: Pharmacological strategies for self-management of asthma exacerbations.*
**Eur Respir J**. 2006;28:182-199. ♦♦

**COMMENT:** *The more perplexing the disease, the more variable the clinical approaches. So it is with atopic dermatitis. This consensus report from the EAACI and the AAAAI brings some order to what is known, from genetics to immunopathology to diagnosis to treatment.*
*R. J. M.*
*Akdis CA, Akdis M, Bieber T et al: Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/ American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report.*
**J Allergy Clin Immunol**. 2006;118:152-169. ♦♦

**COMMENT:** *GERD is a common problem that affects any active allergy practice. Obesity and smoking are weakly associated with it, and genetics may play an important role. This excellent review covers the epidemiology, diagnosis, complications and treatment of this problem.*
*E. J. B.*
*Maayyedi P, Talley N: Gastro-oesophageal reflux disease (GERD).* **Lancet**. 2006;367:2086-2100. ♦♦

**COMMENT:** *This is a comprehensive review of the mechanisms that drive airway inflammation and the hypothesis that multiple "hits" will lead to more severe airway obstruction and phenotypic expression of asthma.*
*B. E. C.*
*Pavord ID, Birring SS, Berry M, et al: Multiple inflammatory hits and the pathogenesis of severe airway disease.* **Eur Respir J**. 2006;27:884-888. ♦♦

**COMMENT:** *How many times have we been asked by a patient or parent, "Why are allergies so much more common now?" This up-to-date review nicely summarizes the data that should serve as the foundation of our answers to that question.*
*S. A. T.*
*Bernsen RMD, van der Wouden JC, Nagelkerke NJD, de Jongste JC: Early life circumstances and atopic disorders in childhood.*
**Clin Exp Allergy**. 2006;36:858-865. ♦♦

**COMMENT:** *This is a very useful piece of literature to use when advising parents or answering questions about food allergy. This information is consensus but evidence- based literature is hard to come by. I would suggest keeping a copy at hand or providing a summary to parents who ask a lot of questions.*
*D. K. L.*
*Flocchi A, Assa'ad A, Bahna S, for the Adverse Reactions to Foods Committee of the American College of Allergy, Asthma, and Immunology: Food allergy and the introduction of solid foods to infants: a consensus document.*
**Ann Allergy Asthma Immunol** 2006;97:10-21. ♦♦

**COMMENT:** *The authors provide an outstanding review of a highly relevant area. The review serves as a great reminder to those of us who prescribe oral and high-dose ICS that we should be evaluating at-risk individuals! Dual-energy x-ray absorptiometry scanning is safe and highly predictive of future risk of osteopenic fractures.*
*A. M.*
*Kearney DM, Lockey RF: Osteoporosis and asthma.*
**Ann Allergy Asthma Immunol**. 2006;96:769-774. ♦♦

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