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 13, Number 3 May - June 2011

LTRAs for Initial or Add-On Asthma Therapy: 'Real-World' Study

RANDOMIZED controlled trials are essential to establish the efficacy of asthma treatments, but they can't address all of the factors that may affect patient responses in clinical practice. Trials comparing oral leukotriene-receptor antagonists (LTRAs) with inhaled glucocorticoids for asthma have produced mixed results. This pragmatic study compared LTRA with inhaled glucocorticoid for initial and add-on therapy in a diverse clinical sample of patients with asthma.

The study consisted of two parallel, multicenter trials, both including U.K. primary care patients, aged 12 to 80, with physician-diagnosed asthma. Eligible patients had a Mini Asthma Quality of Life Questionnaire (MiniAQLQ) score of 6 or less, indicating impaired quality of life; or an Asthma Control Questionnaire (ACQ) score of 1 or above, indicating inadequate asthma control. Patients were randomly assigned to treatment with LTRA or an inhaled glucocorticoid, either as first-line controller therapy, 306; patients or add-on therapy, 352 patients. Both treatments were given in open-label fashion for 2 years. Patients remained under the care of their primary physician.

In both studies, the MiniAQLQ score increased by 0.8 to 1.0 point over the 2-year treatment period. Two-month assessment showed noninferiority of LTRA and inhaled glucocorticoid for this outcome: adjusted mean difference -0.3 to 0.3. At 2 years, the results approached equivalence: adjusted mean difference -0.11 in both trials. Asthma control, based on the ACQ score, was not significantly different between groups. Secondary outcomes, including asthma exacerbation rate and clinic-measured peak expiratory flow, were similar as well.

This "real-world" comparison suggests comparable outcomes with oral LTRA and inhaled glucocorticoid therapy for adolescent and adult asthma patients in primary care. The study demonstrates equivalence as both first-line controller therapy and add-on therapy at 2 months; noninferiority is not proved at 2 years' follow-up. Viewed together with the results of conventional randomized, controlled trials, this pragmatic study could aid in guiding clinical decision making. ➤➤

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

"*AllergyWatch*®" is an official publication and a registered trademark of The American College of Allergy, Asthma & Immunology and is published six times per year in one volume. Subscription rates: U.S., Individual $90.00 Outside the U.S.: $120.00, Residents, Fellows, Students within the U.S.: $65.00, outside the U.S., add $18.00, bulk subscription pricing available upon request of the publisher. Send subscription inquiries to *AllergyWatch*®,85 West Algonquin Road, Suite 550, Arlington Heights, IL, 60005. Address editorial enquiries to: *AllergyWatch*®, c/o Anthony Montanaro, MD., Editor, The Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, PV 320, Portland, Oregon 97201-3098. Telephone (503) 494-8531. ISSN 1521-2440.

COMMENT: *Although randomized, double blind, placebo controlled (RDBPC) trials are essential to validate the safety and efficacy of a particular drug, any asthma clinical research investigator will tell you that only on rare occasion would the average asthma patient in clinic meet the inclusion criteria for a particular study. "Pragmatic trials" have emerged as a way to evaluate a more "real-world" perspective of treatments whose safety and efficacy have already been established. By combining the results of two separate pragmatic trials, Price et al show that relative to alternative treatments, LTRAs fare much better in the real world than would have been predicted by numerous prior RDBPC trials. This study also highlights the difficulty of defining asthma control across the spectrum of asthma severity. The accompanying editorial and "statistics in medicine" articles (Dahlén et al, N Engl J Med. 2011;364:1769-1770; Ware and Hamel, N Engl J Med. 2001;364:1695-1697) help put these results in perspective.*
S.A.T. & A.M.

Price D, Musgrave SD, Sheepstone L, et al: Leukotriene antagonists as first-line or add-on asthma-controller therapy.
N Engl J Med. 2011;364:1695-1707. ♦♦

Acetaminophen in Pregnancy--Strong Evidence for Atopy Risk in Offspring

EPIDEMIOLOGIC data suggest that acetaminophen use may be an important risk factor for asthma. One review found higher rates of asthma and wheezing in children born to mothers who used acetaminophen during pregnancy. This meta-analysis takes a more focused look at the association between prenatal acetaminophen exposure and childhood asthma risk.

A systematic review of the literature identified six studies with data on the association between paracetamol use during pregnancy and childhood asthma. Random-effects meta-analysis focused on the primary outcome of childhood wheezing within the last 12 months. The children in the studies ranged from 30 to 84 months of age.

Offspring of women who used acetaminophen during any stage of pregnancy were 20% more likely to have current wheezing: random-effects odds ratio 1.21. Although there was some variation between studies, significant associations were noted for acetaminophen use during all trimesters of pregnancy. Prenatal acetaminophen exposure was also linked to increased risks of persistent asthma, severe asthma, and atopy.

The meta-analysis supports the association between acetaminophen use during pregnancy and the risk of wheezing and asthma in offspring. The results link acetaminophen use at any stage of pregnancy to wheezing risk in children aged 2.5 to 7 years. More research will be needed to clarify this association.

THE nature of the reported association between acetaminophen and asthma is still unclear. There are few data on how acetaminophen may affect atopic sensitization. Acetaminophen use during infancy and early childhood was evaluated as a risk factor for atopy and allergic disease at age 6.

As part of the New Zealand Asthma and Allergy Cohort Study, the study included data on acetaminophen exposure from birth to age 15 months in 505 infants. Wheezing and atopy, based on skin prick tests, were assessed in 914 children at age 5 to 6. Associations between early acetaminophen exposure and childhood atopy and allergic disease were assessed. Adjustment for potential confounders included number of chest infections and antibiotic use in early childhood.

Children exposed to acetaminophen during the first 15 months of life were more likely to have atopy at age 6: adjusted odds ratio (OR) 3.61. Acetaminophen use between age 5 and 6 was related to wheezing and atopy in dose-related fashion, although not with atopic sensitization. The➤➤

associations with wheezing and asthma increased with number of exposures. Compared to children using acetaminophen 0 to 2 times, ORs for wheezing were 1.83 for 3 to 10 exposures and 2.30 for more than 10 exposures. The ORs for current asthma were 1.63 and 2.16, respectively.

These birth cohort data add further evidence that early-life acetaminophen exposure increases the risk of atopy. Frequency of acetaminophen use also appears to contribute to maintenance of childhood asthma symptoms. Randomized trials are needed to establish the causal nature of these associations before any clinical recommendations can be made regarding acetaminophen use in children.

COMMENT: *These articles add to our understanding of the potential relationship between acetaminophen and atopy/asthma in children. (See also the accompanying editorials by Dharmage et al, Clin Exp Allergy 41:459-460; and Johnson et al, Clin Exp Allergy 41:296-298.) It appears that an association is clear, but important questions regarding causation remain. So far there is reluctance to recommend against using acetaminophen during pregnancy and/or early childhood.*
S.A.T.

Eyers S, Weatherall M, Jefferies S, Beasley R: Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. Clin Exp Allergy 41:482-489.
Wickens K, Beasley R, Town I, et al: The effects of early and late paracetamol exposure on asthma and atopy: a birth cohort.
Clin Exp Allergy 41:399-406. ♦♦

Still More on Acetaminophen and Allergic Disease

COULD increasing use of acetaminophen be a contributor to the rising prevalence of asthma worldwide? To address this question, the researchers analyzed data on adolescents enrolled in the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three.

The study included data on current asthma, rhinoconjunctivitis, and eczema symptoms among 13- and 14-year-olds enrolled in ISAAC Phase Three. Data on possible environmental risk factors included acetaminophen use in the past 12 months. Multivariate analyses included 180,887 adolescents from 77 centers in 36 countries.

On logistic regression analysis, the adolescents' current asthma risk increased along with frequency of acetaminophen use. Odds ratio (OR) for current asthma symptoms was 1.43 for medium exposure (at least once yearly) and 2.51 for high exposure (at least once monthly), compared to no acetaminophen use. There were similar associations for current rhinoconjunctivitis and eczema symptoms. For the latter outcomes, the risk estimates were similar on analysis excluding patients with any history of asthma.

The results show exposure-dependent associations between acetaminophen and current asthma symptoms in a global sample of adolescents. This widely used medication may be an important risk factor for the development and persistence of asthma, rhinoconjunctivitis, and eczema in young patients. If the reported associations were causal, they would have a major impact on the population risk of asthma.

WHEREAS acetaminophen is a possible risk factor for asthma and allergic disease, geohelminth infection--particularly with hookworm--may be a protective factor. The independent effects of these factors were evaluated in a population-based study from East Africa.

The study included 1,006 live infants born to a population-based cohort of 1,065 pregnant women in one Ethiopian town. When the children were 1 and 3 years old, detailed information was collected on history of wheezing, eczema, and acetaminophen use, along with potential confounders. Infection with hookworm or other geohelminths was assessed using stool samples. Samples of children who were free of wheezing or eczema at age 1 (756 and 780 children, respectively) were evaluated to assess the independent effects of acetaminophen exposure and geohelminth infection on the risk of developing these allergic diseases by age 3.

In previously disease-free children, the rate of wheezing developing between age 1 and 3 was 7.7% while the incidence of eczema was 7.3%. Risk of incident wheezing increased in dose-dependent fashion with acetaminophen use: adjusted odds ratio (OR) 1.88 for 1 to 3 tablets in the last month and 7.25 for 4 or more tablets (compared to no use). Acetaminophen use was unrelated to eczema incidence. Because of the relatively low prevalence of geohelminth infection (less than 4%) the effect on allergic disease risk could not be calculated.

The findings add further evidence that acetaminophen use in young children affects the risk of incident wheezing. For children free of wheezing at age 1, the risk of new-onset wheezing by age 3 increases with frequency of acetaminophen use. Longer follow-up is needed, including assessment of the effects of geohelminth infection.

COMMENT: *Two large cohort studies show that exposure to acetaminophen beginning in utero is associated with development of asthma, rhinitis and eczema. This may be explained by decrease in airway and circulating glutathione-S-transferase. The two articles and the accompanying editorial by Stephen Holgate (Am J Respir Crit Care Med. 2011;183:147-151) are quite enlightening.*
B.E.C.

Beasley RW, Clayton TO, Crane J, et al: Acetaminophen use and risk of asthma, rhinoconjunctivitis, and eczema in adolescents: International Study of Asthma and Allergies in Childhood Phase Three. Am J Respir Crit Care Med. 2011;183:171-178.
Amberbir A, Medhin G, Alem A, et al: The role of acetaminophen and geohelminth infection on the inci-➤➤

dence of wheeze and eczema: a longitudinal birth-cohort study.
Am J Respir Crit Care Med. 2011;183:165-170. ♦♦

Swimming May Not Increase Asthma Risk After All

SOME cross-sectional studies have suggested that swimming in chlorinated pools is a risk factor for the development of asthma. However, research on this issue has had important limitations and produced conflicting results. Data from a longitudinal birth cohort study were used to assess the relationship between recreational swimming pool attendance and childhood asthma and allergic disease.

The analysis included data on 5,738 children enrolled in the Avon Longitudinal Study of Parents and Children. Information on swimming pool attendance was collected at intervals from 6 to 81 months of age. Symptoms of asthma and other allergic diseases--along with asthma medications and potential confounding factors--were assessed when the children were 7 to 10 years old. Spirometry and skin prick testing were performed at 7 to 8 years. Swimming at different times during early childhood was evaluated as a risk factor for asthma and allergic symptoms.

At age 7, more than half of the children were swimming at least once weekly. Frequency of swimming was unrelated to the rate of asthma or other symptoms, including rhinitis, wheezing, eczema, and hay fever. Rather, children with high cumulative swimming pool attendance were less likely to have ever or current asthma: odds ratio (OR) 0.88 and 0.50, respectively. Frequent swimming was also associated with a 0.20-standard deviation increase in forced midexpiratory flow. Among children with any history of asthma at age 7, those with high cumulative swimming pool attendance were less likely to have asthma at age 10: OR 0.34.

In contrast to some previous studies, this longitudinal analysis shows no evidence that swimming pool attendance increases the risk of asthma and allergic disease symptoms in U.K. children. To the contrary, frequent swimming was linked to increased lung function and a lower risk of asthma, especially in children with a history of respiratory conditions. There is no evidence of reverse causation, but confounding by physical activity or selection bias is possible.

COMMENT: *This prospective study reaches different results from previously reported retrospective studies. The increased prevalence of asthma in Olympic swimming may not be directly translated to recreational swimming in outdoor pools. A pro-and-con debate in the same issue (Am J Respir Crit Care Med. 2011;183:569-572) leaves the reader with the notion that more research is needed.*
B.E.C.
Font-Ribera L, Villanueva CM, Nieuwenhuijsen MJ, et al: Swimming pool attendance, asthma, allergies, and lung function in the Avon Longitudinal Study of Parents and Children cohort.
Am J Respir Crit Care Med. 2011;183;582-588. ♦♦

Budesonide for Asthma Doesn't Increase Pneumonia Risk

STUDIES of patients with chronic obstructive pulmonary disease (COPD) suggest a possible increase in pneumonia associated with inhaled corticosteroid (ICS) therapy. This raises concerns about a similar risk associated with ICS treatment in asthma. This issue was addressed in a retrospective analysis of clinical trials of budesonide for asthma.

The primary analysis included all double-blind, placebo-controlled trials of budesonide or budesonide/formoterol for asthma, sponsored by one drug company and completed through 2007. In each trial, treatment lasted for at least 3 months. The 26 studies provided data on 9,067 patients receiving budesonide and 5,926 receiving comparator treatments.

A secondary analysis included data from non-placebo-controlled trials of budesonide: 60 studies including 33,496 patients treated with budesonide and 2,773 treated with fluticasone. The relative effects of ICS treatment on the risk of pneumonia were assessed, including pneumonia episodes classified as adverse events (AEs) or serious adverse events (SAEs).

The primary analysis found no significant increase in the rate of pneumonia AEs among patients taking budesonide. In fact, pneumonia AEs were about half as frequent with budesonide, 0.5% (10.0 events/1,000 patient-years [TPY]); compared to placebo, 1.2% (19.3 per TPY). Rates of pneumonia SAEs were similar as well: 0.15% and 0.13% (2.9 and 2.1 per TPY, respectively).

On secondary analysis, total rates were 0.70% for pneumonia AEs (12.7 per TPY) and 0.17% for pneumonia SAEs (3.1 per TPY). Risks did not increase at higher doses of budesonide and did not differ between budesonide and fluticasone.

In contrast to studies in COPD patients, budesonide is not associated with an increased risk of pneumonia in patients with asthma. This is so for pneumonia identified as AEs or SAEs and at higher vs lower ICS doses.

COMMENT: *The results of the study do not support an increased risk for pneumonia in patients with asthma using inhaled corticosteroids. This is in contrast to data in COPD, where fluticasone proprionate--but not budesonide--has shown increased risk for pneumonia.*
B.E.C.
O'Byrne PM, Pedersen S, Carlsson L-G, et al: Risks of pneumonia in patients with asthma taking inhaled corticosteroids.
Am J Respir Crit Care Med. 2011;183:589-595. ♦♦

Does Blood Type Affect Asthma Exacerbation Risk?

VIRAL infections are an important trigger for asthma exacerbations, but some patients seem more susceptible than others. Studies have suggested that blood type O is a risk factor for viral diarrheal illness--evidently related to expression of the O antigen (also called H antigen) on mucosal epithelial surfaces. ➤➤

This study evaluated whether the O-secretor mucin glycan phenotype, previously linked to gastrointestinal viral infection, has any effect on susceptibility to asthma exacerbation.

The investigators performed a case-control study including 23 asthma patients who were prone or resistant to asthma exacerbations, based on a history of exacerbation requiring prednisone treatment within the past 2 years. Based on the presence of H (O), A, B, or AB antigens, asthma patients with the O-secretor mucin glycan phenotype were 5.8 times more likely to be in exacerbation-prone group.

The replication study included 101 exacerbation-prone cases and 103 exacerbation-resistant controls. In this analysis, patients with the O-secretor phenotype were about twice as likely to be in the case group: OR 2.25.

These case-control studies support the hypothesis that patients with the O-secretor mucin glycan phenotype are more susceptible to severe asthma exacerbations. Further insights into the mechanisms of this association are needed to evaluate the possibility of converting exacerbation-prone asthma patients to the exacerbation-resistant phenotype.

COMMENT: *Blood type-directed diets to improve well-being and accelerate weight loss are being reported in the lay press. There are data to support an increased susceptibility to viral gastroenteritis in individuals with type O blood. The current study shows us that this now extends to asthma exacerbations. An interrelationship with mucin glycans may influence the susceptibility to asthma exacerbations. These findings may open new areas of investigation.*
B.E.C.

Innes AL, McGrath KW, Dougherty RH, et al: The H antigen at epithelial surfaces is associated with susceptibility to asthma exacerbation.
Am J Respir Crit Care Med. 2011; 183:189-194. ♦♦

Proteomics Identifies Asthma Biomarkers in EBC

PREVIOUS studies have attempted to identify new asthma biomarkers in exhaled breath condensate (EBC). Proteomics is a promising approach to identifying useful new proteins for early detection of asthma or new therapeutic targets. Proteomic analysis was performed to look for differences in the protein profile from EBC samples from children with vs without asthma.

The researchers analyzed EBC samples from 40 children with asthma, aged 6 to 12 years, and 30 healthy controls. Proteolytic peptides in EBC were separated and detected using liquid chromatography and mass spectrometry. Support vector machine analysis was used to develop protein profiles capable of discriminating between children with and without asthma.

A classification model based on a support vector classifier using 10 peptides correctly classified all patients as having or not having asthma. The model also discriminated between children with controlled vs partially controlled asthma. The peptide patterns were not significantly correlated with conventional exhaled markers such as spirometry or exhaled nitric oxide, or with some newer markers. Identifiable peptides with discriminating capacity included cytokeratins, albumin, actin, hemoglobin, lysozyme, dermicidin, and calgranulin B.

Using proteomic analysis, this study describes proteolytic peptide patterns in EBC samples that can distinguish between children with and without asthma. The findings represent an important step in identification of exhaled biomarkers for asthma. The contributions of the identified proteins to asthma development or pathophysiology are as yet unknown.

COMMENT: *Exhaled breath condensate is a noninvasive way of sampling substances and conditions in the lungs, and it has been used to search for asthma biomarkers. Proteomics is an exciting and relatively new field with the potential to help us understand basic allergic disease responses as well as help differentiate patient phenotypes. This study involved proteomic analysis of EBC in children with asthma. A different peptide pattern was seen in healthy children compared with children with asthma, and this difference could not be explained by previously identified EBC asthma markers. Stay tuned....*
S.A.T.

Bloemen K, Van Den Heuvel R, Govarts E, et al: A new approach to study exhaled proteins as potential biomarkers for asthma.
Clin Exp Allergy. 2011;41:346-356. ♦♦

Nasal Allergy in Infants-- More Common Than We Thought

LITTLE is known about allergic rhinitis (AR) in infancy--when rhinitis occurs in infants, it is often ascribed to infections. There are few data on the relationship between rhinitis symptoms and atopy in children younger than 4. This issue was addressed using data from a French birth cohort study.

The study included 1,850 toddlers who had been enrolled in the "Pollution and Asthma Risk: An Infant Study" (PARIS) birth cohort. Symptoms of AR were assessed at 18-month follow-up examinations. Markers of atopy--blood eosinophil count of 470 eosinophils/mm^3, total IgE of 45 U/mL or higher, and presence of allergen-specific IgE--were assessed in blood samples. The association between AR symptoms and markers of atopy was assessed, with adjustment for potential confounders.

Parents reported AR-like symptoms--runny or blocked nose or sneezing without a cold--in 9.1% of toddlers. Symptoms of AR were commonly accompanied by a dry cough. When both parents had a history of AR, the children were twice as likely to have AR symptoms: odds ratio (OR) 2.09. The presence of AR symptoms was correlated with markers of atopy, particularly blood eosinophilia (OR 1.54) and house dust mite sensitization (OR) 2.91. There were no significant associations with sensitization to foods.

The study provides evidence of early-onset of ➤➤

AR in young children, appearing as early as 18 months. For toddlers with rhinitis, the possibility of AR should be considered especially when parents have a history of AR or when the child has a high blood eosinophil count or evidence of sensitization to inhalant allergens.

COMMENT: *Those of us who see very young patients can attest to the existence of dust mite or cat allergy in 2-year-olds, but there has been little study of AR prevalence in this age group. These authors analyzed data from a French population-based study of healthy newborns followed up for 18 months. Among the findings was an increase in the rate of specific IgE to inhalant allergens in 18-month-olds with rhinitis symptoms.*
S.A.T.

Herr M, Clarisse B, Nikasinovic L, et al: Does allergic rhinitis exist in infancy? Findings from the PARIS birth cohort.
Allergy. 2011;66:214-221. ♦♦

Venom Anaphylaxis in Adults--Don't Discount Low Venom-Specific IgE Levels!

SEVERAL risk factors for severe allergic reactions to Hymenoptera venom have been identified. However, the significance of total and specific IgE levels has been unknown. These and other factors affecting the severity of systemic allergic reactions to Hymenoptera stings were evaluated in a retrospective study.

Out of 1,002 patients referred for evaluation of insect allergy over a 5-year periods, 865 reported systemic allergic reactions to stings--mainly honey bee and wasp stings. Data on total and venom-specific IgE and baseline tryptase levels were available for 758 patients. These levels, along with atopy, age, and sex, were evaluated for association with the severity of sting reactions.

In a model including other potential risk factors, there was no significant association between total and specific IgE levels and the severity of allergic reactions to stings. Highly severe reactions were more likely in patients with a baseline tryptase level of 11.4 μg/L or higher and in adults older than 55. On bivariate analysis, patients with grade IV reactions actually had lower total and honey bee-specific IgE levels than patients with less-severe reactions. Venom-specific IgE levels were higher in patients allergic to honey bee venom than to *Vespula* venom.

Among patients with Hymenoptera allergy, highly severe sting reactions are associated with lower total and venom-specific IgE levels. This relationship is largely explained by the effects of older age, which is associated with lower total IgE levels and higher baseline serum tryptase levels, along with the presence of cardiovascular disease.

COMMENT: *Predicting which venom-allergic patients will have severe systemic reactions from stings has been a challenge. In recent years, we have begun to recognize risk factors--including serum tryptase level as an important predictor of reaction severity. This large retrospective study found that grade IV reactions were more likely in patients over 40 years old. Ironically, patients with grade IV reactions had slightly lower levels of venom-specific IgE than those with less-severe systemic reactions.*
S.A.T.

Blum S, Gunzinger A, Müller UR, Helbling A: Influence of total and specific IgE, serum tryptase, and age on severity of allergic reactions to Hymenoptera stings.
Allergy. 2011;6:222-228. ♦♦

What's the Dendritic Cell Response to Venom Immunotherapy?

DENDRITIC cells (DCs) modulate T-cell differentiation, and thus play a central role in the response to specific immunotherapy (SIT) for allergy. There are few data on what happens to blood DCs before and during SIT. This pilot study evaluated the numbers and characteristics of blood DC subsets in patients undergoing SIT for Hymenoptera venom allergy.

The study included 20 patients undergoing an in-hospital rush SIT protocol for allergy to bee or wasp venom, along with 20 age- and sex-matched controls. Four-color flow cytometry was used to analyze blood myeloid and plasmacytoid DCs before the start of SIT, 52 hours after initiation of the rush SIT protocol, and after 12 months of subcutaneous SIT.

At baseline, plasmacytoid DC numbers were similar in Hymenoptera-allergic patients and controls. In the allergic patients, plasmacytoid DC numbers fell significantly within 52 hours after the start of SIT, returning to baseline 12 months later. At all three times, the allergic patients had higher numbers of myeloid DCs. Analysis of DC characteristics during SIT showed changes in expression of function-associated surface molecules, such as Fc γ receptor 2 and Toll-like receptor 2.

The findings help to clarify the DC response to Hymenoptera venom SIT. Affected patients show elevated numbers of blood myeloid DCs, with changes in expression of functional surface molecules during SIT. Decreases in blood plasmacytoid DCs during venom immunotherapy are only temporary, returning to baseline within 12 months.

COMMENT: *Changes in T-cell differentiation and function are the underlying mechanism driving the clinical benefit of SIT. Using a rush protocol for venom immunotherapy, these researchers report an initial fall in plasmacytoid DCs after the initiation of the SIT, but return to baseline levels after the 12 months of maintenance treatment. Interestingly, there was no change in myeloid DC number. This suggests a specific change in the expression of functional surface molecules on DCs during initiation of SIT. This study only investigated quantitative peripheral DCs. Additional functional studies will be needed to further understand the impact of SIT on dendritic immune responses.*
S.M.F.

Drechsler K, Bratke K, Petermann S, et al: Impact of immunotherapy (SIT) on blood dendritic cells in patients with Hymenoptera venom allergy.
J Allergy Clin Immunol 2011;127:487-494. ♦♦

Six Factors Predict Oral Challenge Response in Food-Allergic Kids

SOME test is needed to predict the outcomes of oral food challenges in children with food allergies. Approaches using serum specific IgE or skin prick tests have been tried, but their value decreases at levels below accepted decision points. This study reports the development and validation of a model incorporating clinical factors for predicting oral food challenge responses in children.

Data on 429 children from a single allergy center were used to generate an initial "proto-algorithm," which was evaluated and modified using data on 289 children from another center. The model was then prospectively validated using blinded data on 70 children undergoing oral challenge for peanut, milk, or egg allergy at the second center. The researchers developed specific models for children with peanut, milk, and egg allergy.

The resultant model included six clinical factors: the results of skin prick testing; serum specific IgE; the difference between total and specific IgE; and patient symptoms, sex, and age. In the prospective validation phase, the model accurately identified 97% of children with positive responses to oral food challenge and 94% of those with negative responses. These accuracy values were significantly higher than prediction based on specific IgE only, skin prick test only, or these two factors in combination.

The described model, based on six readily assessed clinical factors, is highly accurate in predicting the results of oral challenge in children with food allergies. It may have important implications for the health care provision, quality of life, and health resource use among food-allergic children. The authors are developing a simple electronic calculator based on their model.

COMMENT: *"When will my child outgrow his food allergy?" That frequently asked question is addressed in this three-phase study, which reports a predictive modeling tool using six clinical factors to predict results of oral challenges in children with food allergies. The model–which includes age, sex, history of reaction, specific IgE, total IgE minus specific IgE and allergy skin test–had an overall 97% positive predictive value and 94% negative predictive value. It was a more sensitive predictor for peanut allergy than for egg or milk allergy. One interesting finding was that history of reaction was one of the strongest predictors of positive food challenge. Once again, more data supports the lessons from mentors such as Béla Schick: "Listen to the patient."*
SMF

DunnGalvin A, Daly D, Cullinane C, et al: Highly accurate prediction of food challenge outcome using routinely available clinical data.
J Allergy Clin Immunol. 2011;127:633-639. ♦♦

Gene Variant Affects Allergy Risk Associated with Day Care

A recent study found that variation in the Toll-like receptor 2 gene (*TLR2/-16934*) is associated with allergic disease risk among farm children, but not in children who don't live on farms. Like farm children, those attending day care may be exposed to a comparatively high microbial load. The *TLR2/-16934* variant was analyzed as a protective factor against allergic disease in children attending day care.

The study used data from population-based birth cohorts in Manchester, U.K. (727 children), and Tucson, Ariz. (263 children). In both cohorts, the children were recruited before birth and followed up to at least age 5. Associations between *TLR2* genotype and the occurrence of allergic sensitization and wheezing at follow-up were assessed.

Overall, there was no association between *TLR2/-16934* and the occurrence of sensitization and wheezing in either cohort. However, there was a significant interaction between *TLR2/-16934* and day care attendance. In the Manchester cohort, children who were carriers of the T allele and who attended day care had a lower sensitization rate than children who did not attend day care. In contrast, among children who were AA homozygotes, day care attenders tended to have a higher rate of sensitization.

A longitudinal model in the Tucson cohort showed a significant interaction between *TLR2/-16934* and day care attendance for the occurrence of allergic wheezing. The associations remained significant after adjustment for socioeconomic status.

The risk of atopic sensitization and wheezing in children attending day care varies according to the presence of *TLR2/-16934*. Depending on *TLR2* status, day care attendance may increase allergy risk in some children but decrease risk in others. If confirmed, the results may have implications for primary prevention of allergies.

COMMENT: *Toll-like receptor gene 2* (TLR2) *is associated with allergies. Collecting data from two prospective birth cohorts, these researchers found that children with the* TLR2/-16934 *gene who went to day care were less likely to develop asthma than those without* TLR2/-16934. *In the study populations, the* TLR2/-16934 *gene was present, either heterozygous or homozygous, in about three-fourths of children. It is of interest that the outcomes of the same intervention--day care--were so opposite in children without* TLR2/-16934. *The results suggest that certain genetic factors offer a protective effect against the development of asthma for children in day care.*
S.M.F.

Custovic A, Rothers J, Stern D, et al: Effect of day care attendance on sensitization and atopic wheezing differs by Toll-like receptor 2 (TLR2) genotype in 2 population-based birth cohort studies.
J Allergy Clin Immunol. 2011;127:390-397. ♦♦

Wider Range of Microbes Helps Explain Lower Asthma Risk in Farm Children

CHILDREN exposed to a wider range of microbes--especially on farms--have lower rates of asthma and atopy. Previous studies using simple markers of microbial exposure support this observation. The current study examines this relationship using more sophis-➤➤

ticated markers of microbial exposure.

The analysis included data from two cross-sectional studies relating asthma and atopy to diversity of microbial exposure in farm vs nonfarm children. The studies used two different and complementary methods to assess microbial diversity in dust samples: culture techniques in one study and single-strand conformation polymorphism (SSCP) analysis--which detects bacteria that cannot be demonstrated by culture--in the other study.

In both studies, farm children were exposed to a wider variety of environmental organisms and had lower rates of asthma and atopy. Both studies showed significant, inverse relationships between diversity of microbial exposure and asthma risk: odds ratios (OR) were 0.86 for the study using culture techniques and 0.62 for the study using SSCP analysis. Some specific exposures were inversely related to asthma risk, including fungal species of the taxon eurotium: adjusted OR 0.37. Higher exposure to various bacterial species including *Listeria monocytogenes*, bacillus species, and corynebacterium species was also associated with a lower risk of asthma: OR 0.57.

Using both culture and SSCP techniques, the study strengthens the association between the lower rate of asthma in farm children and their exposure to a greater variety of environmental micro-organisms. Wider microbial exposure accounts for much of the protective effect of growing up on a farm. The study also helps to narrow the search for specific microbes that may confer protection.

COMMENT: *The well-known "hygiene hypothesis" tells us that growing up on a farm is associated with a reduced risk of allergies and asthma. This European study increases the granularity of the data. It shows that children who grew up in an environment with more diverse bacteria in their homes had a lower risk of asthma (though not of allergy). Many of the species weren't pathogenic, leading to speculation that colonization of the airways in early life promotes innate, rather than specific, immunity that is protective against asthma. (Contrast these findings with the microbial diversity analysis in uncontrolled adult asthma, below.)*
R.J.M.

Ege MJ, Mayer M, Normand A-C, et al: Exposure to environmental microorganisms and childhood asthma.
N Engl J Med. 2011;364:701-709. ♦♦

Airway Microbiota Linked to Bronchial Hyperresponsiveness

MULTIPLE lines of evidence--including improved lung function in response to macrolide antibiotic therapy--suggest that bacterial colonization of the bronchial mucosa may contribute to asthma pathogenesis. The characteristics of the airway microbiota might thus affect the clinical features of asthma. This pilot study used culture-independent techniques to evaluate the relationship between the airway microbiota and clinical asthma.

The study used high-density 16S ribosomal RNA microarray and parallel clone library-sequencing analysis to profile the airway microbiota of 65 adults with suboptimally controlled asthma. The patients were participants in a trial of extended clarithromycin treatment. The diversity of the airway microbiota was assessed and compared with the asthma clinical characteristics.

Compared to healthy controls, the asthma patients had a higher bacterial burden, as reflected by 16S ribosomal RNA amplicon concentrations, and increased bacterial diversity. Both bacterial burden and diversity were associated with bronchial hyperresponsiveness on multivariate analysis. Certain bacterial phylotypes were specifically associated with higher bronchial hyperresponsiveness, including the families Comamonadaceae, Sphingomonadaceae, and Oxalobacteraceae.

In adults with suboptimally controlled asthma, a higher burden and diversity of airway microbiota are associated with increased bronchial hyperresponsiveness. Further studies are needed to try to identify specific airway microbiota involved with asthma pathogenesis.

COMMENT: *In contrast to the study by Ege et al showing an inverse correlation between microbial diversity and primary asthma risk in children, this study found that increased diversity of bacterial taxa in bronchial washings from adults with uncontrolled asthmatics was correlated with higher bronchial hyperresponsiveness. My question is, which is cause and which is effect? The authors prematurely imply that the bacterial diversity is the cause of the hyperresponsiveness.*
R.J.M.

Huang YJ, Nelson CD, Brodie EL, et al: Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma.
J Allergy Clin Immunol. 2011;127:372-381. ♦♦

Chronic Cough Linked to Irritable Larynx

CHRONIC cough may be related to perennial rhinitis and/or chronic rhinosinusitis (PR/CRS), asthma, or gastroesophageal reflux disease (GERD). In a previous study, the authors reported that most patients with rhinosinusitis, postnasal drip, and pharyngolaryngitis have laryngeal hyperresponsiveness (LHR)--defined as vocal cord adduction on histamine challenge-consistent with irritable larynx. In the current study, they examined the role of LHR in a large sample of patients with chronic cough.

The study included 372 patients with chronic cough, along with 52 asthmatic controls without cough. Both groups underwent assessment of LHR and bronchial hyperresponsiveness to histamine. In 56% of patients, chronic cough was triggered by PR/CRS. The trigger was GERD in 17% of patients and asthma in 11%; the remaining 16% had unexplained chronic cough.

All groups of chronic cough patients had a high prevalence of LHR: 76% for those with PR/CRS, 77% with GERD, 93% with asthma, and 66% with unexplained chronic cough. In contrast, just 11% of asthma controls without cough had LHR. Ninety-five per-➤➤

cent of patients with asthma-triggered chronic cough had upper airway disease, compared to 6% of asthmatic controls.

Bronchial hyperresponsiveness and testing for atopy distinguished asthma and PR/CRS patients, respectively, from those with GERD and unexplained cough. In 172 patients retested after treatment for the specific cause of cough, 63% had resolution of LHR and 57% had resolution of bronchial hyperresponsiveness.

Many patients with chronic cough have LHR, indicating an irritable larynx. This finding appears to be related to upper airway involvement, in the form of PR/CRS, GERD, or idiopathic sensory neuropathy. Monitoring LHR provides objective data on the response to treatment for chronic cough.

COMMENT: *For those of us allergists who evaluate patients who suffer from chronic cough, this study is fascinating. Whether the patients had asthma, GERD, or postnasal drip, they showed increased laryngeal responsiveness to a histamine inhalation challenge, as measured by inspiratory flow rates. The common pathway for most of the authors' chronic cough patients was an irritable larynx, and treatment success was documented by longitudinal improvement in laryngeal histamine hyperresponsiveness. The group with cough due to chronic rhinosinusitis was the most responsive to treatment. Allergists are in the most favorable position to diagnose and treat these chronic cough patients.*
R.J.M.
Bucca CB, Bugiani M, Culla B, et al: Chronic cough and irritable larynx.
J Allergy Clin Immunol. 2011;127:412-419. ♦♦

Observed Therapy at School Improves Outcomes for Urban Kids with Asthma

AMONG children with asthma, those in low income and minority groups have increased morbidity and low rates of recommended preventive therapy. Previous reports from the School-Based Asthma Therapy trial suggested that directly observed use of preventive asthma medications in school reduced asthma symptoms in urban asthmatic children not exposed to smoke. A replication study was performed in a larger group of children.

The study included 530 children, aged 3 to 10, with persistent asthma in Rochester, N.Y. After stratification by home smoke exposure, the children were randomly assigned to school-based care or usual care. In the school-based group, children were observed by school nurses as they took preventive asthma medications. Dose adjustments were made according to current guidelines. In addition, children exposed to smoke received a home-based environmental tobacco smoke reduction program. The primary endpoint was the number of symptom-free days during the peak winter season.

Directly observed therapy at school was associated with a significant reduction in symptom-free days from November through February: the adjusted between-group difference was 0.92 days per 2 weeks. The study intervention was also associated with reductions in nighttime symptoms, rescue medication use, and days with limited activity. Rates of prednisone therapy were 12% in the intervention group versus 18% in the comparison group: relative risk 0.63. Directly observed therapy was associated with improved symptom-free days even for children exposed to smoke at home: 11.6 days per 2 weeks, compared to 10.9 days for smoke-exposed children in the control group.

A school-based intervention including directly observed therapy leads to significant reductions in symptoms for urban children with persistent asthma. During the wintertime, children in the intervention group gain about 2 symptom-free days per month, on average. The authors believe that, by reaching large numbers of affected children, this program might help to reduce disparities for poor children with asthma.

COMMENT: *In this carefully controlled study, a home-based parent education program for inner-city urban asthmatic children was supplemented with a school-based asthma management system. The school component provided daily dosing of asthma control medication to the intervention group, while the comparison group took medication at home only. There was impressive improvement in asthma control in both groups, verifying that regular home contact can help improve asthma control. The interesting aspect of this study was that those children receiving their medication at school had statistically greater improvement in symptom-free days, which translated into 2.5 weeks of additional symptom-free days per school year. Collaborations with schools as well as home visitations can help ensure compliance with medications and improve outcomes in urban children with asthma.*
S.M.F.
Halterman J, Szilagyi PG, Fisher SG, et al: Randomized controlled trial to improve care for urban children with asthma.
Arch Pediatr Adolesc Med. 2011;165:262-268. ♦♦

Poor Air Quality and Pulmonary Function in Children

AMBIENT particulate air pollutants and fungal spores have both been shown to have adverse effects on child health. A longitudinal study was performed to assess the combined effects of air pollutants and fungal spores on respiratory health in Taiwanese children.

One hundred elementary and middle-school children in Taipei County were evaluated using a structured respiratory health questionnaire, followed by monthly spirometry. The findings were compared with air pollutant and fungal spore data from a monitoring "supersite" located near the study schools. The combined effects of air pollutants and fungal spores on lung function were analyzed using mixed-effects models with 1-day lag modeling.

Higher levels of particulate matter with an aerodynamic diameter of 2.5 μm or less 1 day or less before ➤➤

spirometry was associated with a reduction in forced vital capacity. Higher fungal spore levels were associated with both lower forced expiratory vital capacity and lower FEV_1. Higher ozone levels were linked to decreases in forced expiratory flow at 25%, 50%, and 75% of forced vital capacity, as well as reduced average expiratory flow over the middle half of forced vital capacity. The latter findings suggested that ozone independently affected the small airways.

Combined exposure to ambient particular matter and fungal spores may adversely affect vital capacity in healthy school-age children. This and other studies documenting the adverse health effects of air pollution have important implications for air quality standards.

COMMENT: *How does the combination of airborne pollutants and fungal spores affect pulmonary function in children? This small study of Taiwanese schoolchildren (some of whom were potentially atopic) is interesting as it shows a general worsening of various pulmonary function parameters following exposure. Study weaknesses include a lack of focused history and skin testing to determine specific allergic sensitivity, and the identification of allergic rhinitis and asthma in study participants by parental questionnaire.*
K.R.M.

Chen B-Y, Chao J, Chan C-C, et al: Effects of ambient particulate matter and fungal spores on lung function in schoolchildren.
Pediatrics. 2011;127:e690-e698. ♦♦

Keeping Track, with TRACK

THE "Test for Respiratory and Asthma Control in Kids" (TRACK) for monitoring respiratory and disease control in asthmatic preschoolers was developed and validated mainly in asthma specialist practices. The current study was a longitudinal evaluation of the use of TRACK in pediatric practices, focusing on the tool's responsiveness to changes in respiratory and asthma control over time.

In the study, caregivers of 438 children younger than 5 who had asthma symptoms within the past year completed the five-question TRACK at two clinic visits, 4 to 6 weeks apart. Without knowledge of the parents' responses, pediatricians performed a standard respiratory control survey. The physicians were also asked whether the visit would lead to any change in therapy. TRACK's responsiveness to changes in respiratory control status were evaluated, along with reliability and discriminant validity.

Between visits, the mean change in TRACK scores differed in the expected direction for children whose clinical status was better, the same, or worse, based on physicians' evaluations and caregivers' responses. There were also significant differences in TRACK scores in different patient subsets. Children rated as having very poor control, who required step-up therapy, or who had 4 or more episodes of wheezing or other respiratory symptoms in the past 3 months had lower TRACK scores, indicating poorer control.

The TRACK questionnaire is responsive to changes in respiratory control between visits in young children with asthmatic symptoms. The study provides further evidence of TRACK's validity and reliability, including for use by pediatricians. In addition to providing a useful monitoring tool, TRACK could help to focus caregivers' awareness on important areas for their child's respiratory control.

COMMENT: *Assessing asthma control in the youngest of our population presents a challenge. The five-item TRACK questionnaire offers a potential solution. TRACK was first proposed as a possible test in 2009 (J Allergy Clin Immunol. 2009; 123:833-839), The current study assesses its reliability and validity for use among general pediatricians. As presented, this tool seems like one that could be easily administered by clinicians treating preschool-aged children with asthma. (Note: an error appears in Fig. 1 of the original article, in the response selections for test item No. 5.)*
K.R.M.

Chipps B, Zeiger RS, Murphy K, et al: Longitudinal validation of the Test for Respiratory and Asthma Control in Kids in pediatric practices.
Pediatrics. 2011;127:e737-e747. ♦♦

Dogs Trump Cats... in Early Childhood Eczema, at Least!

THE effects of early exposure to aeroallergens on childhood eczema risk remain unclear. Studies of dog and cat ownership have yielded conflicting results. This study evaluated the effects of early environmental exposures, including different patterns of pet ownership, on the risk of eczema in children.

The analysis included prospective follow-up data on 636 infants of atopic parents, including annual clinical evaluations and skin prick testing (SPT) for 15 aeroallegens as well as milk and egg. Information on childhood eczema and environmental exposures was gathered using validated parental questionnaires. Levels of allergen and endotoxin were measured in household dust samples.

By age 4, eczema had occurred in 14% of the children. This risk was significantly higher for children who did not have a dog before age 1 and in those who were SPT-positive for dog at age 1, 2, or 3: adjusted odds ratio (OR) 3.9. However, for children in households with dogs, a positive SPT for dog was not associated with an increased risk of eczema. For children who had cats before age 1, a positive SPT for cat was associated with a greatly increased risk of eczema: OR 13.3. No such association was noted for children without cats in the home.

In young children sensitized to dog, having a dog at home is associated with a lower risk of eczema. In contrast, for children sensitized to cat, owning a cat is linked to an increased risk of eczema. The effects of early pet ownership appear independent of endotoxin levels.

COMMENT: *Contrary to the conventional wisdom of bygone years, being exposed to pets in early childhood does not necessarily increase the risk of atopic dis-*➤➤

ease, and may in fact be somewhat protective. Complexities involved with the timing of exposures are still being determined. This study provides important evidence for a potential differential effect of early dog vs cat exposure. For now, dogs can continue to enjoy their status as "man's best friend."
K.R.M.
Epstein TG, Bernstein DI, Levin L, et al: Opposing effects of cat and dog ownership and allergic sensitization on eczema in an atopic birth cohort.
J Pediatr. 2011;158:265-271. ♦♦

Childhood Atopy... and Elevated Lipoproteins?

SEVERAL studies have suggested possible associations between serum lipid levels and allergy--positive in some studies and negative in others. This study explored the link between lipid levels and allergic sensitization in a population of schoolchildren.

Serum fasting lipid levels were measured in blood samples from 654 Japanese children, age 11. The children also underwent measurement of total IgE and specific IgE for house dust mite and three common pollen allergens (cedar, cypress, and orchard grass). Patients completed an allergic disease questionnaire.

Tests for sensitization to mite were positive in 47% of children; for the three pollen allergens, sensitization rates ranged from 29% to 40%. Total and low-density lipoprotein levels were significantly and positively associated with higher IgE levels and higher rates of allergic sensitization. The associations between lipid levels and sensitization were independent of sex or obesity.

The results suggest an association between hyperlipidemia and allergic sensitization in school-age children. Interventions to prevent hyperlipidemia might be useful in preventing allergic disease, although this would need to be assessed in a prospective study.

COMMENT: *Why would elevations in lipoproteins be a risk factor for atopic disease in children, independent of obesity? There are a number of proposed theoretical explanations, beyond the scope of this cross-sectional study. We must remind ourselves that association does not equal causation, while the underlying issues are probed further.*
K.R.M.
Kusunoki T, Morimoto T, Sakuma M, et al: Total and low-density lipoprotein cholesterol levels are associated with atopy in schoolchildren.
J Pediatr. 2011;158:334-336. ♦♦

New Susceptibility Gene for Aspirin-Intolerant Asthma

PATIENTS with aspirin-intolerant asthma (AIA) have acute bronchoconstriction after ingesting aspirin or other nonsteroidal anti-inflammatory drugs. Solute carrier family 22 member 2 (SLC22A2)--a protein mainly expressed in the luminal membrane of airway epithelial cells, where it mediates luminal release of ACh--is recognized as a novel regulator of airway remodeling. It is also a neurotransmitter of central and peripheral neurons in human airways, and can mediate the prostaglandin transport on the cyclo-oxygenase pathway, regulated by aspirin blockage.

The current study sought evidence of polymorphisms of the *SLC22A2* gene in 163 patients with AIA, compared to 429 controls with aspirin-tolerant asthma (ATA). A polymorphism in intron 5, *rs316021*, was significantly associated with AIA susceptibility: odds ratio 0.60 in a codominant model. The minor allele of *rs316021* was significantly less frequent in AIA patients than in ATA controls. The study also identified a polymorphism in intron 4 (*rs3912161*) and a haplotype (*SLC22A2-ht3*) that were more strongly associated with the aspirin-provoked decrease in FEV_1 in AIA patients than in subjects compared with ATA controls.

The *SLC22A2* gene may affect susceptibility to AIA. The reported associations may aid in developing new methods for diagnosis of aspiring intolerance, as well as new therapeutic strategies for disease control.

COMMENT: *Aspirin-intolerant asthma is a frequent problem for which our specialty is consulted. These authors investigated associations between AIA and genetic polymorphisms of the gene* SLC22A2, *and found that it could be a susceptibility gene for aspirin intolerance in asthmatics. The study provides a new link between organic cation transportation and aspirin hypersensitivity in asthmatics. It also suggests ACh as a novel regulator of airway remodeling.*
M.F.
Park TJ, Kim JH, Bae JS et al: Possible association of SLC22A2 *polymorphisms with aspirin-intolerant asthma.*
Int Arch Allergy Immunol. 2011;155:395-402. ♦♦

CLINICAL TIDBITS

Even in Italy, Low Vitamin D Is Linked to Childhood Asthma

RECENT studies have linked vitamin D deficiency to asthma onset and severity in children, as well as to decreased pulmonary function. The relationship between vitamin D status and asthma control was examined in a sample of asthmatic children in Italy.

Seventy-five 75 children with asthma treated at an Italian clinic were studied in the winter and early spring. Just 9.4% of the children had a "sufficient" serum 25-hydroxy cholecalciferol [25(OH)D] level of at least 30 to 40 ng/mL. There was a significant association between [25(OH)D] and forced vital capacity percent predicted and a nonsignificant trend for FEV_1. Median [25(OH)D] levels were 22.2 for children with well-controlled asthma versus 17.8 and 18.1, respectively, for those with partially controlled or noncontrolled disease. Vitamin D status was also positively correlated with the Childhood Asthma Control Test score.

Most patients in this Italian sample of children ➤➤

with asthma have vitamin D deficiency or insufficiency. Even in a Mediterranean climate, lower vitamin D levels are linked to poorer control of childhood asthma.

COMMENT: *To what extent are low vitamin D levels correlated with asthma control in other countries? Insufficient or deficient vitamin D levels are commonly found--and associated with worsened asthma control in children--even in the sunny Mediterranean climate of Italy. Similar to U.S. studies, children with higher vitamin D levels seem to have better asthma control.*
K.R.M.

Chinelatto I, Piazza M, Sandri M, et al: Vitamin D serum levels and markers of asthma control in Italian children.
J Pediatr. 2011;158:437-441. ♦♦

Metabolomic Asthma Profiling Shows Promise

VARIOUS noninvasive measures of inflammation have been studied for use in guiding asthma therapy. This study evaluated ^{1}H-nuclear magnetic resonance (NMR) of urine samples for use in metabolomic profiling of children with asthma.

The study included 135 children with stable asthma seen in the outpatient clinic, unstable asthma seen in the emergency department, or healthy controls. Urine samples were evaluated by NMR to compare the metabolic profiles of the 3 groups of children. Based on measurements of 70 metabolites per sample, models of separation were created using partial least squares analysis.

The resulting models were 94% accurate in distinguishing children with stable asthma from healthy controls. In contrast, just 1 of 20 controls was wrongly classified as asthmatic. The NMR technique was also 94% accurate in distinguishing between children with controlled versus uncontrolled asthma.

Nuclear magnetic resonance spectroscopy appears to have promise for metabolomic profiling of asthma. The ability to perform these sophisticated analyses in urine samples may be especially valuable in monitoring children with asthma.

COMMENT: *The cellular inflammation in asthmatics results in a variety of metabolic changes that can be measured in the urine. Metabolomics is the analysis of the molecules produced by these cellular metabolic pathways. This technique using NMR on urine samples was found to be 94% accurate at identifying stable and unstable asthma compared to a control group of children, who were only misclassified 5% of the time. What is the best way to monitor our asthmatic patients? We're now using validated questionnaires, pulmonary function tests, and sometimes exhaled nitric oxide. Could a urine spectrometer be a useful tool in the future? We'll see….*
S.M.F.

Saude EJ, Skappak CD, Regush S: Metabolomic profiling of asthma: Diagnostic utility of urine nuclear magnetic resonance spectroscopy.
J Allergy Clin Immunol. 2011;127:757-764. ♦♦

REVIEWS OF NOTE

COMMENT: *Systemic mastocytosis can be a masquerader, as evidenced by the fact that one review reported a median time from symptom onset to diagnosis of 9.5 years. This case discussion reviews the diagnosis and treatment of the disorder. You should know that alcohol, nonsteroidal anti-inflammatory drugs, anesthesia and surgery can trigger episodes, possibly including hypotension. The differential diagnosis is challenging.*
R.J.M.

Murali MR, Castells MC, Song JY, et al: Case 9-2011: a 37-year-old man with flushing and hypotension.
N Engl J Med. 2011;364:1155-1165. ♦♦

COMMENT: *Here's a nice review of asthma in the elderly, including an extensive focus on practical issues related to diagnosis and management.*
S.A.T.

Jones SC, Iverson D, Burns P, et al: Asthma and ageing: an end user's perspective--the perception and problems with the management of asthma in the elderly.
Clin Exp Allergy. 2011;41:471-481. ♦♦

COMMENT: *This is a good review of the management of community-acquired pneumonia in adults.*
B.E.C.

Waterer GW, Rello J, Wunderink RG: Management of community-acquired pneumonia in adults.
Am J Respir Crit Care Med. 2011;183:157-164. ♦♦

COMMENT: *Levocetirizine is the only H1 antihistamine shown to lack clinically relevant adverse effects in 1- to 3-year-old children predisposed to development of allergic disease. This excellent review concludes that, based on currently available data for a wide range of outcomes, levocetirizine seems a suitable treatment for allergic rhinitis and chronic urticaria in children aged 6 months to 12 years.*
M.F.

Pampura AN, Papadopoulos, NG, Špičák V et al: Evidence for clinical safety, efficacy, and parent and physician perceptions of levocetirizine for the treatment of children with allergic disease.
Int Arch Allergy Immunol. 2011;155:367-378. ♦♦