# 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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## Why Steroids May Not Work in Asthma

FOR reasons that are unclear, some patients with asthma do not respond to treatment with glucocorticoids (GCs). Having some way of detecting GC-insensitive asthma would avoid ineffective high-dose steroid treatment and allow patients to be targeted for alternative therapies. This study compared functional responses to steroids in bronchoalveolar lavage (BAL) cells from patients with GC-insensitive and GC-sensitive asthma. The two groups were similar in terms of asthma severity--the clinical differences were confirmed by responses to steroid burst.

Immunostaining was performed to assess nuclear translocation of GC receptor α (GCRα), the first step in the classical GC signaling pathway, in response to treatment with $10^{-6}$ dexamethasone. Intracellular shuttling of GCRα in response to dexamethasone was reduced in BAL cells from patients with GC-insensitive asthma. Macrophages of cells from GC-insensitive patients showed increased cytoplasmic and nuclear GCRβ levels, analyzed by immunofluorescence staining.

In experiments using viral transduction of GCRβ gene into murine DO-11.10 hybridoma cells, the nuclear translocation and transactivation properties of GCRα decreased as GCRβ levels increased. In BAL macrophages from GC-insensitive asthma, the use of specific small interfering RNA to silence GCRβ expression led to enhanced GCRα transactivation in response to dexamethasone.

Patients with GC-insensitive asthma have a reduced GCRα translocation response to steroids. The GCRα transactivation response may be inhibited by increased levels of CGRβ. Measures to increase expression of GCRβ may be a promising therapeutic approach to restoring responsiveness to steroids in GC-insensitive asthma.

**COMMENT:** *The mechanism of glucocorticoid sensitivity in asthma is evolving. This study helps us to* ➤➤

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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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*better understand the role of elevated GCR-β, which may evolve as a therapeutic target.*
*B. E. C.*
*Goleva E, Li L-b, Eves T, et al: Increased glucocorticoid receptor β alters steroids response in glucocorticoid-insensitive asthma.*
**Am J Respir Crit Care Med**. 2006;173:607-616. ♦♦

## The Picture Becomes Clearer in Chronic Urticaria

THERE are still questions regarding the pathogenesis of chronic urticaria (CU). Studies using autologous serum skin tests (ASSTs) and in vitro histamine release assays have yielded contradictory results, suggesting that the two tests may reflect different aspects of the disease. There are also questions regarding the specificity of ASST. Autologous plasma skin testing (APST) was evaluated as an alternative test of skin autoreactivity in CU.

Ninety-six consecutive patients with CU underwent ASST and APST. Fifty-three percent had positive results on ASST. In the first 25 patients, APST was performed using $K_2$EDTA as an anticoagulant, with positive results in 96% of patients. In the remaining 71 cases, APST was performed using Na citrate as the anticoagulant. The results were positive in 86% of patients: 70% of those who were negative on ASST and 98% who were positive on ASST.

A subset of patients underwent measurement of prothrombin fragment 1 + 2 ($F_{1+2}$) plasma levels using a sandwich enzyme-linked immunosorbent assay. Plasma $F_{1+2}$ was 3.06 in patients with CU vs 0.80 in normal controls. Among the CU patients, $F_{1+2}$ was 3.89 for patients who were ASST-positive/APST-positive, compared to 1.33 for those who were ASST-negative/APST-positive. The $F_{1+2}$ level was also correlated with the severity of urticaria.

Most patients with CU have a positive response to APST using plasma anticoagulated with Na citrate. The results also suggest that CU is associated with the generation of thrombin, with a significant relationship between $F_{1+2}$ levels and urticaria severity. The findings have implications for the pathogenesis and treatment of CU.

**COMMENT:** *Previous reports of urticarial responses to autologous serum injection in CU patients were a ray of hope in a vexing disease. Now there is even more to be excited about: injections with autologous plasma (anticoagulated specifically with Na citrate for technical and very cogent reasons) were positive in 86% of CU patients and none of the controls. This is much higher sensitivity and specificity than with the serum test. The results implicate thrombin, a protease capable of activating mast cells, as a key player in the pathogenesis of CU.*
*R. J. M.*
*Asero R, Tedeschi A, Riboldi P, Cugno M: Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum.*
**J Allergy Clin Immunol**. 2006;117:1113-1117. ♦♦

## Old Problem with a New Twist

ENDOGENOUS and exogenous sex hormones may affect the development of asthma and wheezing in women. This includes a possible effect of oral contraceptives (OC), which are widely used by young women. ➤➤

The effects of age at menarche and OC use on the development of wheezing in young women were assessed.

The study included 905 adolescent girls and women, aged 13 to 28 years, drawn from the Children's Health Study. Mean follow-up in the study sample was 7.7 years. The effects of age at menarche and OC use on rates of asthma and wheezing were assessed, including comparison of women with and without a history of asthma.

The rate of physician diagnosed asthma was 21.2%--approximately 52% of women reported using asthma medications within the past year. There was a significant association between age at menarche and the occurrence of asthma after puberty: hazard ratio 2.08 for women who had menarche before age 12.

Among women with a history of asthma, OC use was associated with lower rates of current wheezing or exercise-induced wheeze. In contrast, for women without a history of asthma, these outcomes were more frequent among OC users. Adjusted odds ratios for current wheezing with OC use were 1.75 for asthma-free women vs 0.18 for those with a history of asthma.

Endogenous and exogenous sex hormone status are significantly related to asthma and wheezing in young women. Girls with early menarche are more likely to develop asthma after puberty. Oral contraceptive use is associated with increased risk among women without a history of asthma, but reduced risk for those with an asthma history. The decreasing age at menarche and high rates of OC use may have important implications for the occurrence of asthma in young women.

**COMMENT:** *This population-based study found that female sex hormones played a role in asthma occurrence. Early menarche was associated with an increased risk of asthma developing after puberty. The use of OC was associated with an increased risk of current wheeze and exercise-induced wheeze in women without a history of asthma, although those with a history of asthma using OC had a reduced occurrence of wheezing symptoms. The effect of female hormones on asthma requires further clarification.*

*S. M. F.*

*Salam MT, Wenten M, Gilliland FD: Endogenous and exogenous sex steroid hormones and asthma and wheeze in young women.*

**J Allergy Clin Immunol**. 2006;117:1001-1007. ♦♦

## Unraveling Pathogenesis in Asthma

OVERPRODUCTION of Th2 cytokines plays a pathophysiologic role in asthma, while studies of the effects of interferon-γ (IFN-γ) on airway inflammation have yielded conflicting results. Quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) was performed to measure levels of T-cell cytokine mRNA in sputum from patients with allergic and nonallergic asthma.

Induced sputum samples were obtained from 39 patients with asthma and 15 healthy controls. Cytokine mRNA levels were compared for asthma patients vs controls, patients with allergic vs nonallergic asthma, and patients with mild vs moderate to severe asthma. Cytokine mRNA was also compared with other indicators of airway inflammation.

The asthma patients had elevated sputum expression of interleukin (IL)-5 and IL-13 mRNA, compared with controls. Forty-four percent of asthma patients had detectable IL-4 mRNA while 21% had detectable IFN-γ mRNA, compared to none of the controls. Patients with allergic asthma had higher expression of IL-4, IL-5, and IL-13 mRNA than those with nonallergic asthma. These cytokine mRNA levels were also correlated with sputum eosinophil percentage, but not with asthma severity.

Patients with nonallergic asthma had higher expression of IFN-γ mRNA, compared to allergic asthma patients. Sputum IFN-γ mRNA expression was also higher in moderate to severe than in mild asthma. Sputum IL-5 mRNA was significantly related to exhaled nitric oxide and bronchial hyperreactivity to histamine.

Patients with allergic and nonallergic asthma have a Th2-predominant cytokine profile in induced sputum specimens. The increase in IL-5 mRNA is correlated with eosinophil percentage, exhaled nitric oxide, and bronchial hyperreactivity, while IFN-γ mRNA is correlated with asthma severity. Real-time RT-PCR of induced sputum may provide a useful technique for studying asthma severity and disease activity.

**COMMENT:** *Sputum induction and quantitative real time RT-PCR were used to study differences in the expression of an extensive panel of T-cell cytokines in the airways of healthy controls and asthmatic subjects. They confirmed the predominance of Th2 cytokines in both allergic and nonallergic asthma. Interleukin-4 levels were increased in the allergic asthma group, and IFN-γ was more prominent in severe asthma. Interleukin-5 correlated well with eosinophilic inflammation as well as exhaled nitric oxide and airway hyperreactivity. These interesting observations will require further validation in larger groups of asthmatics who are being actively treated to assess their usefulness as parameters of responsivity.*

*E. J. B.*

*Truyen E, Coteur L, Dilissen E, et al: Evaluation of airway inflammation by quantitative Th1/Th2 cytokine mRNA measurement in sputum of asthma patients.*

**Thorax**. 2006;61:202-208. ♦♦

## Grazax: Ready for Prime Time?

SUBLINGUAL immunotherapy is emerging as a more convenient form of immunotherapy with a lower risk of serious adverse events. A new grass allergen tablet (Grazax) was evaluated as once-daily sublingual immunotherapy for seasonal allergic rhinoconjunctivitis.

The multicenter randomized controlled trial included 855 adult patients with a clinical history of grass pollen allergy-induced rhinoconjunctivitis. All had ➤➤

a positive result on skin-prick testing with *Phleum pretense* and elevated allergen-specific IgE. Patients were randomized to one of three once-daily sublingual doses of Grazax--2,500, 25,000, or 75,000 SQ-T--or placebo. Treatment continued for a mean of 18 weeks.

Ninety-two percent of patients completed the trial. At the 75,000 SQ-T dose of Grazax, rhinoconjunctivitis symptom score during pollen season decreased by an average of 16%, compared with placebo. There was a 28% reduction in the use of allergy medications. Grazax was also associated with improvement in rhinoconjunctivitis-related quality of life and an increased number of "well" days. Efficacy results were improved among patients receiving 8 weeks of recommended preseasonal treatment. Grazax treatment was well tolerated, with just one serious adverse event.

Once-daily sublingual immunotherapy with grass pollen allergen tablets can reduce symptoms and medication use in patients with seasonal allergic rhinoconjunctivitis. The study also shows dose-related improvements in quality of life, with a low risk of severe systemic reactions. Ongoing studies will determine if a longer preseasonal treatment phase can lead to increased efficacy.

**COMMENT:** *This is one of the largest double-blind, placebo controlled trials investigating the use of preseasonal treatment with sublingual grass pollen allergen tablets for seasonal allergic adverse events. There was a dose-dependent response, with the highest reductions in symptoms and medication scores in the group receiving the equivalent of 22 times the recommended subcutaneous immunotherapy dose. Although there was an impressively low number of adverse events, almost 6% of the high-dose treatment group withdrew. The authors speculate that a longer duration of therapy might have improved efficacy. Many patients are averse to needles; SLIT may provide an effective alternative in the future.*
*S. M. F.*

*Durham SR, Yang WH, Pedersen MR, et al: Sublingual immunotherapy (SLIT) with once-daily grass allergen tablets: A randomized controlled trial in seasonal allergic rhinoconjunctivitis.*
**J Allergy Clin Immunol**. 2006;117:802-809. ♦♦

## "Mother Knows Best"

STUDIES suggest that environmental factors early in life, such as exposure to a farm environment, might affect the risk of childhood asthma and allergies. It is also possible that these findings reflect a role of prenatal--maternal--exposures. Maternal exposure to a farm environment was evaluated as a predictor of childhood atopy and asthma.

The study included farm and non-farm families enrolled in a cross-sectional study designed to assess factors associated with childhood asthma and allergies in farming families and those who followed an anthroposophic lifestyle. Questionnaires regarding asthma and atopy were completed by the parents of 8,263 children. Children whose mothers were exposed to stables during pregnancy had a significantly lower rate of atopic sensitization: adjusted odds ratio 0.58. This maternal exposure was also associated with gene expression of receptors of innate immunity, including toll-like receptors (TLR) 2 and 4 and CD14.

In dose-response fashion, indicators of the innate immune response in the children increased along with the number of different farm animals the mother was exposed to during pregnancy. For each additional species, expression of TLR2 increased 1.16-fold, TLR4 by 1.12-fold, and CD14 by 1.10-fold.

Prenatal exposure to a farm environment is associated with decreased atopic sensitization and allergic symptoms. Being exposed to an environment rich in microbial compounds during pregnancy may influence priming of the immune response in offspring. The mechanism by which maternal exposures affect the offspring is unknown, as is the role of continued exposure or other factors later in life.

**COMMENT:** *These European researchers used questionnaire data from 8,263 families in the Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Life Style (PARSIFAL) study and analyzed serum from a subset of children. Both atopic sensitization, measuring IgE, and innate immunity, measuring gene expression of TLR2, TLR4, and CD14 were inversely correlated to the child's mother's exposure to farm animals during pregnancy. These data suggest that maternal exposure to microbes during pregnancy may determine the priming of the child's immune response. Could the mother's exposure to farm animals be even more critical than the child's?*
*S. M. F.*

*Ege MJ, Bieli C, Frei R, et al: Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children.*
**J Allergy Clin Immunol**. 2006;117:817-823. ♦♦

## Vocal Cord Dysfunction: Beyond the Classic Vignette

VOCAL cord dysfunction (VCD) has been described as a somatization disorder associated with high utilization of inpatient health care resources. Ambulatory patients with VCD appear to have a relatively benign presentation, but are still perceived as being high consumers of medical resources. This study compared the resource utilization of patients presenting with VCD vs moderate to persistent asthma.

The study included 25 patients with VCD seen at the authors' pulmonary disease clinic over a 2-year period. All met laryngoscopic criteria for VCD--ie, inappropriate adduction of the vocal cords during respiration. The VCD patients were matched for age and sex to 25 controls with moderate persistent asthma.

The VCD patients were 13 males and 12 females, mean age 40.8 years. In the year before diagnosis, ➤➤

patients with VCD made a total of 477 physician visits, compared with 267 visits for the asthmatic controls. This was equivalent to one physician visit every 19 days per patient with VCD. Patients in the VCD group also had more subspecialty visits than the asthmatic patients, 277 vs 118; and more pulmonary visits, 72 vs 30. There was no significant difference in urgent care visits, hospitalizations, or total prescriptions.

Ambulatory patients with undiagnosed VCD have high medical resource utilization, even compared to patients with moderate persistent asthma. Frequent physician visits may be a useful marker of VCD. The authors call for further studies of strategies for effective diagnosis and management of VCD.

**COMMENT:** *Vocal cord dysfunction is a syndrome that is often assumed to present only in dramatic fashion in women and girls with significant psychiatric impairment. This retrospective case-control study highlights the fact that many VCD patients are male. Compared with asthma patients, VCD patients do not have higher emergency room and inpatient resource utilization. Patients with VCD do have significantly more total physician visits.*
*S. A. T.*
*Mikita J, Parker J: High levels of medical utilization by ambulatory patients with vocal cord dysfunction as compared to age- and gender-matched asthmatics.* **Chest**. 2006;129:905-908. ♦♦

## More on Ciclesonide in Severe Asthma

TO reduce systemic adverse events in patients with persistent asthma, inhaled corticosteroids (ICS) may be substituted for oral corticsteroids (OCS), when possible. Ciclesonide, a new ICS being developed for use in persistent asthma, has a favorable therapeutic and safety profile that may make it appropriate as OCS-sparing therapy. This randomized controlled-trial examined the effects of ciclesonide on oral prednisone requirement and safety outcomes in patients with severe, persistent asthma.

The multicenter trial included 141 adult and adolescent patients with severe, persistent, OCS-dependent asthma. They were randomly assigned to receive ciclesonide, 640 or 1,280 µg/d or placebo via metered-dose inhaler. Prednisone dosage was stepped down according to defined criteria, based on the results of weekly evaluations. The effects of ciclesonide on use of oral prednisone were assessed, along with effects on the hypothalamic-pituitary-adrenal (HPA) axis and on pulmonary function.

After 12 weeks, oral prednisone dose was decreased by 47% in the ciclesonide 640 µg/d group and by 63% in the ciclesonide 1,280 µg/d group. In contrast, OCS dose increased by 4% in the placebo group. About 30% of patients assigned to ciclesonide were able to stop taking prednisone, compared with 11% in the placebo group. Ciclesonide was associated with significant improvement in $FEV_1$, with no increase in adverse events compared with placebo.

Inhaled ciclesonide reduces OCS requirements while maintaining disease control in patients with severe, persistent asthma. Reductions in prednisone dosage are associated with less HPA-axis suppression. With further study, ciclesonide may offer a useful OCS-sparing therapy for patients with persistent asthma.

**COMMENT:** *This phase 3 study demonstrates the ability of inhaled ciclesonide to substantially reduce dependence on chronic systemic corticosteroids in maintaining control of severe asthma. As the first "soft steroid" likely to gain FDA approval, ciclesonide has a variety of desirable qualities that may result in an improved therapeutic index relative to the currently available agents. Ciclesonide's commercial success, however, may depend on whether the FDA allows package insert wording suggesting that it is a "safe steroid."*
*S. A. T.*
*Bateman E, Karpel J, Casale T, et al: Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma.*
**Chest**. 2006;129:1176-1187. ♦♦

## A Prospective Look at the Side Effects of Immunotherapy

SIDE effects have a major impact on the cost-benefit ratio of allergen-specific immunotherapy (SIT). However, most data on this issue are from smaller studies, with varying estimates of the rate of systemic reactions. Findings of a clinical database on side effects of SIT are reported.

For 3 years, four Copenhagen allergy clinics prospectively reported data on every new patient receiving SIT. Reports were required when the patient started treatment, reached the maintenance dose, or experienced a systemic side effect. The analysis included data on 1,038 patients receiving SIT with 1,709 allergens for a total of 23,047 SIT injections.

By the end of the third year, 763 patients had reached their SIT maintenance dose with 1,250 allergens. This included 455 of a subgroup of 625 patients receiving a single allergen per day. Four percent of patients stopped SIT because of systemic or local reactions or worsening allergy symptoms. The percentage of patients reaching the maintenance dose with no side effects was 77% for those treated with one allergen per day and 71% for those treated with more than one allergen per day. This outcome was least likely for patients receiving grass allergen, followed by cat and house dust mite

Three hundred forty-one patients had a total of 582 systemic side effects. Seventy-eight percent were mild, grade 2 reactions, while 20% were grade 3 reactions and 1% were grade 4 reactions. Grass was the allergen most likely to cause systemic side effects; all severe reactions involved timothy. The risk of side effects was unrelated to patient sex or history of asthma.

This prospective study finds a varying risk of side effects in patients receiving SIT, depending on the allergen used. The findings lend insight into rates of side effects, including differences in the side effect pro-➤➤

files of different allergens. Multicenter studies, possibly including an electronic clinical database, are needed to provide more efficient monitoring of side effects of SIT.

**COMMENT:** *Optimizing the therapeutic index of allergen SIT is challenging, yet it is a fundamental responsibility of practicing allergists. This Danish study reports carefully collected prospective safety data from more than 23,000 immunotherapy injections. There were several notable findings, including that neither gender nor a diagnosis of asthma influenced the frequency of systemic reactions. There were, however, striking differences in the reaction profiles for different allergens. For example, grass pollen was the most likely to cause systemic reactions and accounted for the largest proportion of severe reactions. The authors propose the creation of an internet database to register all routine injections in allergy practices. An accompanying editorial by Dr. A.J. Frew asks, "How safe is safe?"* (**Clin Exp Allergy**. 2006;36:251-253.)
*S. A. T.*
*Winther L, Arnved J, Malling H-J, et al: Side-effects of allergen-specific immunotherapy: a prospective multicentre study.*
**Clin Exp Allergy**. 2006;36:254-260. ♦♦

## "Green Acres Is the Place for Me!"

INFORMATION is needed not only on risk factors, but also on factors protecting against the development of allergic disease in children. Rates of allergic disease and sensitization were compared for children from farm, anthroposophic, and reference families, including identification of protective factors.

Part of the Prevention of Allergy Risk Factors for Sensitization In children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) project, the cross-sectional study included nearly 15,000 children, aged 5 to 13 years, from five European countries. Allergic disease outcomes and associated factors were compared for children growing up on family farms; children attending Steiner schools, whose families follow an anthroposophic lifestyle (limited use of antibiotics and vaccinations, among other features), and children from reference families.

Compared with reference children, farm children had lower rates of current rhinoconjunctivitis, adjusted odds ratio (OR) 0.50; and atopic sensitization (based on allergen-specific IgE measurement), OR 0.53. Growing up on a farm was also associated with lower rates of wheezing, atopic eczema, and asthma. Although the anthroposophic lifestyle also appeared to have a protective effect, the differences were not as great: adjusted OR 0.69 for current rhinoconjunctivitis and 0.73 for atopic sensitization.

Growing up on a farm has a protective effect against atopic sensitization and allergic disease in children. This may be related to increased exposure to microbes associated with farm animals, although further study of specific protective factors is needed. A protective effect of the anthroposophic lifestyle is observed, but is not as strong or consistent as for farm children.

**COMMENT:** *This large study compares the prevalence of allergic diseases and sensitization from farm or anthroposophic families and their respective reference groups in five European countries. It adds to the mounting evidence that the farming lifestyle is protective against allergic disease. Living on a farm results in exposure to endotoxin, helminths, lactobacilli, and saprophytic mycobacteria, which suggests a diversity of factors may interact in inhibiting allergic disease. Though not necessarily applicable to all individuals, the key is identifying those who are likely to benefit the most.*
*E. J. B.*
*Alfvén T, Braun-Fahrländer C, Brunekreef B, et al: Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle--the PARSIFAL study.*
**Allergy**. 2006;61:414-421. ♦♦

## However, "He That Lies Down with Dogs, Shall Rise Up with Fleas!"

IN developing countries such as India, living in a rural area may be associated with a lower rate of childhood asthma. Rates of asthma and allergic disease were compared for children living in urban vs rural areas of India, including assessment of the role of animal and microbial exposures.

The study included random samples of 50 children from an urban area and 50 from a rural area of southern India. A questionnaire and home visits were used to assess the presence of allergic disease and asthma. Factors related to health, lifestyle, and environment were assessed as well, including endotoxin measurement in dust samples. The children underwent skin prick testing for common allergens.

Asthma was reported for 8% of rural vs 30% of urban children. Rhinitis was also less common in rural children, 22% vs 42%. Rates of atopic sensitization were 36% for rural children vs 58% for urban children.

Median endotoxin levels in dust samples were 6.50 and 1.27 x $10^4$ EU/$m^2$ in the rural vs urban households. On multivariate analysis, outdoor animal contact and exclusive breast-feeding through age 6 months were independently associated with reduced risk of atopic sensitization: adjusted odds ratios were 0.3 and 0.2, respectively. Children living in homes with mud floors (on which cow dung was routinely used) had a lower rate of wheezing--adjusted odds ratio 0.1.

Indian children living in rural areas have lower rates of atopy and allergic disease, compared with urban children. Factors in the household environment seem to play an important role in this protective effect, including contact with animals and mud flooring. The study has several important limiting factors, including the small sample size.

**COMMENT:** *While direct evidence supporting the hygiene hypothesis continues to accumulate, it is an unlikely explanation for the worldwide epidemic of allergic disease. In this small study with multiple* ➤➤

*variables, the chance of a type II error in data interpretation clearly exists. Nonetheless, these geographically and medically unique observations are intriguing, although it is unlikely that the cow will become sacred (or cow dung routinely used) in the United States.*
*A. M.*
*Vedanthan PK, Mahesh PA, Vedanthan R, et al: Effect of animal contact and microbial exposures on the prevalence of atopy and asthma in urban vs rural children in India.*
**Ann Allergy Asthma Immunol**. 2006;96:571-578. ♦♦

## Oral Montelukast in Acute Childhood Asthma

ACUTE asthma exacerbations are associated with elevated levels of urinary leukotrienes, which decrease as the attack resolves. Leukotriene receptor antagonists are included in recommendations for the treatment of chronic asthma, but not in acute asthma. This trial evaluated the safety and efficacy of adding oral montelukast to the initial treatment of acute asthma in young children.

The study included 50 children, aged 2 to 5 years, seen for the treatment of mild to moderate acute asthma exacerbations. All children had a clinical history of intermittent asthma for which they were receiving only short-acting $\beta_2$-agonist bronchodilators. Children were randomly assigned to initial treatment included oral montelukast 4 mg or oral placebo; both groups received inhaled salbutamol. In double-blind fashion, pulmonary index score, respiratory rate, and pulse were monitored through 4 hours after treatment.

Beginning at 90 minutes, pulmonary index score and respiratory rate were significantly lower in children receiving montelukast. The differences remained significant at 120, 180, and 240 minutes. Mean pulse rate was also lower in the montelukast group. One hour after the start of treatment, oral steroids were required by 20.8% of children assigned to montelukast vs 38.5% of the placebo group. There was no difference in hospitalization rate.

For preschool-aged children with acute asthma, adding oral montelukast to inhaled salbutamol yields greater clinical improvement, including a reduced need for oral steroid therapy. Montelukast is well-tolerated, with no evidence of adverse effects.

**COMMENT:** *The package inserts for all current leukotriene modifiers include a statement that this is a therapy for chronic management and should not be used for acute asthma. Having participated in a clinical trial of intravenous montelukast in acute asthma, I am convinced there is clinical benefit. This observation has been confirmed in published data with oral zafirlukast and oral and IV montelukast. This paper adds to the literature on acute asthma by using oral montelukast in young children with acute asthma. The hospitalization rate was no different between the placebo and montelukast groups; however, the study was too small to detect a difference. I would consider this treatment in the ER today.*
*D. K. L.*
*Harmanci K, Barkirtas A, Turktas I, et al: Oral montelukast treatment of preschool-aged children with acute asthma.*
**Ann Allergy Asthma Immunol**. 2006;96:731-735. ♦♦

## Time Will Tell: "The Anvil Lasts Longer Than the Hammer"

EXPRESSION of phosphodiesterase type 4 (PDE4) has been demonstrated in inflammatory cells involved in the pathogenesis of asthma. Roflumilast is one of several selective PDE4 inhibitors being developed as treatments for asthma and other obstructive airway diseases. Roflumilast was evaluated for safety and efficacy in the treatment of mild-to-moderate asthma.

The dose-ranging trial included 693 patients with mild to moderate asthma. During a 1- to 3-week placebo run-in period, patients had a mean $FEV_1$ of 73% predicted. They were then randomly assigned to receive oral roflumilast in a dose of 100, 250, or 500 µg once daily. Changes in $FEV_1$ and in morning and evening peak expiratory flow were compared among dose groups.

All three groups showed improvements in $FEV_1$ compared with baseline: by 260 mL at the 100 µg dose, 320 mL at the 250 µg dose, and 400 mL at the 500 µg dose. The difference between the 100 and 500 µg doses was significant. Treatment was also associated with a 3% to 6% improvement in morning peak expiratory flow. For morning as well as evening peak expiratory flow, the difference between the lowest and highest doses of roflumilast was significant. Treatment was well tolerated, although adverse events were slightly more frequent at the 500 µg dose. There were no clinically significant changes in laboratory variables.

Oral roflumilast improves $FEV_1$ in patients with mild-to-moderate asthma in dose-related fashion. The pulmonary function improvements are of similar magnitude to those achieved with other asthma treatments. Further study is needed to compare this oral PDE4 inhibitor with other anti-inflammatory medications.

**COMMENT:** *The need for additional therapy of asthma is evidenced by the lack of patient acceptance of some of our inhaled regimens and the evidence of unmet need perceived by patients. This study finds a convincing, albeit shallow, dose response with roflumilast. The results show an increase in $FEV_1$ with increased dose, but no such difference in symptom scores. The role of such an oral, relatively safe therapy will be debated until a long-term, head-to-head trial is performed with low-dose inhaled steroids or leukotriene modifiers. In the interim, physicians will have to make their best guess as to where selective phosphodiesterase inhibitors fit into our therapeutic regimen. See also the accompanying editorial by Dr. Lipworth.* (**Ann Allergy Asthma Immunol** 2006;96:640-642.) ➤➤

*D. K. L.*
*Bateman ED, Izquierdo JL, Hamest U, et al: Efficacy and safety of roflumilast in the treatment of asthma.*
**Ann Allergy Asthma Immunol**. 2006;96:679-686. ♦♦

## "Whatsoever Was the Father of a disease, an Ill Diet Was the Mother"

THERE are few population-based data on the rates of food hypersensitivity, whether allergic or nonallergic, among infants. This study assessed the incidence of food hypersensitivity--as reported by parents and as confirmed by objective testing--among children during the first year of life.

The birth cohort study included 969 infants born on the Isle of Wight, United Kingdom, during a 1-year period. Parents provided information on feeding practices and symptoms of atopy when the children were 3, 6, and 9 months old. Medical examination and skin prick tests were performed at age 12 months. Food challenges were performed in infants reported to have adverse reactions to foods.

Rates of parent-reported adverse food reactions were 14.2% at age 3 months, 9.1% at 6 months, and 7.2% at 9 months. Skin prick tests found that 1.0% of infants were sensitized to aeroallergens and 2.2% to food allergens. Open food challenges led to the diagnosis of food hypersensitivity in 1.4% of infants between 6 and 9 months and 2.8% between 9 and 12 months. Rates of diagnosis by double-blind, placebo-controlled food challenge (DBPCFC) were 0.9% and 2.5%, respectively. Overall throughout the first year of life, the diagnosis of food hypersensitivity was confirmed in 3.6% of infants by oral food challenges and in 1.5% by DBPCFC. Including patients with a clear history not requiring food challenge, the cumulative incidence of food hypersensitivity was 4.0%.

One-fourth of parents report food hypersensitivity in infants during the first year of life. However, only 1 in 8 of these infants are diagnosed as having food hypersensitivity on the basis of oral food challenges. The authors urge the need for accurate diagnosis of food hypersensitivity in infants to avoid unnecessary dietary restrictions.

**COMMENT:** *There are several studies of the prevalence of food allergy in infants, but few have prospectively and objectively studied children with parent-reported food "hypersensitivity." This study was conducted prospectively in a cohort of 969 British children and incorporated history, skin prick testing, open food challenges, and then DBPCFC. The highest rates of parent-reported symptoms occurred in the first 3 months of the child's life, but many were gastrointestinal and were probably nonallergic. Interestingly, on challenge, egg (not milk) accounted for the vast majority of immediate/early reactions (at 0 to 5 hours; eg, hives), and milk for most delayed reactions (eg, diarrhea more than one day after challenge).*
*R. J. M.*

*Venter C, Pereira B, Grundy J, et al: Incidence of parentally reported and clinically diagnosed food hypersensitivity in the first year of life.*
**J Allergy Clin Immunol**. 2006;117:1118-1124. ♦♦

CITING a possible increase in allergy risk, current guidelines recommend waiting at least 4 months before introducing solid foods to the diet of infants. The research supporting this recommendation was evaluated by meta-analysis.

The literature was searched for studies of the effects of early solid feeding on the risks of allergic disease. Thirteen studies were identified, assessing outcomes such as eczema, asthma, wheezing, and food allergy. Just one was a randomized trial. Five studies suggested that early solid feeding was associated with an increased risk of eczema. In one report, the increased risk of eczema was still present 10 years later. However, another four studies found no effect on eczema risk.

There was one result suggesting an increased risk of pollen allergy with early feeding. No significant associations were noted for any of the other outcomes evaluated, including persistent asthma, persistent food allergy, allergic rhinitis, or animal dander allergies.

The available data provide no convincing evidence of any association between early introduction of solid foods and allergic disease risk. The findings have implications for clinical guidelines and parent counseling. The authors note the deficiencies of the research in this area.

**COMMENT:** *This meta-analysis identified 13 studies of early introduction of solid foods that were randomized controlled trials, case-control studies, or cohort series. Five studies found a positive association between early solid feeding and eczema, while four found no such association. The bottom line is that evidence linking early solid feeding and the development of allergic disease is inconsistent and conflicting. We should probably revise our advice to parents of infants regarding strict avoidance of all solids during the first 4 months.*
*S. M. F.*
*Tarini BA, Carroll AE, Sox CM, Christakis DA: Systemic review of the relationship between early introduction of solid foods to infants and the development of allergic disease.*
**Arch Pediatr Adolesc Med**. 2006;160:502-507. ♦♦

## Maybe By Asking the Impossible, We Obtain the Possible!

EDUCATION in asthma self-management is a major priority for children with asthma and their families. The development and evaluation of an emergency department (ED)-based asthma education program are reported.

The Hawaii Child Asthma Research to Elevated Standards (CARES) program was implemented at four hospitals serving diverse communities in and➤➤

around Honolulu. An initial data collection phase included an educational program for ED and community-based health care professionals, focusing on compliance with asthma care guidelines, use of the asthma chronic severity classification system, and the importance of long-term controller medications and written asthma action plans. This was followed by an educational intervention for patients and families during ED visits for asthma. The intervention included a temporary written asthma action plan, based on the child's chronic severity classification and emphasizing the need for long-term controller medication and prompt follow-up with the primary care physician (PCP).

Evaluation and follow-up included 706 patients seen during phase I and 353 during phase II. At the time of the ED visit, most patients were not using long-term controller medications and did not have a written asthma action plan. The percentage of patients with a written action plan increased from 13.6% at admission to 91.2% at discharge. The intervention was also associated with a significant increase in the daily use of controller medications by patients with persistent asthma.

The Hawaii CARES project demonstrates that asthma education can be effectively delivered in the ED setting. The project highlights the importance of having ED physicians prescribe long-term asthma controller medications and provide temporary asthma action plans. In asthma and other chronic diseases, ED physicians can shift from providing acute care only to providing chronic care in partnership with community physicians.

**COMMENT:** *Some of the important issues for the child treated in the emergency department for acute asthma are timely follow-up with the child's PCP or a new PCP, continuation or start of an asthma controller medication, and re-emphasis or start of an asthma management plan. The authors report on a comprehensive community plan in Hawaii, which allowed the emergency physician to write prescriptions for controller medications and "temporary" written asthma management plans, until the child could be seen by a PCP--preferably within a day. Three months' follow-up of children with persistent asthma indicated that the regular use of asthma controller medications had doubled, from 18% to 36%.*
*J. A. A.*

*Boychuk RB, DeMesa CJ, Kiyabu KM, et al: Change in approach and delivery of medical care in children with asthma: results from a multicenter emergency department educational asthma management program.*
**Pediatrics**. 2006;117:S145-S152. ♦♦

## More on Probiotics

FOOD sensitization may be associated with the development of atopic dermatitis (AD) in young children. Previous studies have suggested that probiotic treatment can reduce the severity of AD in infants in young children; one study found significant improvement only in atopic children. A combination of probiotics was evaluated in children with established AD.

The randomized controlled trial included 59 atopic children with current dermatitis. One group received the probiotics *Lactobacillus rhamnosus* and *Bifidobacteria lactis*, 2 x $10^{10}$ colony forming units/g, in the form of a powder to be mixed with food or water. The other group received placebo. Treatment continued for 4 weeks. Effects on AD severity were evaluated using the SCORing Atopic Dermatitis (SCORAD) instrument.

After adjustment for baseline SCORAD scores, there was no significant improvement in AD after 12 weeks of probiotic treatment. However, there was a significant benefit of probiotics among food-sensitized children: SCORAD geometric mean ratio 0.73. There was no group difference in antibiotic use during the study.

Among children with AD, probiotic treatment appears to reduce disease severity only among patients sensitized to foods, not to environmental allergens. Although further study is needed, the benefits of probiotics in AD may reflect local gastrointestinal effects.

**COMMENT:** *Probiotics, or "health-promoting bacteria," are hypothesized to help prevent or improve AD by promoting gut mucosal immunologic tolerance to nonbacterial antigens. In this study, daily oral administration of probiotics resulted in minor improvement in eczema only in food-sensitized children with AD. Although data are accumulating regarding the efficacy of probiotic therapy, it remains to be seen whether this approach will gain widespread acceptance.*
*S. A. T.*

*Sistek D, Kelly R, Stanley T, et al: Is the effect of probiotics on atopic dermatitis confined to food sensitized children?*
**Clin Exp Allergy**. 2006;36:629-633. ♦♦

# CLINICAL TIDBITS

## Azathioprine for AD

OPEN trials have suggested that azathioprine might be an effective treatment for moderate to severe atopic eczema. This randomized, placebo-controlled trial evaluated the clinical benefits of azathioprine in 89 patients who continued to have active atopic eczema, despite optimum topical therapy. Azathioprine dosing was adjusted according to thiopurine methyltransferase (TMPT) activity, accounting for the effects of *TMPT* polymorphism on drug toxicity. Study completion rate was 86%. Mean disease activity score improved by 37% with azathioprine vs 20% with placebo. Azathioprine was well-tolerated, despite drug hypersensitivity in two patients. Azathioprine is a clinically useful treatment for moderate to severe atopic eczema. Basing dosage on TMPT activity limits toxicity while preserving treatment effectiveness.

**COMMENT:** *This study indicates that azathioprine as systemic monotherapy is an effective and well-tolerated adjunctive therapy for moderate and severe* ➤➤

*atopic eczema. By measuring TPMT activity, these authors were able to largely avoid severe azathioprine toxicity and maximize dosing. The study permitted continued use of topical steroids and emollients. Further studies will be needed to assess azathioprine's effectiveness compared to a topical immunomodulator such as tacrolimus.*
*E. J. B.*
*Meggitt SJ, Gray JC, Reynolds NJ: Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial.*
**Lancet**. 2006;367:839-846. ♦♦

## One Bad Apple Does Not Spoil the Lot!

ALLERGIC reactions to apples are common, but little is known about the allergenicity of different varieties of this popular fruit. The antigenic and allergenic profiles of 10 apple varieties were compared, including determination of Mal d 3 content. On sodium dodecyl sulfate-polyacrylamide gel electrophoresis, there were significant differences in antigenic profile. All specimens showed a 9 kDa band corresponding to Mal d 3. On skin prick testing in patients with oral allergy syndrome, the apple variety with the highest content of this protein yielded the largest wheals. Different apple varieties differ significantly in antigenicity and allergenicity. The "Starking" variety appears to be most allergenic, and may be the best choice for use in diagnostic extracts.

**COMMENT:** *While patients have recognized clinical apple sensitivity for decades, we have had precious little information on the relative antigenicity of different varieties. It appears that while there is substantial antigenic variation, there are no "safe apples!"*
*A. M.*
*Carnés J, Ferrer A, Fernández-Caldas E: Allergenicity of 10 different apple varieties.*
**Ann Allergy Asthma Immunol**. 2006;96:564-570. ♦♦

## Guidelines May Misrepresent Young Asthmatics

THE National Asthma Education Prevention Program (NAEPP) guidelines for asthma severity classification are based on expert opinion, not research evidence. This study evaluated the performance of the NAEPP criteria in classifying asthma severity in an inner-city population of children. Guideline severity was compared with asthma morbidity in the previous year. The retrospective analysis included 826 asthmatic children evaluated at a mobile asthma clinic in Southern California. Age was 2 years or younger in 10.8% of children, 3 to 5 years in 26.9%, and older than 5 years in 62.3%. Boys accounted for 60.5% of patients, while 80.9% were Hispanic. Severity classification was mild intermittent in 34.4%, mild persistent in 10.2%, moderate persistent in 31.5%, and severe persistent in 24.0%. Severity based on NAEPP criteria was clearly related to asthma morbidity. However, the relationship between health care utilization and severity was only borderline significant for children aged 3 to 5, and was nonsignificant for children aged 2 or younger. The NAEPP guidelines may underestimate asthma severity in children under age 5. Asthma morbidity in the previous year may be an important consideration in this age group.

**COMMENTS:** *When the mother asks the asthma consultant if her 3-year-old, happily playing in the office, has asthma, the answer may not be simple. At this age, episodes of respiratory difficulty usually are intermittent and seasonal. The consultant often has to rely on other people's observations and on treatment trials. The child is too young for pulmonary function testing. Perhaps the most objective information is evidence of repeated episodes of respiratory problems, ideally documented by examination by a medical professional, that respond favorably to a nebulized bronchodilator. I agree with the authors of this California study that asthma management decisions for younger children should be made on the basis of the previous year's experiences, not just "day and night time symptoms."*
*J.A.A.*
*Galant SP, Morphew T, Amaro S, Liao O: Current asthma guidelines may not identify young children who have experienced significant morbidity.*
**Pediatrics**. 2006;117:1038-1045. ♦♦

## Reduced Histamine Degradation in AD

PREVIOUS studies have suggested that non-IgE-mediated food intolerance caused by histamine may be related to diminished histamine degradation, reflected by reduced diaminoxidase activity. Symptoms of histamine intolerance (HIT) and diaminoxidase levels were assessed in 162 patients with actopic eczema (AE), 124 non-AE patients with HIT, and 85 healthy controls. Patients with AE were more likely than controls to have reduced serum diaminoxidase levels, leading to HIT symptoms such as chronic headache, premenstrual headache and dysmenorrhea, and intolerance of histamine-rich foods and alcohol. Reduced diaminoxidase levels were unrelated to levels of vitamin B6, copper, or zinc. Seventeen AE patients with low diaminoxidase and HIT symptoms had significant clinical improvement on a histamine-free diet and oral antihistamine treatment. For some patients with AE, high histamine level and reduced histamine degradation capacity may affect the clinical course. The findings have implications for the management of AE patients with symptoms of HIT.

**COMMENTS:** *Some individuals with atopic eczema don't have detectable allergies. This article suggests that a subgroup of such patients has reduced histamine degradation capacity, based on reduced diaminox-*➤➤

*idase activity. Improvement may be aided by a low-histamine diet.*
*R. J. M.*
*Maintz L, Benfadal S, Allam J, et al: Evidence for a reduced histamine degradation capacity in a subgroup of patients with atopic eczema.*
**J Allergy Clin Immunol**. 2006;117:1106-1112. ♦♦

## C1-Inhibitor Concentrate in Hereditary Angioedema

GIVEN intravenously by health care professionals, C1-inhibitor concentrate offers effective treatment and prevention of angioedema attacks caused by C1-inhibitor deficiency. An experience with self-administration of C1-inhibitor concentrate in patients with hereditary or acquired C1-inhibitor deficiency is reported. After training, all patients were able to perform self-treatment with C1-inhibitor concentrate; the technical failure rate was under 2%. In 31 patients receiving on-demand treatment, time to initiation of relief from attacks was shortened by about 2 hours and time to complete resolution by 8 hours. In 12 patients using prophylactic C1-inhibitor, the monthly attack rate decreased from 4.0 to 0.3. Self-treatment with intravenous C1-inhibitor concentrate is of benefit for the prevention or treatment of severe angioedema attacks caused by C1-inhibitor deficiency. This is a feasible option to facilitate rapid treatment of attacks or to prevent angioedema in patients with very frequent attacks.

**COMMENT:** *Not only did prompt self-administration of C1-esterase inhibitor concentrate reduce the severity and duration of attacks in patients with hereditary angioedema, regular weekly treatment provided prophylaxis against future attacks. Although not specifically addressed by the current study, this therapy could provide significant improvement in the quality of life for these patients.*
*S. M. F.*
*Levi M, Choi G, Picavet C, Hack CE: Self-administration of C1 inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency.*
**J Allergy Clin Immunol**. 2006;117:904-908. ♦♦

## Asthma Prevalence in the U.K.

STUDIES in some European countries suggest that recent increases in childhood asthma have leveled off. A U.K. survey was performed to assess changes in childhood asthma prevalence over the past 30 years. Results of a 2003 survey of 12-year-old schoolchildren in South Wales were compared with the findings of surveys performed in 1973 and 1988. Prevalence of reported wheezing increased from 9.8% in 1973, to 15.2% in 15.2%, and 19.7% in 2003. Rates of reported asthma were 5.5%, 12.0%, and 27.3%. Wheeze attributed to running also increased. The prevalence of exercise-induced bronchoconstriction, which increased between 1973 and 1988, decreased in 2003. In contrast to reports from other European countries, the prevalence of asthma continues to increase in Wales.

**COMMENT:** *A survey of 12-year-old children was conducted in schools in South Wales, where similar surveys were performed in 1973 and 1988. The investigation included a parental questionnaire and an exercise challenge test. The study showed that the prevalence of asthmatic symptoms has continued to rise since 1988. This conflicts with studies in Italian, Swiss and German children, in whom asthma prevalence has stabilized. The decline in exercise-induced asthma was attributed to better control of underlying asthma.*
*E. J. B.*
*Burr ML, Wat D, Evans C, et al: Asthma prevalence in 1973, 1988, and 2003.*
**Thorax**. 2006;61:296-299. ♦♦

## REVIEWS OF NOTE

**COMMENT:** *The hygiene hypothesis, first proposed 15 years ago, has led to many promising avenues of research into the genesis of atopy. However, as yet there is still no unifying hypothesis to explain all the observations. Perhaps that is because such a hypothesis would have to account for multiple simultaneous variables, such as viral and bacterial infections, genotypic and phenotypic traits, as well as environmental exposures.*
*R. J. M.*
*Bloomfield SF, Stanwell-Smith R, Crevel RWR, Pickup J: Too clean, or not too clean: the Hygiene Hypothesis and home hygiene.* **Clin Exp Allergy**. 2006;36:402-405.
*AND*
*Schaub B, Lauener R, von Mutius E: The many faces of the hygiene hypothesis.*
**J Allergy Clin Immunol**. 2006;117:969-977. ♦♦

**COMMENT:** *There is some interest in the development of sublingual immunotherapy (SLIT), primarily based on the purported ease of administration and safety. However, data on which to base a comparison with conventional subcutaneous immunotherapy (SCIT) are severely lacking. This exhaustive review presents the existing data on efficacy and safety of SLIT. It underscores the abundance of unanswered questions about such basic criteria as optimal dosing and intervals, patient compliance (or lack thereof) with unsupervised home therapy, and dose adjustments for reactions and gaps. There are few studies in patients with asthma or using multiple antigen mixtures. There is no FDA-approved product for SLIT. You will be surprised to learn that, as well as can be determined, "severe reactions" were more frequent in the combined SLIT studies than "near fatal" reactions in SCIT. There is much* ➤➤

*more to be learned about SLIT before it should be used.*
*R. J. M.*

*Cox LS, Linnemann DL, Nolte H, et al: Mechanisms of asthma and allergic inflammation.*
**J Allergy Clin Immunol**. 2006;117:1021-1035. ♦♦

**COMMENT:** *Other than allergic bronchopulmonary aspergillosis, understanding of the role of fungi in severe asthma is a work in progress. This review proposes that fungal sensitization may be more pervasive in severe asthmatics.*
*B. E. C.*

*Denning DW, O'Driscoll BR, Hogabom CM, et al: The link between fungi and severe asthma: a summary of the evidence.*
**Eur Respir J**. 2006;27:615-626. ♦♦

**COMMENT:** *This review gives a better understanding regarding the cellular mechanisms and clinical implications of the interaction between inhaled corticosteroids and the airway vasculature.*
*B. E. C.*

*Horvath G, Wanner A: Inhaled corticosteroids: effects on the airway vasculature in bronchial asthma.*
**Eur Respir J**. 2006;27:172-187. ♦♦

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