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

Volume 12, Number 4 July - August 2010

EFFECTS OF VITAMIN D ON ALLERGIC DISEASE

Don't Let the Sun Go Down

PATIENTS vary in their clinical responsiveness to inhaled corticosteroids (ICS); steroid resistance may lead to suboptimal asthma control. Based on recent studies, lower levels of vitamin D could affect the glucocorticoid response in asthma. This study evaluated the effects of vitamin D status on disease phenotype and glucocorticoid response in adult asthma patients.

The study included 54 nonsmoking adults with persistent asthma: mean age 38.3 years and mean FEV_1 82.9% predicted. The relationship of serum 25-hydroxy vitamin D levels with lung function and airway hyperresponsiveness was assessed.

Asthma patients with higher vitamin D levels had better lung function. For each 1 ng/mL increase in vitamin D, there was a 22.7 mL increase in FEV_1. Vitamin D deficiency, defined as a level less than 30 ng/mL, was associated with increased AHR: methacholine PC_{20} was 1.03 mg/mL for patients with vitamin D deficiency, compared to 1.92 mg/mL in those with higher vitamin D levels.

An in vitro study examined the association between vitamin D and glucocorticoid response, measured in terms of dexamethasone-induced expression of MAP kinase phosphatase-1 (MKP-1) by peripheral blood mononuclear cells. For patients not receiving ICS, dexamethasone-induced MKP-1 expression increased along with vitamin D levels. For each 1 ng/mL increase in vitamin D, there was a 0.05-fold increase in MKP-1 expression, with no accompanying increase in interleukin-10 expression.

In patients with asthma, lower vitamin D levels are associated with lower FEV_1, increased AHR, and reduced glucocorticoid responsiveness. Measurement of vitamin D levels should be considered in adult asthma patients with a suboptimal response to ICS. For patients with vitamin D deficiency, supplementation may help to improve asthma control and treatment response.

COMMENT: *This is an important addition to our understanding of the modifying factors that cause* ➤➤

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The American College of Allergy, Asthma & Immunology expresses its appreciation to MERCK for its unrestricted grant in support of the publication of *AllergyWatch*®.

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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blunted response to glucocorticoids. A prenatal vitamin D deficiency has been reported to increase the incidence of allergic disease in offspring. The occurrence of low vitamin D levels in obese patients, who often respond poorly to ICS, deserves close attention.
B. E. C.
Sutherland ER, Goleva E, Jackson LP, et al: Vitamin D levels, lung function, and steroid response in adult asthma.
Am J Respir Crit Care Med. 2010;181:699-704. ♦♦

Low Vitamin D Linked to Increased Steroid Use in Asthmatic Children

RECENT reports have implicated lower vitamin D levels as a contributor to the increasing prevalence of asthma. However, there are few data on vitamin D levels in children with asthma, or on the asthma characteristics related to vitamin D status. This study examined the relationship between vitamin D levels and the characteristics of asthma in children.

Serum 25-hydroxyvitamin D levels were measured in 100 asthmatic children and compared with the patients' clinical characteristics. The median 25-hydroxyvitamin D level was 31 ng/mL. This was just above the 30 ng/mL cutoff for "insufficient" vitamin D levels, which were found 47% of children. Vitamin D deficiency, less than 20 ng/mL, was present in 17%.

Vitamin D levels were inversely correlated with $\log_{10}$ IgE and with the number of positive aeroallergen skin prick test responses, and positively correlated with FEV_1 percent predicted and the ratio of FEV_1 to forced vital capacity. Children with lower vitamin D levels used more inhaled and oral steroids and had a higher oral steroid dose.

In peripheral blood mononuclear cells, adding vitamin D to dexamethasone increased the induction of mitogen-activated protein kinase phosphatase 1 and interleukin-10 mRNA. An experimental model of steroid resistance showed dose-dependent suppression of cell proliferation by vitamin D plus dexamethasone, whereas dexamethasone alone did not inhibit T-cell proliferation.

In children with asthma, lower vitamin D levels are associated with increased corticosteroid use and worsening airflow limitation. This, together with the in vitro findings, suggests that vitamin D enhances the anti-inflammatory effects of corticosteroids. If the results are confirmed, the results suggest that vitamin D supplementation could be a potential steroid-sparing treatment in patients with moderate to severe asthma.

COMMENT: *Low vitamin D levels have recently been linked to asthma severity. This retrospective analysis reaffirms the inverse relationship of vitamin D levels with the use of corticosteroids for asthma and atopic sensitization. In an additional part of this report, vitamin D restored the immunosuppressive effect of dexamethasone in an in vitro model of steroid resistance. This suggests that vitamin D and sunlight may help corticosteroids work better in our pediatric asthma patients.*
S. M. F.
Searing DA, Zhang Y, Murphy JR, et al: Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use.
J Allergy Clin Immunol. 2010;125:995-1000. ♦♦

Food Allergy Risk Varies by North vs South, Summer vs Winter

LITTLE is known about the geographic distribution of anaphylaxis. One recent study suggested that the rate of prescriptions for self-injectable epinephrine is higher in the northeastern United States than in the southwest. This study looked for a similar geographic gradient in emergency ➤➤

department (ED) visits for anaphylaxis and other acute allergic reactions.

Using the National Hospital Ambulatory Medical Care Survey, the investigators identified 17.3 million ED visits for acute allergic reactions between 1993 and 2005. These accounted for 1.3% of total ED visits. The rate of visits for acute allergic reactions was 5.5 per 1,000 population in northeastern states versus 4.9 per 1,000 in southern states. On multivariate analysis, the rate was significantly higher in the northern states: odds ratio 1.31. The geographic difference was even greater, odds ratio 1.33, for food-related allergic reactions.

The higher rate of ED visits for acute allergic reactions in northern states supports the hypothesis that vitamin D may play an etiologic role in anaphylactic reactions. This effect may be most pronounced for acute reactions to food allergens. Further study of vitamin D's role in these reactions is needed.

AS the prevalence of food allergies continues to rise, some studies have suggested that vitamin D status may contribute to atopic disease risk. Vitamin D status is affected by UV-B exposure, which varies significantly between seasons. The effects of season of birth on the risk of food allergy were assessed.

A review of records from 3 Boston EDs identified 1,002 patients seen for food-related acute allergic reactions from 2001 through 2006. Of food-allergic patients who were less than 5 years old, 59% were born in fall or winter while 41% were born in spring or summer. This ratio differed significantly from that in children seen in the ED for conditions other than food allergies.

The odds of food allergy were 53% higher for children under 5 born in fall or winter compared to control children, independent of the food allergen involved or other allergic conditions. There was no similar association with season of birth among older children or adults with food allergies.

Among preschool-aged children, those born in fall or winter have a higher rate of food allergies than those born in spring or summer. Seasonal differences in UV-B exposure may underlie this association, which supports the hypothesis that vitamin D plays a pathogenetic role in food allergy.

COMMENT: *How far is the vitamin D relationship with allergy going to go? These are two more bricks in the vitamin D ziggurat suggesting that the effects of long, gray winters increase allergy and anaphylaxis as well as increase depression. Maybe movement to the Sun Belt has been partially motivated by the increasing prevalence of allergy. Who knows--perhaps a trial assessing prolonged infant exposure to bili lights or tanning beds and the development of food allergy will be next.*
D. K. L.

Vasallo MF, Banerji A, Rudders SA, et al: Season of birth and food allergy in children.
Ann Allergy Asthma Immunol 2010;104:307-313.
Rudders SA, Espinola JA, Camargo CA: North-south differences in US emergency department visits for acute allergic reactions.
Ann Allergy Asthma Immunol. 2010;104:413-416. ♦♦

Asthma and Air Pollution: "Location, Location, Location"

EXPOSURE to air pollution is known to worsen existing asthma. Because of limitations of previous research, it's still unclear whether air pollution contributes to the development of asthma and allergies. Data from a prospective birth cohort study were used to study the link between traffic-related air pollution and the development of asthma and allergies from birth to age 8.

The study included 3,863 children from the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study. Parents completed yearly questionnaires regarding asthma, hay fever, and related symptoms. At age 8, a subgroup of children underwent testing for allergic sensitization and bronchial hyperresponsiveness. Land-use regression models were used to estimate exposure to nitrogen dioxide, particulate matter ($PM_{2.5}$), and soot at each child's birth address. Exposure to traffic-related pollutants was evaluated for association with the development of asthma, allergies, and related symptoms.

The children had an annual asthma prevalence of 3% to 6%, with a 12% to 23% prevalence of asthma symptoms. The annual incidence of asthma was 6% at age 1, and between 1% and 2% from age 2 through 8. Higher estimated exposure to $PM_{2.5}$ was associated with increased incidence and prevalence of asthma, odds ratio 1.28 and 1.26, respectively; and increased prevalence of asthma symptoms, odds ratio 1.15. Similar patterns were noted for NO_2 and soot.

The associations were stronger among children still living at their birth address, who were the only ones to show a relationship between pollutant exposures and hay fever. Other disease outcomes--atopic eczema, allergic sensitization, and bronchial hyperresponsiveness--were unrelated to traffic-related pollutants.

This prospective study provides evidence that exposure to traffic-related air pollutants plays a causal role in childhood asthma. Exposure at the birth address is a good indicator of early-life exposure, although not necessarily for exposure later in childhood. More study is needed to determine which pollutant or pollutants are responsible for these effects.

COMMENT: *This study continues to support the association of asthma developed in early childhood with ambient exposures. The cohort had parent-reported physician-diagnosed asthma. An interesting finding is that the only related atopic condition was the development of allergic rhinitis in children who did not move their place of residence.*
B. E. C.

Gehring U, Wijga AH, Brauer M, et al: Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life.
Am J Respir Crit Care Med. 2010;181:596-603. ♦♦

A GROWING body of evidence suggests that neighborhood environments can have a significant impact on health outcomes. The propensity score ➤➤

method was used to look for possible neighborhood effects on the incidence of asthma.

The retrospective cohort study included children born in Rochester, Minn., from 1976 to 1979. The propensity score method was used to match children who did and did not live in census tracts facing intersections with major highways or railroads. Asthma incidence was 6.4% for children living in census tracts facing intersections, compared to 4.5% those not living in such areas. With propensity score-matched analysis, children living near highways or railroads were at significantly higher risk of asthma, compared to matched controls--hazard ratio 1.385 to 1.669, depending on the matching method used.

Neighborhood factors may have an important impact on the risk of childhood asthma. The propensity score method provides a useful tool for studying such neighborhood environment effects.

COMMENT: *The propensity score is a statistical tool used for measuring the probability of relationships. Analyzing a retrospective cohort of children, these researchers found that children living in homes facing intersections with major highways or railroads had a higher risk of developing asthma. This suggests that "location, location, location" is also an important factor for the incidence of pediatric asthma.*
S. M. F.
Juhn YJ, Qin R, Urm Sanghwa, et al: The influence of neighborhood environment on the incidence of childhood asthma: a propensity score approach.
J Allergy Clin Immunol. 2010;125:838-843. ♦♦

No Effect of *ADBR2* Genotype on Response to Salmeterol

VARIATIONS of the β_2-adrenergic receptor gene (*ADBR2*) have been linked to possible variations in clinical response to β-agonists. This raises questions as to whether asthma patients homozygous for arginine at *ADBR2* codon 16 should be treated with long-acting β-agonists. Responses to salmeterol alone or with an inhaled corticosteroid were compared in patients with differing Arg16Gly genotypes.

A total of 2,211 patients with persistent asthma who were using only as-needed albuterol underwent two sequential, open-label run-in periods: 8 weeks on as-needed albuterol and 8 weeks on as-needed ipratropium. Of these, 544 patients were divided into Arg16Gly genotype groups and randomly assigned to 16 weeks of treatment with salmeterol alone, 50 µg; or salmeterol 50 µg plus fluticasone propionate 100 µg. The change in morning peak expiratory flow (PEF) was compared between treatments for patients with Arg/Arg, Gly/Gly, and Arg/Gly genotypes.

Salmeterol alone and salmeterol/fluticasone produced similar and sustained improvements in morning PEF. Within the two treatment groups, there was no significant difference between genotypes. With salmeterol alone, the mean change in morning PEF was 19.4 L/min for Arg/Arg patients, 24.6 L/min for Arg/Gly patients, and 12.4 L/min for Gly/Gly patients. With salmeterol/fluticasone, the values were 32.6, 25.9, and 24.9 L/min, respectively. Genotype also had no effect on other measures of asthma control.

For patients with persistent asthma, treatment responses to salmeterol alone and salmeterol/fluticasone appear to be unaffected by Arg16Gly genotype. The results show no evidence of a pharmacogenetic effect of *ADBR2* polymorphisms. They also confirm the benefits of combining a long-acting β-agonist with an inhaled corticosteroid for asthma.

COMMENT: *Here are more data supporting the lack of association with* ADRB2 *polymorphisms. This adds to previous studies: the LARGE Study in adults (*Lancet *2009;374:1754-1764) and BADGER in children (*N Engl J Med. *2010;362:975-985). The accompanying editorial and authors' response (*Am J Respir Crit Care Med. *2010;181:647-654) give insight regarding this smoldering controversy.*
B. E. C.
Bleecker ER, Nelson HS, Kraft M, et al: β_2-Receptor polymorphisms in patients receiving salmeterol with or without fluticasone propionate.
Am J Respir Crit Care Med. 2010;181:676-687. ♦♦

How Do Steroids Prevent the Proasthmatic Effect of LABAs?

PATIENTS with chronic use of long-acting β_2-adrenergic agonists (LABAs) experience increased asthma morbidity related to β_2-adrenergic receptor desensitization. Combining LABAs with inhaled corticosteroids improves asthma control; thus glucocorticoids may protect against the LABA-induced effects on airway smooth muscle (ASM) contractility. A series of in vitro experiments were performed to examine the mechanisms by which glucocorticoids protect against the proasthmatic effects of LABA exposure.

Human and rabbit ASM cells were exposed to salmeterol for 24 hours, in the presence and absence of dexamethasone. In cells exposed to salmeterol alone, cyclic adenosine monophosphate and relaxation responses to isoproterenol were significantly decreased, while acetylcholine-induced contractility was increased. These effects of LABA exposure were shown to result from upregulation of phosphodiesterase 4 (PDE 4) activity, and were prevented by dexamethasone pretreatment.

The upregulation of PDE4 expression in salmeterol-exposed ASM cells was found to result from activation of the mitogen-activated protein kinases extracellular signal-regulated kinases 1 and 2 (ERK1/2), which was prevented by dexamethasone. These inhibitory effects of dexamethasone could be prevented by gene silencing, or by drugs that blocked dexamethasone-induced expression of mitogen-activated protein kinase phosphatase 1 (which deactivates ERK1/2 signaling).

The findings lend new insights into the mechanism by which inhaled corticosteroids prevent the decreased asthma control associated with chronic LABA therapy. Interventions targeting this mechanism could lead ➤➤

to the development of new treatments to improve asthma control.

COMMENT: *Although we know that corticosteroids have a protective effect on β_2 receptors in asthmatic smooth muscle, these researchers further characterized the mechanism of this effect. They found that the proasthmatic effect of LABA exposure was attributed to upregulated PDE4. This was ablated by dexamethasone by via upregulation of mitogen-activated protein kinase phosphatase 1, which suppresses ERK1/2. The take-home message for clinicians is that there may be targeted interventions on the horizon that can block this β_2 proasthmatic effect, and that may have fewer side effects than corticosteroids.*
S.M.F.
Nino G, Hu A, Grunstein JS, Grunstein MM: Mechanism of glucocorticoid protection of airway smooth muscle from proasthmatic effects of long-acting β2-adrenoceptor agonist exposure.
J Allergy Clin Imunol. 2010;125:1020-1027. ♦♦

High eNO Marks 'Worrisome' Severe Asthma Phenotype

IN mild to moderate asthma, high exhaled nitric oxide (eNO) is a marker of increased airway inflammation, that decreases in response to anti-inflammatory therapy. In contrast, little is known about the relationship between eNO and airway inflammation in patients with severe asthma, who have a poor response to conventional therapies. This study evaluated the use of eNO in severe asthma to identify patients with a more reactive, at-risk asthma phenotype.

The study included 446 patients with asthma and 49 healthy controls, drawn from the Severe Asthma Research Program. Asthma was classified as severe in 175 patients and nonsevere in 271. Associations between eNO and asthma phenotype were assessed, including the asthma characteristics of airway inflammation, airflow limitation, hyperinflation, hyperresponsiveness and atopy.

Mean eNO was 42 ppb in the severe asthma group and 43 ppb in the severe asthma group. In both groups, about 40% of patients had high eNO of greater than 35 ppb, even though corticosteroid use was greater in the patients with severe asthma. Regardless of severity group, the presence of high eNO in asthma patients was associated with increased airway reactivity, increased sputum eosinophils, and greater hyperinflation. At the same time, patients with high eNO had lower symptom awareness. Patients with severe asthma and high eNO had the greatest levels of airflow obstruction and hyperinflation and the most frequent use of emergency care.

Measurement of eNO provides a definition of asthma phenotype that is independent of current asthma severity classifications. This, along with other biologic markers, could one day provide a useful cumulative index for definition of asthma severity. Among patients with severe asthma, high eNO appears to be associated with a particularly "reactive and worrisome" phenotype.

COMMENT: *This group of patients with severe asthma and eNO greater than 35 ppb was characterized by greater airflow obstruction, hyperinflation, more frequent use of emergency care and oral corticosteroid. These characteristics may help identify a group of patients who have poor perception of early warning symptoms. They may also lead to identification of patients who need alternate treatment strategies.*
B. E. C.
Dweik RA, Sorkness RL, Wenzel S, et al: Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma.
Am J Respir Crit Care Med. 2010;181:1033-1041. ♦♦

Multiple Epinephrine Doses for Food Allergic Reactions

SOME reports have suggested that children with a history of food-related anaphylaxis should carry more than one vial of epinephrine. Compliance with this and other recommendations was evaluated in a multicenter sample of children with anaphylactic reactions to foods.

The study included 605 children receiving emergency department (ED) care for food-related acute allergic reactions from 2001 through 2006. Sixty-two percent of the patients were boys; the median age was 5.8 years. Peanuts were the most commonly involved food, 23% of patients; followed by tree nuts, 18%, and milk, 15%. Diagnostic criteria for food-related anaphylaxis were met by 52% of patients.

Of the children with anaphylaxis, 31% received a single dose of epinephrine before arriving in the ED, while 3% received more than one dose. Treatment in the ED included antihistamines in 59% of patients, corticosteroids in 57%, and epinephrine in 20%. Overall, 44% of the children received epinephrine sometime during their episode of anaphylaxis. The percentage receiving more than one dose of epinephrine was 6% overall and 12% of those receiving any epinephrine.

Older children and those transferred from other hospitals were more likely to receive multiple doses of epinephrine. The rate of hospital discharge was 88%. At the time of ED discharge, 43% of the children received a prescription for self-injectable epinephrine while 22% were referred to an allergist.

Less than half of children seen in the ED for food-related anaphylaxis receive epinephrine, and only a small percentage receive multiple doses of epinephrine. The findings support the recommendation that children at risk of anaphylactic reactions to foods carry two doses of self-injectable epinephrine. The authors call for further study to provide better and more consistent outcomes of care for children with food-related anaphylaxis and to evaluate their long-term outcomes.

COMMENT: *What seems to be a commonsense approach followed by many allergists--prescribing more than one dose of epinephrine for food-allergic patients--actually has relatively little supporting data in the existing literature. Thus, this study adds nec-*➤➤

essary information to address our current practice.

I am startled, though, by the finding here that only 1 in 5 children had received a recommendation to see an allergist upon ED discharge (not known, though, if some had been previously evaluated). And that slightly less than half were prescribed epinephrine! A high percentage of pediatric food reactions in this retrospective study occurred at home. Extrapolating from the data, these home reactions necessarily include a proportion of patients in whom a specific food allergen was previously identified. Allergist/immunologists remain uniquely qualified to address food allergies, and opportunities for education are, sadly, being missed.

K. R. M.

Rudders SA, Banerji A, Corel B, et al: Multicenter study of repeat epinephrine treatments for food-related anaphylaxis.

Pediatrics. 2010;125:e711-718. ♦♦

Newborn Screening for SCID

PARTICULARLY with the potential to improve patient outcomes through hematopoietic stem cell transplantation, there is interest in ways of identifying children with severe combined immunodeficiency (SCID) before they become symptomatic. The authors performed a systematic review of the research evidence on newborn screening and treatment of SCID.

The review identified 26 eligible articles regarding screening and early treatment for SCID. The publications included cohort studies, case-control studies, case series, and a cost-effectiveness analysis. The results of several small studies suggested that screening for SCID is possible, although none addressed the feasibility of population-based newborn screening. No studies looked at the potential harms of newborn screening. In interviews with experts, the researchers learned that two states had instituted pilot screening programs.

Large case series reported improved outcomes in children receiving early hematopoietic stem cell transplant, compared to later treatment. No firm conclusions could be drawn regarding the need for donor-recipient matching or pretransplant chemotherapy. The lone study of the issue suggested that newborn screening for SCID was likely to be cost-effective, at a threshold of $100,000 per quality-adjusted life-year.

Despite limitations, the available data support the possibility of newborn screening for SCID. Ongoing pilot programs will provide important data on the feasibility and effectiveness of newborn screening for SCID.

COMMENT: *In the March-April, 2010, issue of* AllergyWatch, *articles about SCID and progress toward universal neonatal screening were highlighted. Since that publication, personal communication with Dr. John Routes at the Medical College of Wisconsin finds that SCID screening programs have been successfully launched--first in Wisconsin and more recently in Massachusetts. Furthermore, in January of this year, a recommendation for nationwide newborn screening for SCID was submitted to the U.S. Secretary of Health and Human Services (HHS), by the Advisory Committee on Heritable Disorders.*

The systematic review summarized here contains much of the data presented to that committee, summarizing relevant articles published through October 2008. More evidence in support of universal screening has been obtained since then. Shortly before this printing, the proposal for nationwide newborn screening for SCID was accepted by HHS!

K. R. M.

Lipstein EA, Vorono S, Browning MF, et al: Systematic evidence review of newborn screening and treatment of severe combined immunodeficiency.

Pediatrics. 2010;125:e1226-e1235. ♦♦

Peanut Allergy--An Early Marker for Asthma Severity?

MORE than one-third of children with food allergies also have asthma, and food allergy is a risk factor for increased asthma morbidity. Milk and peanut allergy have previously been linked to asthma morbidity in young children. This study evaluated peanut allergy as a marker of asthma morbidity beyond age 3.

The investigators reviewed the records of 160 children with asthma and food allergy treated at a large children's hospital. The presence of peanut allergy was defined according to specific, validated criteria. Asthma morbidity beyond the age of 3 years--;including frequency of systemic steroid use and asthma hospitalizations--;was compared for children with and without peanut allergy.

In this group of children with asthma, 28.75% also had peanut allergy. Peanut-allergic children were more likely to have atopic dermatitis, to be sensitive to specific aeroallergens, and to be allergic to other foods, especially milk. The presence of peanut allergy was significantly associated with increased asthma morbidity. After adjustment for covariates, peanut-allergic children were 1.59 times more likely to receive systemic steroids and had a 2.32-times greater risk of asthma hospitalization.

Among school-aged children with asthma, peanut allergy may be a marker of increased asthma morbidity. These children may benefit from early prevention and intervention, including instructing parents about tangible risk factors for exacerbations.

COMMENT: *Previous literature highlights the risk of asthma development in young children with egg allergy. Now, here is further evidence that food-allergic children will have higher morbidity from their asthma. What is surprising here is that peanut allergy, not egg allergy, seems to impart the highest relative risk of all variables assessed. The retrospective nature of the study may have introduced selection bias, but despite this concern, the results remain provocative.*

K. R. M.

Simpson AB, Yousef E, Hossain J: Association between peanut allergy and asthma morbidity.

Pediatrics. 2010;156:777-781. ♦♦

Flu Vaccine Safe for Most Egg-Allergic Children--Even Without Skin Testing

FOR patients with egg allergy, vaccine skin testing has been recommended before influenza vaccination. The authors report on the safety of an alternative approach to influenza vaccination in egg-allergic children, skipping the vaccine skin test.

The retrospective study included 261 children with egg allergy, aged 6 months to 18 years, evaluated for influenza vaccination. Between influenza seasons 2002-03 and 2006-07, patients underwent vaccine skin testing before influenza vaccination. Beginning in the 2006-07 season, patients were managed without vaccine skin testing. Rather, influenza vaccine was given in graded, 2-dose fashion: one-tenth dose followed by nine-tenths dose. Adverse reactions were assessed.

Influenza vaccine was given to 171 children: 56 with vaccine skin testing and 115 with the graded protocol. Vaccination was tolerated with no serious adverse reactions by 95% and 97% of children, respectively. Six children developed systemic reactions after the one-tenth dose; they did not receive the subsequent dose. There was one systemic reaction after the nine-tenths dose. In both groups, 79% of children tolerated vaccination with no adverse reactions, local or systemic.

The 2-dose protocol evaluated in this study allows influenza vaccine to be safely administered to most children with egg allergy, without vaccine skin testing. The authors emphasize that this approach should be used only by experienced staff who are prepared to manage serious adverse reactions.

COMMENT: *How well does an influenza vaccine skin test predict which egg-allergic child will have an allergic reaction to the immunization? The answer would seem to be "not very." So can the skin test step be safely skipped in these patients? Adding to existing evidence in our allergy/immunology literature, the answer would seem to be "yes." Caveats: the study excluded children with a history of anaphylaxis to egg; "non-anaphylaxis" to egg was categorized for these purposes as isolated cutaneous, gastrointestinal, or respiratory findings. A larger study would provide reassurance--ideally before next flu season!*
K. R. M.
Chung EY, Huang L, Schneider L: Safety of influenza vaccine administration in egg-allergic patients. **Pediatrics**. 2010;125:e1024-1030. ♦♦

'Less Conservative' Approach to Flu Vaccination for Patients with Egg Allergy

PATIENTS with egg allergy are at risk of anaphylaxis if given influenza vaccines containing egg protein. Children, young adults, and patients with asthma--who are among the target groups for influenza vaccination--have relatively high rates of egg allergy. Based on a review of the data on influenza vaccination in egg-allergic patients, the author suggests a less conservative approach to this issue.

The rate of anaphylactic reactions to influenza vaccine is extremely low, although exclusion of patients with egg allergy could be one reason for this. Studies of influenza vaccination in patients with egg allergy suggest that relatively few patients react to the vaccine, whether given in a single dose or in graded fashion. In contrast, influenza causes many deaths that are potentially preventable by vaccination.

Studies have found that the amount of egg protein in influenza vaccines is very low. Most package inserts state that the content is less than 1 µg per 0.5 mL dose, although independent studies show that the true content is even lower. Various protocols have been recommended for influenza vaccination of egg-allergic patients, some involving skin testing with the vaccine. However, vaccines with low ovalbumin content are well tolerated by patients with egg allergy, regardless of the skin test results. Thus routine skin testing does not appear necessary.

The author suggests that choosing a vaccine with low ovalbumin content "seems prudent." Vaccination should be performed in settings where anaphylaxis can be recognized and treated, and patients should be observed for at least 30 minutes. Other precautions may be appropriate for patients with histories of severe reactions to egg, or if only higher ovalbumin vaccines are available. If these considerations are observed, the author believes that patients with egg allergy "can and should be vaccinated" against influenza, if indicated.

COMMENT: *Primary care doctors are understandably reluctant to administer influenza vaccines to egg-allergic patients. Allergists have been providing a valuable service by skin testing with the vaccines and then injecting the patients while being prepared to treat anaphylaxis. In reality, this conservative approach might be unnecessary, as proposed by this article by a well-known expert. As a service to your primary care colleagues, you might send them this most-up-to-date article and invite them to comfortably manage this problem in their own offices during the coming vaccination season.*
R. J. M.
Kelso JM: Administration of influenza vaccines to patients with egg allergy.
J Allergy Clin Immunol. 2010;125:800-802. ♦♦

Foods Labeled "May Contain Milk" Probably Do

FOR patients with milk allergy, food labels play a critical role in allergen avoidance. Many manufacturers are using voluntary food advisory labeling, such as "may contain (allergen)," for which there are no regulations or established criteria. The authors evaluated the likelihood of milk exposure in patients using products with different types of milk advisory labeling.

The researchers tested 100 different products with advisory statements regarding milk. Of these, 81 had advisory labeling, such as "may contain," "manufactured on shared equipment with," or "manufactured in the same facility with" milk. On testing with an ➤➤

enzyme-linked immunosorbent assay, 34 of these products were found to have detectable milk residues. This included 61% of products with "may contain" labels, 33% with "shared equipment" labels, and 29% with "shared facility" labels.

Milk was especially likely to be found in dark chocolate and in products with milk fat listed as a minor ingredient. However, some products with a "minor ingredient" label did not contain any detectable milk. The milk content of products with advisory labels varied widely, from 3 to 15,000 ppm, and was unrelated to the type of advisory statement. Estimated milk doses from these products ranged from 0.027 to 620 mg.

Many food products with various milk advisory labels contain detectable milk. Although most of these items would lead to a milk dose of less than 10 mg if ingested, some would lead to much higher doses. Highly sensitive patients should be advised to avoid products with milk advisory labels or with milk as a minor ingredient, and all patients with milk allergy should probably avoid dark chocolate.

COMMENT: *Sometimes important scientific data are found in unexpected places. This letter to the editor details a study very germane to the following important clinical questions: What does food-allergen labeling really mean? Are there any real differences if the labels say "may contain (allergen)," or "manufactured on shared equipment with," or "manufactured in the same facility with"? In my practice, I get several questions about food labeling every day, and now I think I know the answer. These statements all represent a similar degree of risk (at least for milk).*
R. J. M.
Crotty MP, Taylor SL: Risks associated with foods having advisory milk labeling (letter).
J Allergy Clin Immunol. 2010;125:935-937. ♦♦

Breast-Feeding Reduces Wheezing...But Increases Eczema

PARTICULARLY in infants at high risk, breast-feeding has been recommended to reduce the risk of eczema, wheezing, and sensitization. However, the evidence for such a protective effect is inconclusive, with some studies even suggesting increased risks. This study evaluated the protective effect of breast-feeding against allergic disease in high-risk infants.

The analysis included 411 infants from the Copenhagen Prospective Study on Asthma in Childhood, all with a maternal history of asthma. The effects of breast-feeding on the occurrence of eczema and wheezy disorders by age 2 were assessed. To deal with the potential for inverse causation, the analysis focused on the effect of duration of breast-feeding before disease onset. The potential protective effect of the fatty acid composition of the mother's milk was evaluated as well.

Breast-fed infants had a twofold increase in their risk of developing eczema. Relative risk (RR) was 2.09, after adjustment for demographic characteristics, filaggrin variants, parental eczema, and household pets. However, there was a significant protective effect of breast-feeding against wheezy episodes, RR 0.67; and severe wheezy exacerbation: RR 0.16. Allergic disease outcomes were unaffected by the fatty acid composition of the mother's milk.

For infants with a maternal history of asthma, breast-feeding is associated with a reduced risk of developing wheezy disorder during the first 2 years of life. In contrast, the risk of eczema appears to be increased for breast-fed infants. Extended breast-feeding should not be recommended for prevention of eczema in high-risk infants.

COMMENT: *It is often assumed that breast-feeding infants is a "magic bullet" for the prevention of allergies. Although breast milk probably is the best overall nutrition for infants, data from this and multiple other studies fail to confirm a consistent benefit on the development of atopic diseases. Often the results have been discordant, as in this study: the incidence of wheezing was reduced, but eczema was increased. Previous studies have shown the opposite. New parents and their doctors should be realistic in their expectations from breast-feeding.*
R. J. M.
Giwercman C, Halkjaer LB, Jensen SM, et al: Increased risk of eczema but reduced risk of early wheezy disorders from exclusive breast-feeding in high-risk infants.
J Allergy Clin Immunol. 2010;125:866-871. ♦♦

HHV-6 and the Hygiene Hypothesis

THE hygiene hypothesis is based on studies suggesting that reduced exposure to childhood infections, including viral infections, may lead to a higher rate of allergic diseases. Human herpesvirus type 6 (HHV-6) is a common infection in infants, generally occurring in the first year of life. This study examined the association between early HHV-6 infection and IgE formation and Th2 development in infants.

Serum samples were collected from 64 infants, aged 18 months, most with a parental history of allergy. Fifteen of the children had eczema, food allergies, or other allergic diseases. Levels of IgE to common allergens and IgG to common herpesviruses were assessed. In an in vitro study, cord blood plasmacytoid dendritic cells (pDC) were exposed to HHV-6 and mixed with allogeneic cord blood CD4+ T cells, and the cytokine responses were analyzed.

Forty-five percent of the children were seropositive for HHV-6. This group had a significantly lower rate of IgE sensitization than children who were seronegative for HHV-6: odds ratio 0.08. The protective association was even stronger, odds ratio 0.047, compared to children who were not infected with any type of herpesvirus. In the in vitro study, CD4+ T cell production of interleukin-5 and interleukin-13 was lower in co-culture with allogeneic cord blood pDC. In pDC exposed to HHV-6, production of interferon-α was increased.

Infection with HHV-6 in infancy may lead to down-regulation of Th2 responses, resulting in reduced ➤➤

Th2 formation in response to common allergens. The negative association between HHV-6 infection and allergic sensitization in 18-month-olds suggests that HHV-6 could help to explain the hygiene hypothesis.

COMMENT: *The hygiene hypothesis has many wrinkles, and no simple observation appears to explain the phenomenon completely. Human herpes virus type 6 is an interesting candidate, because it preferentially infects T cells and it very commonly infects infants. In this study, early childhood infection with HHV-6 resulting in a high titer against the virus was associated with a decreased prevalence of IgE sensitization. The authors speculate that HHV-6 downregulates Th2 responses and may prevent IgE sensitization.*
S. A. T.
Nordström I, Rudin A, Adlerberth I, et al: Infection of infants with human herpesvirus type 6 may be associated with reduced allergic sensitization and T-helper type 2 development.
Clin Exp Allergy. 2010;40:882-890. ♦♦

Low-Energy Use Homes Have Fewer Dust Mites

ENVIRONMENTAL factors affecting mite growth may have an important impact on the level of exposure among mite-allergic patients, beyond the effects of avoidance measures. This study measured indoor mite allergen concentrations in modern energy-efficient buildings.

Mattress and carpet dust samples were obtained from two groups of buildings: 5 low-energy use buildings and 6 control buildings. The low-energy buildings had features such as mechanical ventilation with heat recovery, optimal thermal insulation, and absence of thermal bridges. Mite and other allergen levels were assessed and compared with the residents' ratings of perceived health and comfort.

Overall mite allergen levels were lower in the low-energy use buildings. Median mattress Der f 1 concentration was 67 ng/g in the low-energy use buildings, compared to 954 ng/g in conventional buildings; there was no significant difference in Bla g 1 or Fel d 1 levels. The low-energy use buildings had higher temperature but lower relative humidity. Residents of the low-energy use buildings rated their overall comfort higher.

Low-energy use buildings have lower concentrations of dust mite allergen than conventional buildings. These new building techniques, designed to lower energy costs, may also reduces dust mite growth up to 10-fold.

COMMENT: *In this study, energy efficient homes (with a mechanical ventilation system, heat recovery from exhaust air, and passive solar design) had significantly lower levels of* D. farinae *than control homes. This was probably due, at least in part, to lower relative humidity than in the naturally ventilated control homes.*
S. A. T.
Spertini F, Berney M, Foradini F, Roulet CA: Major mite allergen Der f 1 concentration is reduced in buildings with improved energy performance.
Allergy. 2009;65:623-629. ♦♦

SLIT Effect Persists 3 Years After Stopping

SUBLINGUAL immunotherapy (SLIT) using the SQ-standardized grass allergy immunotherapy tablet (Grazax) is an effective treatment for allergic rhinoconjunctivitis with grass pollen allergy. Follow-up from a randomized trial was performed to assess the lasting impact of SLIT at 1 year after the end of treatment.

The study included 157 patients who received 3 years of SLIT for moderate to severe grass pollen-induced rhinoconjunctivitis. At 1-year follow-up, quality of life was assessed using the standardized rhinoconjunctivitis quality of life questionnaire, completed weekly during pollen season. Outcomes were compared with those of 126 patients who had received placebo treatment.

Active SLIT was associated with a significant 23% improvement in quality of life score throughout pollen season, compared to placebo. During peak pollen season, the difference was 28%. The benefit of SLIT during the follow-up year was similar to that reported during the 3 treatment years. The difference was particularly apparent when quality of life score was analyzed as a function of weekly average pollen counts.

In patients receiving 3 years of SLIT, the quality of life benefits of SLIT persist through 1 year after the end of treatment. The benefits appear greatest when pollen levels are highest. Gains are apparent in all quality of life domains, including sleep.

COMMENT: *As the SLIT literature accumulates, it appears that the way SLIT works is quite similar to subcutaneous immunotherapy (SCIT). This multicenter study of grass pollen SLIT is the first large-scale demonstration that, in patients treated with SLIT for 3 years, quality-of-life improvements SLIT persist during the season following SLIT discontinuation. Prior similar observations in SCIT have led to the practice of discontinuing SCIT after 3 to 5 years in most cases. Although this disease modification effect is statistically significant and analogous to SCIT, it remains unclear if the magnitude of clinical improvement with SLIT matches that seen with SCIT.*
S. A. T.
Frølund L, Durham SR, Calderon M, et al: Sustained effect of SQ-standardized grass allergy immunotherapy tablet on rhinoconjunctivitis quality of life.
Allergy. 2010;65:753-757. ♦♦

CLINICAL TIDBITS

Angioedema Can Be Caused By Sun Exposure

ANGIOEDEMA can occur as hereditary or acquired disease. There are many possible causes, while no cause is identified in close to 40% of cases. Five ➤➤

patients with angioedema related to sunlight exposure are reported.

Five patients with angioedema following sun exposure were identified from a series of more than 2,000 patients with photosensitivity disorders. Median age was 38 years, and median age at onset 12 years. All patients had angioedema with intense, stinging pain and deep swelling in fixed areas exposed to sunlight, such as the lips, eyelids, and extremities.

Laboratory and phototesting data ruled out other acquired or inherited causes of photosensitivity. Treatment with antihistamines was ineffective; intravenous prednisone shortened the attacks and provided some relief. Three patients underwent photoprophylaxis with narrow-band UVB. After 8 weeks, the UVA dose that had previously provoked angioedema no longer had its pathologic effect.

Five cases of apparent solar angioedema are reported. As with solar urticaria, histamine does not appear to be the pathogenetic mediator of this novel clinical disorder.

COMMENT: *Angioedema is a difficult diagnostic problem for many allergists. In addition to hereditary or acquired disease, it is often idiopathic and heterogeneous, with many etiologies including physical stimuli. This interesting article describes 5 patients who developed an angioedema without urticaria, when exposed to solar light, without relief from antihistamines. The authors propose that solar angioedema should be considered a novel clinical entity. Whether this condition is inherited or acquired, mediators other than histamine may play the main pathogenetic role.*
M.F.

Calzavara-Pinton P, Sala R, Venturini M ,et al: Local angioedema following sun exposures: a report of five cases.
Int Arch Allergy Immunol. 2010;153:315-320. ♦♦

Omalizumab Can Be Effective in Patients with Low IgE

ANTI-IgE therapy with omalizumab is not currently indicated for use in patients with low serum IgE levels (less than 30 kU/L). However, some patients have severe problems with allergies despite low IgE levels. The results of anti-IgE therapy in 2 patients with severe allergies but low IgE levels are reported.

Both patients had severe allergic asthma and rhinoconjunctivitis that did not respond to conventional medications. Both had IgE antibody fractions of 1% to 14%. Omalizumab doses adjusted to the patients' IgE body pool had minimal effect. When the dose was doubled, some effect was noted, including a decrease in allergen threshold sensitivity (CD-sens). When the dose was doubled again, the patients became symptomatic, although 1 patient needed additional medications. The CD-sens results became negative to 5 of 7 allergens.

Omalizumab can be effective in patients with severe allergic disease but low IgE levels. Despite the low total IgE, the dose needs to be adjusted to the size of the IgE antibody fraction to be effective.

COMMENT: *In this article, 2 atopic patients suffering from severe allergy that didn't respond to conventional medication were given Xolair, despite an IgE level less than 30 kU/L. Allergen threshold sensitivity (CD-sens) measures CD63 up-regulation on CD203c-identified basophils and has been reported by these authors to be very useful for determining a patient's allergen sensitivity and monitoring the efficacy of anti-IgE. Increasing dosages were given and monitored by clinical evaluation and CD-sens to clinically relevant allergens. The authors conclude that Xolair is also most useful in atopic patients with an IgE level of less than 30 kU/L. However, the dose must be adjusted to the size of the IgE antibody fraction, adding all non-cross-reacting, clinically relevant specificities.*
M. F.

Ankerst J, Nopp A, Johansson SG, et al: Xolair is effective in allergics with a low serum IgE level.
Int Arch Allergy Immunol. 2010;152:71-74. ♦♦

Menstrual Cycle Affects BHR

FEMALE sex hormones may influence asthma exacerbations. Previous studies of perimenstrual asthma have yielded unclear results. The effects of the menstrual cycle on bronchial hyperreactivity (BHR) were studied in a population-based cohort of menstruating women.

The 571 women, aged 28 to 58, were not receiving hormonal therapy. All underwent methacholine challenge to assess BHR. The relationship between day of the menstrual cycle and BHR (defined as a 20% or greater fall in FEV_1, up to a maximal cumulative methacholine dose of 2 mg) was assessed. The analysis was adjusted for predictors of BHR and stratified for asthma (present in 6% of women).

There was a 13% prevalence of BHR. Methacholine challenge was performed within 3 days before and after the first day of menstruation, in 143 women. Within this "window of risk," there was a significant increase in BHR: odds ratio 2.3. The effect was modified not only by asthma status but also by oral contraceptive use--the odds ratio was less than 1 in women taking oral contraceptives.

Risk of BHR varies during the menstrual cycle, consistent with a hormonal influence on asthma. Oral contraceptive use appears to protect against this cyclic association. The results may have important implications for treatment recommendations and respiratory function testing in women.

COMMENT: *These researchers studied a relatively large cohort to analyze the effect of hormonal changes on BHR. The menstrual cycle did influence BHR, which increased just prior to menses. We should probably pay more attention to menstrual dates when evaluating women with asthma.*
S. M. F.

Dratva J, Schindler C, Curjuric I, et al: Perimenstrual increase in bronchial hyperreactivitiy in premenopausal women: results from the population-based SAPALDIA 2 cohort.
J Allergy Clin Immunol. 2010;125:823-829. ♦♦

New Probiotic Shows Effect in AEDS

STUDIES have suggested a clinical benefit of probiotic supplementation in infants with early-onset atopic eczema-dermatitis syndrome (AEDS). This trial evaluated the newly identified probiotic strain *Lactobacillus sakei* KCTC 10755BP in children with established AEDS.

Eighty-eight children with AEDS, present for at least 6 months and with a minimum SCORAD total score of 25, were randomly assigned to daily *L. sakei* supplementation or placebo. At 12 weeks, baseline-adjusted SCORAD scores were significantly lower in the probiotic group. Children receiving *L. sakei* had a 13.1-point (31%) improvement in mean disease activity, compared to 5.2 points (13%) in the placebo group. The probiotic was also associated with lower levels of serum chemokine markers of AED severity (CCL17 and CCL27).

The new probiotic supplement *L. sakei* appears to reduce disease activity in children with AEDS. Responses to treatment varied; longer follow-up is needed to confirm the efficacy of *L. sakei*.

COMMENT: *On one hand, there are unmet needs in the treatment of atopic dermatitis, and the safety and simplicity of lactobacillus nutritional supplements is generally accepted. On the other hand, using diet or supplements to change gastrointestinal flora in older children or adults is very difficult, if not impossible. If this small study can be replicated, I am looking for this supplement for some of my persistent eczema patients, and maybe for me as well.*
D. K. L.
Woo S-I, Kim J-Y, Lee Y-J, et al: Effect of Lactobacillus sakei *supplementation in children with atopic eczema-dermatitis syndrome.*
Ann Allergy Asthma Immunol. 2010;104:343-348. ♦♦

Montelukast Beats Salmeterol for Children with EIB

EXERCISE-induced bronchoconstriction (EIB) is common problem with a significant impact on children's lives. This trial compared long-term montelukast versus salmeterol for protection against EIB in children.

The international study included 154 children, aged 6 to 14 years, with persistent asthma and EIB. All performed a standardized exercise challenge before and after 4 weeks of treatment with montelukast, 5 mg, and 4 weeks on inhaled salmeterol, 50 µg. Both treatments were given in addition to inhaled fluticasone.

The mean maximum percentage decrease in FEV_1 in response to exercise was 10.6% on montelukast vs 13.8% on salmeterol. Mean area under the curve for the first 20 minutes after exercise was 116.0%/min with montelukast and 168.8%/min with salmeterol; median recovery time was 6 vs 11 minutes, respectively.

Montelukast is superior to salmeterol for asthmatic children with EIB, added to inhaled corticosteroid. Both the reduction in FEV_1 and the response to albuterol are superior with montelukast.

COMMENT: *Montelukast appears to outperform long-acting β-agonists, notably salmeterol, in attenuating exercise-induced bronchospasm. This is not really new news, but is now well-confirmed news.*
D. K. L.
Fogel RB, Rosario N, Aristizabal G, et al: Effect of montelukast or salmeterol added to inhaled fluticasone on exercise-induced bronchoconstriction in children.
Ann Allergy Asthma Immunol. 2010;104:5511-5517. ♦♦

Pneumococcal Vaccine Doesn't Lower MI Risk

INFLUENZA vaccination has been shown to reduce the risk of myocardial infarction (MI) and other vascular events. This study evaluated the effect of pneumococcal vaccination on the risk of MI.

The analysis included 84,170 men, aged 45 to 69 years, participating in a prospective men's health study. Five-year follow-up data were used to look for a possible association between pneumococcal vaccination and the incidence of acute MI and stroke.

The rate of initial MI during follow-up was 10.73 per 1,000 vaccinated person-years, compared to 6.07 per 1,000 unvaccinated person-years. The risk of stroke was also higher in men receiving pneumococcal vaccine: 5.30 versus 1.90 per 1,000 person-years. On propensity score adjustment, there was no significant difference in the risk of MI or stroke between vaccinated and nonvaccinated men.

Unlike influenza vaccine, pneumococcal vaccine does not appear to reduce the risk of MI or stroke in middle-aged and older men. An apparent increase in risk for vaccinated men disappears after adjustment for differences in patient characteristics.

COMMENT: *These results will have no effect on my recommending pneumococcal vaccine to subjects with chronic asthma or other airflow limitation. There is debate on the efficacy of pneumococcal vaccine, but from my perspective there is almost no negative effect and there is the potential for significant benefit. The question of the frequency and number of booster vaccinations in younger subjects is without an answer in the current literature.*
D. K. L.
Seng HF, Slezak JM, Quinn VP, et al: Pneumococcal vaccination and risk of acute myocardial infarction and stroke in men.
JAMA. 2010;303:1699-1706. ♦♦

Parents Starting Steroids--Not So Safe?

HAVING parents start oral steroid at the first sign of an asthma attack in children has been recommended as a means to ensure prompt treatment. The safety and efficacy of this approach were evaluated in a randomized trial.

The study included 230 school-aged children with at least four recurrent episodes of acute asthma over the past year. In crossover fashion, subsequent attacks were treated with parent-initiated prednisolone, 1 mg/kg/d, or placebo. Over a 3-year period, 308 exacerbations were treated in 131 children.

Mean daytime symptom scores were 15% lower in attacks treated with prednisolone. This difference was significant, although a similar reduction in nighttime symptoms was not. Parent-initiated steroid treatment reduced the use of health care resources, although the hospitalization rate was unaffected. There was a small (less than one-half day) reduction in school absences.

Having parents initiate oral prednisolone therapy has modest benefits for acute asthma in children. Questions still remain as to the potential adverse effects of repeated courses of oral steroid.

COMMENT: *There is a temptation to allow well-minded parents to administer oral steroids to children at the first sign of an asthma exacerbation. Managed care executives like the idea too. After all, what are 5 days of prednisolone at 1 mg/kg/d? Sadly, this study in school-age children demonstrated only slight benefit in daytime and nighttime symptoms and resource utilization. With evidence that only five courses of oral steroids (in a 4-year period) are associated with decreased bone mineralization, we and our pediatrician colleagues must be wary of indiscriminant recommendations of parental ad lib oral steroids for acute exacerbations.*
S.F.W.

Vuillermin PJ, Robertson CF, Carlin JB, et al: Parent initiated prednisolone for acute asthma in children of school age: randomized controlled crossover trial. **BMJ**. 2010;340:c843. ♦♦

REVIEWS OF NOTE

COMMENT: *Well-done systematic reviews are useful for consensus on a particular topic. They may also uncover gaps in our knowledge, which at times raise questions about long-held views. The link between GERD and pediatric asthma becomes less clear, under scrutiny. Although a relationship certainly exists between these disorders, determining causality remains elusive. The difficulty here lies with various study designs (mostly cross-sectional, lacking longitudinal assessment), definitions of asthma, and diagnostic criteria for GERD.*
K.R.M.

Thakkar K, Boatright RO, Gilger MA, et al: Gastroesophageal reflux and asthma and children. **Pediatrics**. 2010;125:e925-e930. ♦♦

COMMENT: *This review provides little new information to an informed allergist/immunologist, but does provide an up-to-date perspective on prevalence and treatment considerations. I am impressed with the amazingly limited body of consistent information for optimizing diagnosis and treatment for such a common clinical problem as food allergies. This is a good reference for referring physicians.*
D. K. L.

Chafen JJS, Newberry SJ, Riedl MA, et al: Diagnosing and managing common food allergies: a systematic review.
JAMA. 2010;303:1848-1855. ♦♦

COMMENT: *These two reviews by experienced, knowledgeable adult and pediatric clinicians are a valuable reference for clinical decision making in challenging patient presentations.*
D. K. L.

Peters SP: Special considerations in adults for diagnoses that may coexist with or masquerade as asthma.
Ann Allergy Asthma Immunol. 2010;104:455-460.
Chipps BE: Evaluation of infants and children with refractory lower respiratory tract symptoms.
Ann Allergy Asthma Immunol 2010;104:279-283. ♦♦

COMMENT: *This is an excellent review of current research on the effects of indoor air pollution on asthma done at Johns Hopkins University.*
B.E.C.

Breysse PN, Diette GB, Matsui EC, et al: Indoor air pollution and asthma in children.
Proc Am Thorac Soc. 2010;7:102-106. ♦♦