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 15, Number 5 September - October 2013

Weight Loss Improves Asthma in Obese Children

OBESITY is common in asthmatic children and is linked to worse clinical outcomes. Although studies of weight loss for asthma patients have shown improvement in asthma outcomes, nearly all were performed in adults. This pilot study evaluated the effects of a 10-week dietary intervention on asthma outcomes in obese children with asthma.

The randomized controlled trial included 28 obese asthmatic children and adolescents, aged 8 to 17 years. Obesity was defined as a body mass index z-score of 1.64 standard deviation or greater. One group of children received a 10-week dietary intervention, targeting an energy reduction of 500 kcal/d, with required counseling sessions with a dietitian. The other group served as waiting-list controls. At the end of 10 weeks, asthma-related outcomes were compared between groups, including lung function values, Asthma Control Questionnaire (ACQ) score, and sputum and systemic inflammatory markers.

The BMI z-score decreased by 0.2 in the diet group vs no change in the control group. The study diet was associated with a 0.7 L increase in expiratory reserve volume along with a 0.4-point reduction in ACQ score, but no change in airway and systemic inflammatory markers.

The waiting-list control group had a significant increase in C-reactive protein, which was significantly associated with changes in BMI z-score and ACQ score. Change in body weight was also associated with change in exhaled nitric oxide.

Acute weight loss is associated with improvement in static lung function and ACQ score in obese children with asthma. Although diet and weight loss do not lead to decreased inflammation, changes in body weight are associated with changes in systemic and airway inflammatory markers. Based on this preliminary trial, the authors call for larger studies of the effects of weight loss on childhood asthma outcomes.

COMMENT: *Obesity continues to be problematic in children and adults and has a number of adverse* ➤➤

CONTENTS

The American College of Allergy, Asthma & Immunology expresses its appreciation to MERCK for its 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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effects on respiratory health. This study from Australia is the first randomized controlled trial of weight loss in asthmatic children. Fifteen obese children were assigned to an intensive 10-week dietary intervention group and compared to 13 obese children who were wait-listed. Despite the very brief intervention, the diet group not only lost weight, but had improvement in asthma control and residual volume. Markers of airway inflammation did not change, however. The small study is impressive in that, in a very brief time, obese children were able to lose weight and have improvement in asthma control. Further studies will be required to determine the applicability and durability of this approach. Nevertheless, as allergists, it is important for us to emphasize the importance of weight loss in our overweight and obese asthma patients. Less is more.
D.A.K.
Jensen ME, Gibson PG, Collins CE, et al: Diet-induced weight loss in obese children with asthma: a randomized controlled trial.
Clin Exp Allergy. 2013;43: 775-784. ♦♦

Eosinophilic Esophagitis: More Than Just Eosinophils?

QUESTIONS remain about the difference between allergic and nonallergic eosinophilic esophagitis (EoE)--ie, with and without increased IgE. Although cysteinyl leuktotrienes contribute to Th2-type immune responses, their presence in esophageal tissues cannot differentiate EoE patients from controls. This study evaluated leukotriene C4 synthase (LTC_4S) mRNA as a marker of EoE in esophageal biopsy specimens.

The researchers performed digital mRNA expression profiling in proximal and distal esophageal biopsy specimens from 30 children and adolescents with EoE and 40 controls without EoE. The results showed significant elevations of LTC_4S in the EoE group: by 2.6-fold in proximal and 2.9-fold in distal esophageal specimens.

A 28% subgroup of EoE patients were identified as having increased LTC_4S mRNA, associated with higher serum IgE levels: 669 versus 106 U/mL. The high-LTC_4S group also had higher thymic stromal lymphoprotein mRNA and CD4, but lower IL-23 mRNA. Higher IL-23 mRNA was also found in esophageal specimens from children with reflux esophagitis. The EoE patient subgroups and non-EoE patients could not be distinguished by LTC_4S mRNA in whole blood or by urinary leukotriene E_4 excretion.

Some children with EoE have increased expression of LTC_4 mRNA expression in esophageal biopsy specimens. This patient subgroup has increased serum IgE levels and a more active EoE transcriptome associated with a "more-pronounced allergic phenotype." Esophageal LTC_4S mRNA measurement could be a useful part of a more personalized approach to EoE diagnosis and treatment.

COMMENT: *Eosinophilic esophagitis is a well-known entity characterized by an eosinophil-rich tissue inflammation and Th2 inflammation. This study from Boston evaluated pediatric patients with EoE for the presence of mRNA for LTC_4S. The results showed upregulation of LTC_4S in the esophagus of EoE patients, with some having higher levels than others. The lack of correlation between LTC_4S and eosinophils suggested other cellular sources may exist. Of interest, 88% of patients with high LTC_4S were enrolled during pollen season, compared to 29% of those with low LTC_4S. These data suggest that high LTC_4S may identify a subgroup of EoE patients, and that other cells may play a role in EoE. The clinical relevance of these findings remains to be established.*
D.A.K.
Lexmond WS, Pardo M, Rooney K: Elevated levels of leukotriene C4 synthase mRNA distinguish a subpopulation of eosinophilic oesophagitis patients.
Clin Exp Allergy. 2013;43:902-913. ♦♦

Omalizumab May Have Benefits in Nonallergic Asthma

AS many as half of patients with severe asthma have no evidence of allergy. Anti-IgE therapy with omalizumab has clinical benefits for a subgroup of patients with moderate to severe allergic asthma. This trial evaluated the biologic and clinical effects of omalizumab for patients with severe, difficult-to-control nonatopic asthma.

The study included 41 adults with severe asthma despite guideline-based treatments, with or without oral maintenance corticosteroids. Patients were randomly assigned to treatment with omalizumab or placebo. Biologic and clinical outcome measures were compared after 16 weeks.

Omalizumab was associated with a significant reduction in the primary endpoint of change in expression of high-affinity IgE receptor (FcεRI): by 89.8% on basophils and 56.1% on plasmacytoid dendritic cells (compared to 9.5% and 4.3%, respectively, in the placebo group). Patients receiving omalizumab also had a 250 mL increase in FEV_1, with trends toward improved global evaluation of treatment effectiveness and decreased asthma exacerbations.

In severe nonatopic asthma as in atopic cases, omalizumab leads to decreased expression of FcεRI. The study provides evidence of improvement in lung function and clinical outcomes as well. Further trials of omalizumab for severe, persistent, nonatopic asthma are needed.

COMMENT: *Omalizumab has been shown to be effective in allergic asthma. Since intrinsic asthma may also be associated with Th2 inflammation and enhanced FcεRI expression, these authors performed a study to assess FcεRI expression as a primary outcome (along with secondary clinical outcomes) in a group of patients with severe, poorly controlled asthma who were not atopic. Not surprisingly, FcεRI expression was reduced on both basophils and plasmacytoid dendritic cells in the group randomized to omalizumab for 16 weeks compared to placebo. Omalizumab-treated patients had a 9.5% increase in FEV_1% compared to placebo, which was statistically different. However, other clinical outcomes--including exacerbations, asthma control, and exhaled NO--were not different between groups. Since omalizumab may exert several downstream immunologic effects, it is possible that patients with nonatopic diseases may benefit. Larger studies with primary clinical outcomes will be required to answer this question.*
D.A.K.
Garcia G, Magnan A, Chiron R, et al: A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma.
Chest. 2013;144:411-419. ♦♦

Ragweed Sublingual Immunotherapy: 'Ready for Prime Time'

RAGWEED is a major cause of allergic rhinitis in North America. Previous studies have shown promising results with sublingual immunotherapy for grass allergy. The current study compared two doses of allergen immunotherapy tablets (AIT) for ragweed allergy in North American patients.

The randomized trial included 565 patients with ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, drawn from 67 U.S. and 13 Canadian centers. Patients were assigned to receive daily ragweed AIT, at a dosage of 6 or 12 Amb a 1 units, or placebo. Treatment continued for approximately 1 year: before, during, and after ragweed season.

Compared to placebo, peak-season total combined score improved by 21% with the 6-Amb a 1 unit dose and by 27% with the 12-Amb a 1 unit dose of ragweed AIT. Significant improvements in daily symptom and medication scores were achieved as well. Evaluation of peak- and entire-season scores showed similar efficacy. Adverse events were typically mild oral reactions, with no systemic allergic reactions. One patient receiving the 6-Amb a 1 unit dose was treated with epinephrine for "sensation of localized pharyngeal edema."

The results support the clinical effectiveness and safety of ragweed AIT for U.S. and Canadian patients with ragweed allergy and allergic rhinitis. This provides a convenient new treatment for ragweed-allergic patients in North America.

COMMENT: *In terms of safety and efficacy, ragweed sublingual immunotherapy is now "ready for prime time" in the North American adult population. The 6- and 12-Amb a 1 unit doses used in this investigation significantly improved daily symptoms and treatment scores as well as reducing peak season total symptom score, compared to placebo. Over a 52-week course of immunotherapy, only local adverse reactions occurred.*
C.C.R.
Nolte H, Hébert J, Berman G, et al: Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults.
Ann Allergy Asthma Immunol. *2013;110:450-456.* ♦♦

Which Children Are at High Risk for Subsequent Asthma Admissions?

ASTHMA is an important cause of hospital admissions in children, including many repeat admissions. Information is needed on the risks of repeat hospitalizations and the risk factors contributing to adverse health outcomes among children hospitalized for asthma. The long-term risk of subsequent hospitalization was analyzed in a large group of children admitted for asthma.

The researchers analyzed a Washington State database of nearly 82,000 children hospitalized from ➤➤

2004 to 2008. Of these, 4,744 children had a primary diagnosis of asthma. The risk of subsequent hospitalization for any cause was compared with that of 77,172 children admitted with other diagnoses.

Compared to the reference group, children in the asthma cohort were younger (5.8 versus 9.1 years), more likely to be male (61.0% versus 54.2%), and more likely to be on Medicaid (41.8% versus 38.1%). At up to 5 years' follow-up, children with asthma had a significant increase in risk of subsequent hospitalization: hazard ratio 1.33, after controlling for other factors. The increase was significant for all age groups under 13 years but was greatest for children aged 3 to 5 years: hazard ratio 1.50. Nearly three-fourths of readmissions were for asthma; about 8% were for pneumonia and 4% for acute respiratory infections.

The results document the high risk of subsequent admission among children hospitalized for asthma. This risk is most pronounced in preschool-aged children. The researchers hope their findings will contribute to the development of effective interventions to prevent and reduce hospitalizations and improve care for pediatric asthma patients.

COMMENT: *Asthma is one of the most common diseases resulting in pediatric hospitalizations. In this study of more than 80,000 pediatric hospitalizations, asthmatic children had a 33% increased risk of subsequent hospitalization, compared to a reference cohort of children hospitalized for other diagnoses. Age groups younger than 13 years--particularly 3 to 5 years--were at highest risk. This indicates an urgent need for allergy specialty attention to educational intervention with an asthma action plan, controller medication, education in proper administration of inhaled medications with dose counters, and multidisciplinary attention to psychosocial issues affecting adherence with medications. These interventions could reduce pediatric hospital admissions, complications, and health care costs, improving patient care and quality of life.*
C.C.R.
Shaw MR. Daratha KB, Odom-Maryon T, et al: Pediatric patients with asthma: a high-risk population for subsequent hospitalization.
J Asthma. 2013;50:548-554. ♦♦

TNFA Variant May Protect Against Asthma

TUMOR necrosis factor-α (TNF-α) is a proinflammatory cytokine that may play a role in asthma pathophysiology. Previous studies have reported increased expression of TNF-α in the airways of asthma patients and a possible link to corticosteroid sensitivity. This study assessed genetic variation in the promoter region of the *TNFA* in patients with versus without asthma.

The study comprised 94 adults and children, mainly African American, including asthma patients receiving step 1 versus step 2 or 3 therapy and nonasthmatic controls. Quantitative real-time polymerase chain reaction was performed on total RNA isolated from the buccal mucosa to assess expression of *TNFA* mRNA. Commercial assays were performed to study *TNFA*-1031T/C, -857C/T, and -308G/A polymorphisms on genomic DNA isolated from blood.

The genotyping results showed that the *TNFA*-857C/T polymorphism was significantly associated with asthma. Three percent of asthmatic children had the *TNFA*-857 T allele, compared to 29% of those without asthma. The same allele was found to be significantly underrepresented in African-American subjects. The study also identified a *TNFA* haplotype combination, consisting of -1031T/-857C/-308G and -1031T/-857T/-308G, associated with decreased expression of TNF-α mRNA.

The *TNFA*-857T allele, underrepresented in patients with asthma, may have a protective effect against asthma development. In addition, a haplotype combination including the *TNFA*-857T allele influences mRNA expression of TNF-α. This genotype/haplotype relationship may be relevant to predicting the response to treatments targeting TNF-α.

COMMENT: *The* TNFA-*857T allele may be protective against asthma development in children and African=American patients. Other alleles may be related to asthma diagnosis.*
C.C.R.
Jones BL, Graham BK, Riffel AK, et al: Genetic variation in the TNFA *promoter region and* TNFA *gene expression in subjects with asthma.*
J Asthma. 2013;50:541-546. ♦♦

Auvi-Q and EpiPen Are Bioequivalent

EPINEPHRINE autoinjectors play an essential role in first aid for anaphylaxis. The Auvi-Q is a new type of autoinjector, designed for easy and intuitive use and reduced potential for errors. This study compared the bioavailability of epinephrine delivered by Auvi-Q vs the traditional EpiPen.

The randomized, crossover study included 71 healthy adults. In three sequences over three treatment periods, nurses administered 0.3 mg doses of epinephrine using Auvi-Q and EpiPen. Blood samples were obtained for pharmacokinetic measurements, and adverse events were assessed.

The peak concentration of and total exposure to epinephrine were comparable between the two devices. Both peak plasma concentration and area under the concentration-time curve supported the bioequivalence of epinephrine delivered via Auvi-Q and EpiPen. Treatment-emergent adverse events were almost all mild, and always resolved spontaneously. There was a 13% rate of injection-site pain with Auvi-Q versus 24% with EpiPen. Rates of injection-site bleeding were 5% and 10%, respectively.

The study demonstrates the bioequivalence of 0.3 mg doses of epinephrine administered with the new Auvi-Q devices compared to EpiPen. Safety and tolerability are similar with the 2 devices; Auvi-Q may be associated with less pain and bleeding. ➤➤

COMMENT: *Epinephrine is the first-line therapy for anaphylaxis. The self-administered epinephrine market now includes Auvi-Q, an innovative form of self-injectable epinephrine with a safety guard at the end of the needle and a prompting audiovisual system. This comparative study of the traditional EpiPen vs Auvi-Q indicates that the 0.3 mg dose of epinephrine was bioequivalent, with similar peak and epinephrine exposure. Safety and tolerability were similar as well, but the Auvi-Q had less injection-site pain and bleeding. Auvi-Q offers a convenient and self-instructing delivery system that should ease the anxiety of users unfamiliar with injections and the pressure of emergent care.*
C.C.R.
Edwards ES, Gunn R, Simons ER, et al: Bioavailability of epinephrine from Auvi-Q compared with EpiPen.
Ann Allergy Asthma Immunol. 2013;111:132-137. ♦♦

Effects of Chronic Propranolol in Asthma: Placebo-Controlled Trial

ASTHMA has been regarded as a contraindication to treatment with beta-blockers because of the potential risk of bronchospasm. However, nonblinded studies in steroid-naive asthma patients have suggested possible benefits of chronic treatment with nadolol. This randomized trial evaluated the effects of chronic nonselective beta-blockade with propranolol added to inhaled corticosteroid (ICS) therapy for asthma.

The study included 18 patients receiving ICS for persistent, mild to moderate asthma. In random order, patients received 6 to 8 weeks of treatment with placebo or propranolol, after which they crossed over to the other treatment. Propranolol was titrated as tolerated up to 80 mg/d; tiotropium was given during the first 4 to 6 weeks of both treatment periods. Response to methacholine challenge was compared between treatments, along with other outcomes.

There was no significant difference in the methacholine challenge results after propranolol vs placebo, with a doubling dilution difference of just 0.04. The response to histamine challenge was similar as well. Albuterol recovery 20 minutes after histamine challenge was somewhat improved with propranolol, with a mean FEV_1% difference of 5.28, compared to placebo. At the end of the propranolol treatment period, there was a nonsignificant 2.4% worsening of FEV_1%. Asthma control and quality of life scores were not significantly different between treatments.

The results support the safety of chronic nonselective beta-blockade in patients with asthma. Responses to methacholine or histamine challenge are similar after a period of treatment with propranolol vs placebo; secondary outcomes are similar as well. In selected patients with stable asthma, "careful titration of nonselective beta-blockers may be safe to use without any worsening of airway hyperresponsiveness," the investigators conclude.

COMMENT: *This report is an important addition to the previously reviewed study of nadolol, a selective beta-blocker, for treatment of asthma. (See Hanania NA, et al: Eur Respir J. 2010;36:963-9650.) The new data speak to the safety of beta-blockers in asthma, but should not be extrapolated to the safety of using these drugs in patients receiving allergy immunotherapy.*
B.E.C.
Short PM, Williamson PA, Anderson WJ, Lipworth BJ: Randomized placebo-controlled trial to evaluate chronic dosing effects of propranolol in asthma.
Am J Respir Crit Care Med. 2013;187:1308-1314. ♦♦

Inhaled Corticosteroids and Risk of Adrenal Insufficiency

ACUTE adrenal insufficiency is a serious potential complication of inhaled corticosteroid (ICS) therapy. Some studies have reported that this risk is highest in patients receiving fluticasone, a higher-potency steroid. Data from Canada, where fluticasone is the preferred agent, were analyzed to clarify the relationship between ICS and adrenal insufficiency.

Quebec health databases were used to identify patients treated for respiratory conditions between 1990 and 2005, with follow-up to 2007. From this group, 392 case patients with acute adrenal insufficiency were identified, for an incidence rate of 1.1 per 10,000 person-years. Each case was matched with up to 10 controls; the effects of ICS type and dose on adrenal insufficiency risk were analyzed.

Current ICS users were not at increased risk of adrenal insufficiency. However, on analysis of dose of the most recent ICS prescription, risk was significantly increased for patients exposed to a higher ICS dose: OR 1.84. Risk was also increased for patients in the highest tertile of cumulative dose over the preceding year. For each additional oral corticosteroid prescription, the OR for adrenal insufficiency was 1.65.

High doses of ICS, rather than ICS treatment per se, are an independent risk factor for adrenal insufficiency. Especially in patients receiving doses equivalent to fluticasone 1,000 μg/d or greater, physicians should be alert for signs and symptoms of adrenal insufficiency.

COMMENT: *These data reinforce the systemic effect of fluticasone equivalent 1,000 μg or greater. It should be noted that the beclomethasone studies with chlorofluorocarbon need to be decreased by 50% with the new hydrofluoroalkane preparation. These findings, in addition to the well-known flat dose response curve for ICS, should dissuade the use of higher doses of inhaled steroid for the vast majority of patients with asthma.*
B.E.C.
Lapi F, Kezouh A, Suissa S, Ernst P: The use of inhaled corticosteroids and the risk of adrenal insufficiency.
Eur Respir J. 2013;42:79-86. ♦♦

Ethnic Differences in Lung Function in Children May Be Genetic in Origin

PREVIOUS studies have reported ethnic variations in lung function, including higher FEV_1 and FVC in white compared to South Asian individuals. The ➤➤

explanation for these differences--whether related to genetics, environment, or both--has been unclear. This issue was addressed in a population-based cohort of white and South Asian children in the United Kingdom.

The study comprised a community-based sample of 1,088 white and 275 South Asian children. All children in both groups were born in the United Kingdom and grew up in the same city (Leicester). Differences in spirometric lung function values were analyzed, including adjustment for cultural factors, socioeconomic indicators, intrauterine growth, environmental factors, and personal and family history of wheezing.

After adjustment for height and sex, FEV_1 was 9% lower and FVC 11% lower in South Asian compared to white children. There was no significant difference in peak expiratory flow or in forced expiratory flow 50%. The ratio of FEV_1 to FVC was 1.8% higher in South Asian versus white children. The differences were unchanged in all five models of potential explanatory factors.

The results confirm significant differences in lung volume between South Asian and white children, and suggest that the variations are largely genetic in origin. The researchers highlight the need for reference equations to predict ethnicity-specific lung function values for South Asian children.

COMMENT: *A study of children aged 9 to 14 years from a population-based UK cohort confirmed important differences in lung volumes (eg, lower FVC and FEV_1) between South Asian and white children. These differences were not affected by adjustment for differences in cultural, socioeconomic, or environmental or other factors. That raises the possibility that ethnic differences in height-adjusted lung function between white and South Asian children may be largely genetic in origin. Reference equations for predicting lung function specifically for South Asian need to be developed.*
C.D.

Strippoli M-PF, Kuehi CE, Mihai C, et al: Etiology of ethnic differences in childhood spirometry.
Pediatrics. 2012;131:e1842-1849. ♦♦

Both SCIT and SLIT are Efficacious in Children with Asthma/Rhinitis

OPTIONS for treatment of allergic rhinitis and asthma in children include subcutaneous immunotherapy (SCIT), which is approved in the United States; and sublingual immunotherapy (SLIT), which is commonly prescribed off-label. The authors performed a systematic review of the research evidence on SCIT and SLIT for treatment of pediatric asthma and allergic rhinoconjunctivitis.

The review identified 13 randomized controlled trials comparing SCIT with usual care, including 920 children; and 18 trials comparing SLIT with usual care, including 1,583 children. Three trials directly compared SCIT with SLIT in a total of 135 children. There was moderate evidence that SCIT improved asthma and rhinitis symptoms in children, but only low evidence of benefit in terms of conjunctivitis symptoms and asthma medication scores.

There was strong evidence supporting the effectiveness of SLIT in improving asthma symptoms, with moderate evidence that it improved rhinitis and conjunctivitis symptoms and decreased medication use. There was only weak evidence to suggest that SCIT was superior to SLIT in terms of reducing asthma or rhinitis symptoms or medication use.

Both treatments were associated with frequent local and systemic reactions. One case of anaphylaxis was reported in a child receiving SCIT; there were no deaths.

Both SCIT and SLIT appear to be effective for treatment of allergic rhinitis and asthma in children. The authors call for "real world" studies of SCIT and SLIT for children, including issues of compliance and long-term outcomes.

COMMENT: *A systematic review of trials in children receiving SCIT compared to usual care, SLIT compared to usual care, and SCIT with SLIT head-to-head showed that both SCIT and SLIT were efficacious in the treatment of asthma and rhinitis. Local reactions were frequent with SCIT (up to 54%) and SLIT (up to 50%). The evidence base appeared stronger for SLIT than for SCIT, perhaps because there are fewer studies evaluating SCIT exclusively in children and few head-to-head comparisons of SCIT and SLIT.*
C.D.

Kim JM, Lin SY, Suarez-Cuervo C, et al: Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review.
Pediatrics. 2012;131:1155-1167. ♦♦

Higher Vitamin D Levels May Protect Against Pneumococcal Disease in Asthma Patients

PREVIOUS studies have linked serum 25-hydroxyvitamin D (25[OH]D) to asthma. A recent report found a positive association between serum 25(OH)D and pneumococcal antibody titers (PATs) among patients with atopy or asthma. However, it is unknown whether vitamin D status affects the waning of PATs over time, and whether the change is affected by atopy.

This issue was addressed in a prospective follow-up study including 20 asthmatic patients and 19 nonasthmatic controls. Fifteen percent of the participants were children; all were white. Pneumococcal antibody titers and serum 25(OH)D levels were measured at baseline and at follow-up, an average of 12 months later.

Serum 25(OH)D levels were negatively correlated with the reduction in PATs at follow-up--ie, participants with the highest 25(OH)D concentration at baseline had a smaller reduction in PATs over time. This trend was significant only among the asthmatic patients, after controlling for duration of follow-up and pneumococcal colonization. Similar trends were noted in patients with other atopic conditions.

Specifically in patients with asthma and atopy, higher serum 25(OH)D levels may be linked to reduction in waning of PATs over follow-up. "Vitamin D may be ➤➤

an important immune modulatory that affects humoral immunity depending on the underlying immune milieu," the researchers write. They call for further studies to replicate and clarify the mechanisms of this inverse association.

COMMENT: *The authors of this study recently reported that 25(OH)D levels and pneumococcal titers correlated positively in atopic and asthmatic patients, as compared to the inverse correlation seen in nonatopic patients. This was the first prospective study to look at the levels of 25(OH)D and waning pneumococcal titers over time in atopic and nonatopic patients, performed in light of the recommendation for pneumococcal vaccination in adult asthmatics. Patients with the highest baseline levels of 25(OH)D had the lowest decrease in pneumococcal titers over time.*

The authors recommend further studies to investigate whether supplementation with vitamin D could decrease the risk of pneumococcal disease. For practicing allergists, this study raises an interesting possibility to further improve the long-term care of our asthmatic patients.

V.H.-T.

Ryoo E, Kumar R, Kita H, Juhn YJ: Serum 25-hydroxyvitamin D concentrations and waning pneumococcal antibody titers among individuals with atopy.

Allergy Asthma Proc. 2013;34:370-377. ♦♦

Are ADHD Patients at Increased Risk of Atopic Disease?

PREVIOUS studies have examined the possibility of a relationship between attention-deficit/hyperactivity disorder (ADHD) and allergic diseases. Some environmental risk factors have been implicated in both ADHD and allergic asthma. The association of ADHD with atopic diseases and skin infections in children was evaluated using a large primary care database.

From the U.K. General Practice Research Database, the investigators identified 884 boys with an initial diagnosis of ADHD and treatment with methylphenidate. Each case was matched for age and practice to four controls who did not have ADHD or any ADHD medication. Associations of ADHD with asthma and other atopic disorders, skin infections, and medications to treat these disorders were analyzed.

After adjustment for age and low birthweight or preterm delivery, boys with ADHD were more likely to have a history of asthma, odds ratio (OR) 1.4; or impetigo, OR 1.5. Cases with ADHD were also more likely to have been prescribed any antihistamine drug, OR 1.6.

Boys with ADHD also had higher rates of cow's milk and tolerance and prescription of antiasthmatic drugs, respiratory corticosteroids, topical steroids, antibacterial drugs, or antifungal drugs. However, these associations were not independent on adjusted analysis.

These observational data add to the evidence that childhood ADHD may be linked to atopic disease and impetigo. Further studies are needed to investigate possible mechanisms of these associations, as well as possible preventive, diagnostic, and treatment measures.

COMMENT: *Because of the increased prevalence of allergic disease and ADHD, there is increasing interest in the possibility of an association between the two diseases. This large U.K. case-control study looked at patients with ADHD on medication. Patient history of atopic dermatitis was associated with ADHD, and boys with asthma or impetigo were at increased risk of ADHD. There was an even stronger association between ADHD and cow's milk intolerance. Use of prescription medications to treat asthma and impetigo was also associated with increased risk of ADHD. The authors believe their study supports the hypothesis that atopic diseases increase the risk of ADHD. For pediatric allergists, this information is important in light of the increasing numbers of patients with the diagnosis of ADHD. Further studies are needed to better understand the implications regarding possible prevention and treatment options for these patients.*

V.H.-T.

Hak E, de Vries TW, Hoekstra PJ, Jick SS: Association of childhood attention-deficit/hyperactivity disorder with atopic diseases and skin infections? A matched case-control study using the General Practice Research Database.

Ann Allergy Asthma Immunol. 2013;111:102-106. ♦♦

Perimenstrual/Catamenial Anaphylaxis--No Uniform Treatment

CATAMENIAL or cyclical anaphylaxis is an uncommonly reported condition in which women have recurrent episodes of multisystem allergic reactions occurring at the time of menstruation. Eight patients with catamenial anaphylaxis are reported, focusing on the clinical presentation and responses to treatment.

The patients were treated at three academic medical centers between 1998 and 2011. All had recurrent, life-threatening perimenstrual allergic reactions in the absence of identifiable triggers. The women had a median of 10 menstrual anaphylactic episodes, with a range of 4 to 24; median age at onset was 34 years.

Most cases were associated with cutaneous and gastrointestinal symptoms. In addition to anaphylactic triggers, conditions that might mimic anaphylaxis were ruled out. None of the women had elevated IgE levels; 3 out of 4 patients had negative results of skin testing for progesterone.

Responses to suppressive treatments were variable, but none of the women responded to high-dose systematic steroid treatment. There was no evidence of response to ketotifen, celecoxib or rofecoxib, or oral contraceptives. Antihistamines were tried in all 8 patients, only 1 of whom improved. Other treatments associated with response included leuoprolide, medroxyprogesterone, and salpingo-oophorectomy.

These cases of catamenial anaphylaxis illustrate the variable clinical presentation and unpredictable response to suppressive therapy. The authors conclude that it is a heterogeneous disorder which may involve a number of different mechanisms and mediators. The optimal treatment for this "probably underrecognized entity" is unclear. ➤➤

COMMENT: *This was an interesting multicenter, retrospective review of female patients with anaphylaxis around the time of menses. Because this is a diagnosis of exclusion, the diagnosis and treatment are challenging. None of the patients had elevated IgE levels. The response to a variety of medications differed among the small group of patients. While some patients did respond to hormone suppressive agents, only one responded to high-dose antihistamines. None responded to systemic steroids. Two were treated with hysterectomy and oophorectomy.*

The authors remind us that many factors are likely associated with this disease entity. Further studies and increased recognition of patients with catamenial anaphylaxis are needed to better understand this disease and improve the treatment of affected patients.

V.H.-T.

Bauer CS, Kampitak T, Messieh ML, et al: Heterogeneity in presentation and treatment of catamenial anaphylaxis.

Ann Allergy Asthma Immunol. 2013;111:107-111. ♦♦

Is Obesity Linked to Leukotriene Production in Asthma Patients?

LEPTIN, a proinflammatory adipokine, may play a role in the development of asthma and allergies. This could help explain why obese patients with asthma and corticosteroid resistance may respond to anti-leukotriene therapy. A group of asthmatic children underwent exercise challenge to examine the association of serum leptin with bronchial hyperresponsivness (BHR), as well as changes in relevant urinary markers.

The study included 86 children, aged 6 to 10 years, divided into four groups: obese and normal-weight children with asthma, obese children without asthma, and healthy controls. The children underwent serum leptin measurement and spirometry before and 30 minutes after exercise challenge. Urinary release of the mast cell marker 9α,11β-prostaglandin F_2 and leukotriene E_4 (LTE_4) in response to exercise were assessed as well.

Obese children with asthma had higher serum leptin levels compared to normal-weight asthmatic children: 11.5 versus 3.3 ng/mL. In the nonasthmatic groups, obese children also had higher serum leptin. After exercise, the obese asthmatic children showed significant increases in urinary LTE_4 and 9α,11β-prostaglandin F_2. The same markers increased in normal-weight asthmatic children, but to a lesser extent.

Serum leptin levels were related to BHR in response to exercise. Logarithmic serum leptin levels were significantly associated with logarithmic maximum percentage change in FEV_1, change in urinary LTE_4, and change in urinary 9α,11β-prostaglandin F_2 in both the obese and normal-weight children with asthma.

The results show that serum leptin values are associated with BHR and urinary LTE_4 and 9α,11β-prostaglandin F_2 release after exercise in asthmatic children. Thus leptin levels may be synergistically related to exercise-induced BHR in asthma, but not exclusively in obese patients. Further studies are needed to clarify the mechanisms of leptin-related effects on inflammation and BHR.

COMMENT: *With increasing concerns regarding obesity, the effects of proinflammatory leptin are of interest. This study was the first to look at levels of serum leptin, along with urinary leukotriene and prostaglandin levels, in asthmatic children after exercise. Leptin levels in serum were higher among obese asthmatics, and significantly associated with BHR. Increases in urinary leukotriene levels were seen in both obese and normal-weight asthmatics after exercise challenge. This study further supports the literature regarding the risks of asthma exacerbations associated with obesity in asthma.*

V.H.-T.

Baek H-S, Choi J-H, Oh J-W, Lee H-B: Leptin and urinary leukotriene E_4 and 9α,11β-prostaglandin F_2 release after exercise challenge.

Ann Allergy Asthma Immunol. 2013;111: 112-117. ♦♦

CYP3A4 Variant Affects Response to Fluticasone in Asthma

GENETIC variations affecting the metabolism of fluticasone propionate (FP) might help in understanding pharmacodynamic differences in response to inhaled corticosteroid therapy for asthma. Single-nucleotide polymorphisms (SNPs) of genes encoding cytochrome P450 3A enzymes were evaluated for their effects on asthma control in children receiving inhaled FP.

The study included 734 children with asthma, mean age 8.8 years. Most of the children were receiving daily inhaled corticosteroid therapy, with about two-thirds of treated children using inhaled FP. Genetic variations in drug metabolism were assessed by genotyping nine SNPs in the *CYP3A4*, *CYP3A5*, and *CYP3A7* genes. Asthma control was rated on a 0-to-15 scale (0 indicating good control), based on the National Heart, Lung and Blood Institute's Expert Panel 3 guidelines.

The *CYP3A5* and *CYP3A7* SNPs were unrelated to asthma control scores in children treated with FP. However, the presence of the *CYP3A4*22* allele was associated with significant improvement in asthma control. Average asthma control score was score 2.9 for the 7% of children with the variant allele, compared to 5.0 for children who did not have this SNP. Median scores were 3 and 4, respectively.

A variant *CYP3A4*22* allele is associated with significantly improved asthma control in children receiving daily inhaled FP. The same variant is associated with reductions in hepatic *CYP3A4* expression and activity. Pending further studies to determine the mechanisms of this effect, asthmatic patients with decreased *CYP3A4* activity might achieve better asthma control with inhaled FP therapy.

COMMENT: *The finding that the* CYP3A4*22 *allele is associated with better asthma control in children treated with inhaled fluticasone is provocative. This may be related to increased local and/or systemic concentrations of FP. Poor compliance is the most important* ➤➤

cause of treatment failure, but genetic differences may detect the appropriate treatment responders. Although the study was small, the findings deserve to be investigated in larger and diverse populations.
S.F.W.
Stockman CS, Fassl B, Gaedigk R, et al: Fluticasone propionate pharmacogenetics: CYP3A4*22 *polymorphism and pediatric asthma control.*
J Pediatr. 2013;162:1222-1227. ♦♦

No Predictors of Cortisol Response to ACTH Testing

ADRENAL insufficiency is a potential complication of treatment with supraphysiologic doses of glucocorticoids. The low-dose adrenocorticotropic hormone (ACTH) test is widely used for diagnosis of ACTH/cortisol insufficiency. This study sought to identify biologic or clinical predictors of the peak cortisol response to low-dose ACTH stimulation after supraphysiologic glucocorticoid therapy in pediatric patients.

The retrospective analysis included 103 children and adolescents, median age 8.0 years, undergoing low-dose ACTH stimulation at one hospital from 2008 to 2010. Asthma was the most frequent reason for glucocorticoid therapy, 30 patients. Other indications included hematologic, dermatologic, and rheumatologic disorders. Growth deceleration was present in 37% of patients, excessive weight gain in 33%, and both conditions in 14%.

The median duration of glucocorticoid treatment was 374 days, with a median 118 days of physiologic hydrocortisone replacement. The median maximum daily dose, in hydrocortisone equivalents, was 200 mg/m^2/d, with a cumulative dose of 16,728 mg/m^2. Median time since last dose was 43 days.

The response to ACTH stimulation testing was normal, with peak stimulation cortisol greater than 500 nmol/L, in 58% of patients. The peak cortisol level was unrelated to sex, prior morning cortisol, duration of glucocorticoid treatment, or cumulative dose. However, 28% of children with normal baseline cortisol levels still had a subnormal response to ACTH.

None of the biologic or clinical parameters analyzed can predict the cortisol response to ACTH stimulation in children who have received supraphysiologic doses of glucocorticoids. Based on their findings, the authors suggest two options: empiric glucocorticoids stress coverage for 18 months after the end of high-dose glucocorticoid treatment or serial ACTH testing until normal peak cortisol levels are achieved.

COMMENT: *Periodically, we need a wake-up call regarding some of our common treatments. Corticosteroids, both topical and systemic, are extremely beneficial for most of the diseases allergists treat. Nevertheless, there are significant side effects associated with this treatment, which have been apparent for over half a century. These authors attempted to tease out which factors might be associated with adrenal suppression. After treatment with supraphysiologic steroid doses, neither dose, duration, nor morning cortisol levels could accurately predict which children would respond to low-dose ACTH stimulation. We should continue to empirically prescribe steroid coverage for physiologic stress for 18 months after such treatment.*
S.F.W.
Wildi-Runge S, Deladoëy, J, Bélanger C, et al: A search for variables predicting cortisol response to low-dose corticotropin stimulation following supraphysiological doses of glucocorticoids.
J Pediatr. 2013;163:484-888. ♦♦

Alveolar NO linked to Disease Control in Mild Asthma

THE peripheral airways may be an important therapeutic target for optimizing asthma control. The alveolar fraction of exhaled nitric oxide ($C_{alv}NO$) is not reduced by inhaled fluticasone and remains elevated in patients with steroid-resistant asthma. The researchers measured $C_{alv}NO$ to evaluate the contribution of small airway inflammation to lack of disease control in mild asthma.

The study included 78 patients with mild asthma, with FEV_1 of more than 80% predicted and no regular treatment. Disease control was assessed using the Asthma Control Test (ACT). Exhaled nitric oxide was measured at multiple constant flows for calculation of bronchial NO and $C_{alv}NO$.

The mean ACT score was 20, with a range of 5 to 25. Mean bronchial NO was 27.1 ppb and mean $C_{alv}NO$ 5.7 ppb. The ACT score was unrelated to bronchial NO, but was significantly correlated with $C_{alv}NO$: r_s = 0.25. Mean $C_{alv}NO$ was 6.7 ppb in patients with uncontrolled asthma versus 4.9 ppb in those with controlled or partially controlled disease.

A subgroup of 55 patients underwent treatment with extra-fine inhaled corticosteroids. The asthma control benefit of this treatment was positively correlated with baseline $C_{alv}NO$ at 1 and 3 months: r_s = 0.39 and 0.49, respectively.

In patients with mild, untreated asthma, $C_{alv}NO$ is significantly related to lack of asthma control. The findings suggest that the peripheral airways contribute to the clinical presentation in the mildest cases of asthma. Measuring the alveolar fraction of NO could aid in assessing future risk and guiding the choice of treatment.

COMMENT: *We are always looking for ways to improve the monitoring of asthma control. The two-compartment model of nitric oxide production can be used to differentiate exhaled NO from more distal or alveolar airways from that of general bronchial NO concentrations. These authors show that alveolar eNO may reflect the major contributor of inflammation in patients with persistent asthma and seems to be a good predictor of asthma control. It is also of interest that extra-fine inhaled corticosteroids made an impressive improvement in alveolar eNO, suggesting that the smaller, peripheral airways play an important role in mild persistent asthma.*
S.M.F. ➤➤

Scichilone N, Battaglia S, Taormina S, et al: Alveolar nitric oxide and asthma control in mild untreated asthma.
J Allergy Clin Immunol 2013;131:1513-1517. ♦♦

Omalizumab Helps Patients with Persistent CIU

EVEN with high doses of H_1-antihistamines and/or add-on therapies, many patients with chronic idiopathic urticaria (CIU) experience persistent symptoms. Previous studies have suggested that anti-IgE therapy with omalizumab may be useful in this situation. This placebo-controlled trial evaluated omalizumab for safety as add-on treatment for patients with persistent CIU despite treatment.

The multicenter trial included 336 patients with persistent symptomatic CIU despite H_1-antihistamines at up to 4 times the approved dose plus H_2-antihistamines and/or leukotriene receptor antagonists. In a 3:1 ratio, patients were randomly assigned to treatment with omalizumab, six 300 mg sc injections at 4-week intervals, or placebo. Treatments were followed by a 16-week observations period.

The overall incidence and severity of adverse events and serious adverse events were similar between groups. The safety profile of omalizumab was similar to that documented in patients with allergic asthma. On secondary analysis, there was significant improvement in efficacy outcomes with omalizumab. At 12 weeks, the mean reduction in weekly itch severity score was 8.6 with omalizumab versus 4.0 with placebo. Improvements in hives, quality of life, and other efficacy outcomes were also noted at 12 weeks, and persisted to 24 weeks.

The trial supports the efficacy as well as safety of omalizumab for patients with persistent symptoms of CIU despite standard combination therapies. Further studies are needed to clarify the mechanisms by which anti-IgE therapy might improve outcomes in patients with CIU.

COMMENT: *Although this was initially designed as a safety study, the rapid onset of impressive improvement in pruritus symptoms in patients with CIU receiving omalizumab was remarkable. The improvement continued throughout the 24-week treatment period but was not sustained after discontinuation of omalizumab. Since we don't know the precise mechanism triggering CIU, one wonders how a therapy that targets IgE receptors can work. The authors speculate that the mechanism of action may be through normalization of basophils. Looks like omalizumab may be a potential new option for patients with this challenging condition.*
S.M.F.
Kaplan A, Ledford D, Ashby M, et al: Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy.
J Allergy Clin Immunol. 2013;132:101-109. ♦♦

Do Oral Steroids Help in Wheezing Preschoolers?

CHILDREN with severe wheezing are commonly prescribed oral corticosteroids (OCS). However, there are few data to support this treatment for wheezing episodes in preschool-aged outpatients. Data from previous studies of young children were used to evaluate the benefits of OCS in preschoolers with severe wheezing associated with acute lower respiratory tract infections (LRTIs).

Post hoc and replication analyses were performed in two previously reported cohorts of 1- to 5-year-old children with episodic wheezing. Symptom scores were compared during LRTIs that were and were not treated with OCS, with adjustment for disease and episode severity. A propensity score approach was used to classify episode severity. The benefits of OCS were assessed in terms of total symptom scores for the more severe episodes.

Analysis of 215 children from the Acute Intervention Management Strategies trial included 798 acute LRTIs, 112 of which were classified as severe. Area under the curve of total symptom scores was not significantly different for 70 episodes treated with OCS vs 42 in which OCS were not used. The AUC results were similar on analysis of 133 severe LRTIs in 278 children enrolled in the Maintenance Versus Intermittent Inhaled Corticosteroids in Wheezing Toddlers trial.

The findings question the benefits of OCS therapy for episodes of wheezing in preschool-aged children. Symptom severity during acute LRTIs is not significantly different for episodes treated with vs without OCS, even though most are treated using asthma controller medications. The authors call for a randomized controlled trial of OCS treatment in this common clinical situation.

COMMENT: *Performing post hoc and replication analyses in two cohorts of children with episodic wheezing, these authors suggest that OCS did not significantly reduce symptom severity during LRTI. This is somewhat counterintuitive to our usual practice. The main limitation of this study is that the authors employed statistical propensity modeling methodology from two prior trials that were not specifically designed to study the effect of OCS. Nevertheless, their report does raise the question of the risk vs benefit of OCS. We need to improve our understanding of the impact of LRTI and wheezing, particularly when recommending treatment for children with this resulting phenotype.*
S.M.F.
Beigelman A, King TW, Mauger D, et al: Do oral corticosteroids reduce the severity of acute lower respiratory tract illnesses in preschool children with recurrent wheezing?
J Allergy Clin Immunol. 2013;131:1518-1525. ♦♦

Cephalosporin IDT Not Useful in Predicting Immediate Hypersensitivity

INTRADERMAL skin testing (IDT) is commonly performed to predict immediate hypersensitivity reactions to cephalosporin antibiotics. However, the validity of this test has not been established.

In a prospective study, IDT was performed using four cephalosporins: one each from the first- through fourth generation cephalosporin drugs. Testing with penicillin G was performed as well. The study included 1,421 patients requiring preoperative cephalosporins. After testing, and regardless of the results, each patient received one of the study cephalosporins intravenously, followed by careful observation.

Overall, 5.2% of patients had positive results to testing with at least one cephalosporin. However, when these patients received a challenge dose with the same or a different cephalosporin, none had an immediate hypersensitivity reaction. In addition, 4 patients who experienced generalized urticaria and itching after challenge had negative results on skin testing with the same drug. Thus cephalosporin IDT had a sensitivity of 0% and specificity of 97.5%, with positive and negative predictive values of 0% and 99.7%, respectively.

Intradermal skin testing for cephalosporins has poor diagnostic value, including sensitivity and positive predictive values of zero. The authors conclude that cephalosporin IDT to predict immediate hypersensitivity before drug administration is not a useful test.

COMMENT: *We all know that skin testing to cephalosporins is less helpful than skin testing to penicillins, although historically this has been due to poor sensitivity. Using a non-irritating cephalosporin skin test concentration, these authors prospectively tested and challenged subjects without a known history of beta-lactam allergy. They found that cephalosporin skin testing was essentially worthless--including a 5% false positive rate! These results underscore the importance of not performing cephalosporin skin testing when the pretest probability is low.*
S.A.T.

Yoon S-Y, Park SY, Kim S, et al: Validation of the cephalosporin intradermal skin test for predicting immediate hypersensitivity: a prospective study with drug challenge.
Allergy. 2013;68:938-944. ♦♦

New Upper-Airway Inflammatory Mediators in AERD

EOSINOPHIL activation is now thought to play an important role in upper and lower airway inflammation associated with aspirin-exacerbated respiratory disease (AERD). This study used a proteomics approach to study the mechanisms of eosinophil activation in AERD, including evaluation of novel inflammatory mediators.

The study included 18 patients with AERD and 14 with aspirin-tolerant asthma, based on positive and negative responses to the lysine-aspirin nasal provocation test. Nasal lavage specimens were obtained before the test, at intervals within 1 hour, and at 3 hours after the test. An ImmunoCAP assay was used to measure eosinophil cationic protein and an enzyme-linked immunosorbent assay to measure cysteinyl leukotriene (Cys LT) levels. A comparative proteomics approach was used to identify novel proteins involved in AERD.

Early after testing, specimens from AERD patients showed significantly increased levels of ECP and CysLT. The late specimens showed continued increases in ECP, but not CysLT. Proteomic analysis showed upregulation of apolipoprotein A1 (ApoA1), α2-macroglobulin (α2M), and ceruloplasmin (CP), with levels significantly higher in AERD than those observed in chronic rhinosinusitis. The ECP response during the early period after testing in AERD patients was significantly correlated with ApoA1, α2M, and CP levels.

The results provide evidence of eosinophil activation in the upper airway as part of both the early and late responses to lysine-aspirin nasal challenge in patients with AERD. In addition to CysLT, ApoA1, α2M, and CP are identified as potentially important mediators of eosinophilic inflammation. These proteins may be useful biomarkers of chronic rhinosinusitis in AERD.

COMMENT: *Using a proteomics approach, these authors analyzed serial nasal lavage specimens during lysine-aspirin nasal challenge in patients with AERD. The results showed consistent eosinophilic activation and CysLT production, along with upregulation of a variety of proteins, including several not previously known to be involved in AERD. The findings provide a new perspective on how AERD differs from allergic respiratory disease.*
S.A.T.

Choi G-S, Kim J-H, Shin Y-S, et al: Eosinophil activation and novel mediators in the aspirin-induced nasal response in AERD.
Clin Exp Allergy. 44:43;730-740. ♦♦

Lessons from the Hygiene Hypothesis: An Animal Model for Treatment

EXPOSURE to a farming environment has been shown to have a protective effect against allergic disease in children. Such children show increased expression of Toll-like receptor 2 (TLR-2)--perhaps related to TLR2 ligands from gram-positive bacteria found in dust from these farms. Building from these data, the researchers developed a synthetic lipopeptide and evaluated its effects on the development of allergy in animals.

The triacyl lipopeptide was derived from a germination protein of *Bacillus cereus* (LPGerD). In a mouse model of asthma, treatment with LPGerD showed protection against sensitization as well as a strong reduction in airway inflammation. Bone marrow-derived dendritic cells pretreated with LPGerD resulted in reduced secretion of proinflammatory cytokines in response to stimulation with lipopolysaccharide. These dendrit-➤➤

ic cells also showed upregulation of mRNA for IRAK-M, which is critically involved in inducing lipopolysaccharide tolerance.

These experiments help to clarify the immunologic mechanisms by which exposure to a farm environment might protect against the development of allergies. The synthetic LPGerD--a TLR2 agonist similar to those found in cowshed dust extracts--may induce lipopolysaccharide tolerance, thus permitting antigen-presenting cells to mount a Th2 response. The synthetic LPGerD may offer a promising new approach to allergy prophylaxis.

COMMENT: *The epidemiologic highlights of the hygiene hypothesis are well known to practicing allergists and many of our patients, but so far few treatments have emerged from this model. This study demonstrates the potential of a novel synthetic peptide in an animal model as a way to prevent primary allergic sensitization. Although we are a long way from being able to prescribe this type of treatment, it is a promising strategy for preventing allergic diseases in the future. Stay tuned!*
S.A.T.
Stiehm M, Peters K, Weismüller K-H, et al: A novel synthetic lipopeptide is allergy-protective by the induction of LPS-tolerance.
Clin Exp Allergy. 2013;43:785-797. ♦♦

REVIEWS OF NOTE

COMMENT: *New clinical guidelines for the management of children 1 to 18 years of age with acute bacterial sinusitis include the addition of a clinical presentation designated as "worsening course (worsening or new onset of nasal discharge, daytime cough, or fever after initial improvement)." Also new is the option to treat immediately or to observe children with persistent symptoms for 3 days before treating, along with a recommendation that imaging is not necessary in children with uncomplicated acute bacterial sinusitis. Amoxicillin with or without clavulanate is the recommended first-line treatment. An accompanying systematic review of the evidence regarding management of acute uncomplicated sinusitis shows that there are no reliable diagnostic criteria to distinguish between children with acute viral and bacterial sinusitis. Greater severity of illness at the time of presentation seems to be associated with increased likelihood of antimicrobial efficacy.*
C.D.
Wald ER, Applegate KE, Bordley C, et al: Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years.
Pediatrics. 2013;132:e262-e280.
Smith MJ: Evidence for the diagnosis and treatment of acute uncomplicated sinusitis in children: a systematic review.
Pediatrics. 2013;132:e284-e296. ♦♦

COMMENT: *This is an excellent position statement regarding the diagnosis and management of patients with exercise-induced bronchospasm.*
B.E.C.
Parsons JP, Hallstrand TS, Mastronarde JG, et al: An official American thoracic society clinical practice guideline: exercised-induced bronchoconstriction.
Am J Respir Crit Care Med. 2013;187:1016-1027. ♦♦

COMMENT: *This "Images in Clinical Medicine" presents a child with generalized itching, rash and systemic symptoms after eating canned mackerel. While many of us know that this is a classic differential diagnosis in the work-up of urticaria/anaphylaxis, we have never seen it. The images and description of the clinical course help make this diagnosis real and vivid.*
C.D.
Vickers J, Safai B: Scomboid poisoning.
N Engl J Med. 2013;368:e31. ♦♦

COMMENT: *A number of national and international clinical practice guidelines have been developed to assist practitioners in optimizing health care for specific clinical conditions, including asthma. This study evaluated asthma guidelines in a systematic approach to assess the quality of asthma guidelines. The authors used the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument and analyzed 18 asthma guidelines that met their criteria. Factors analyzed included scope of purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, editorial independence, and an overall evaluation. None of the guidelines were classified as recommended, but nine (50%) were recommended with modifications (including the GINA and NAEPP guidelines). There was improvement in quality assessment of guidelines published in 2007-09 compared to those from 2001-06. A main limitation of this type of analysis is not evaluating any changes in clinical outcomes that may have occurred through implementation of the guidelines. The development of clinical guidelines is very challenging and many elements of guidelines, such as assessment of evidence, remain a moving target. While a perfect guideline will never exist, continued effort is required to optimize guideline development in order to maximize their potential benefit.*
D.A.K.
Acuña-Izcaray A, Sanchez-Angarita E, Plaza V, et al: Quality assessment of asthma clinical practice guidelines: a systematic appraisal.
Chest. 2013;144:390-397. ♦♦