

# 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 14, Number 2

March - April 2012

## Pediatric Anaphylaxis: The Mount Sinai Experience

**A**NAPHYLAXIS is increasing in general, and food-induced anaphylaxis among children in particular. Epinephrine is the treatment of choice, with delays in epinephrine administration linked to an increased risk of death. The authors present their 5-year experience with anaphylaxis at a New York City pediatric emergency department (ED).

From 2004 through 2008, the Mount Sinai pediatric ED treated a total of 213 anaphylactic reactions in 192 children and adolescents. The patients were 97 males and 95 females, median age 8 years. The event was initially coded as anaphylaxis in 62 cases; another 151 cases met the "Second Symposium" criteria. Foods triggered 71% of reactions; the cause was "unknown" in 15% of reactions, while 9% were triggered by drugs. Foods were more likely to be the trigger in patients with multiple reactions.

Epinephrine was used in 79% of cases, including treatment before ED arrival in 27%. Medicaid patients

were less likely to receive epinephrine before arrival. The hospital admission rate was 14.6%. Nine patients were admitted to the ICU.

Two doses of epinephrine were used in 13 reactions. The hospitalization rate was 69% in these cases, compared to 12% when a single dose was used. Patients receiving both doses of epinephrine before ED arrival were less likely to be admitted than those receiving epinephrine in the ED.

The Mount Sinai experience highlights the importance of foods in triggering episodes of anaphylaxis seen in the pediatric ED. Hospital admission is more likely for children who require two doses of epinephrine and less likely for those receiving epinephrine before ED arrival. The authors call for focused education to increase epinephrine use before ED arrival among patients on Medicaid.

**COMMENT:** *This was an interesting report from Mount Sinai Hospital ED reviewing children who presented with anaphylaxis over a 5-year period. The trigger for anaphylaxis was attributed to food allergy in over 70% of the cases. The authors point out that this may be influenced by the strong allergy division in >>>*

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The American College of Allergy, Asthma & Immunology expresses its appreciation to



**MERCK** for its grant in support of the publication of *AllergyWatch*®.

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*The following journals have been selected as the primary focus of review in the preparation of materials within "AllergyWatch®".*

- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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this institution and their focus on food allergy. In spite of that, antihistamines and steroids were used in more patients than epinephrine, which should be considered the first-line treatment. Only 6% of patients required treatment with two doses of epinephrine, although most of these were hospitalized for further treatment. Once again, the data confirm that early treatment with epinephrine reduced the risk for more severe reactions. S.M.F.

Huang F, Chawla K, Järvinen KM, et al: Anaphylaxis in a New York City pediatric emergency department: triggers, treatments, and outcomes. *J Allergy Clin Immunol.* 2012;129:162-168. ♦♦

## Preventive Asthma Medication Use Shows Improvement in Children (Finally)

**P**REVIOUS studies have reported underuse of effective preventive medications among children with asthma—particularly in minority children. The 1991 treatment guidelines of the National Asthma Education and Prevention Program emphasized the importance of preventive asthma medications for children with persistent asthma. This study examined trends in use of preventive asthma medications by children over the past two decades.

The researchers analyzed National Health and Examination Nutrition Survey data on 2,499 children and adolescents with current asthma during three time periods: 1988-94, 1999-2002, and 2005-08. Trends in the use of preventive medications—inhaled corticosteroids, leukotriene receptor antagonists, long-acting  $\beta$ -agonists, mast-cell stabilizers, and methylxanthines—were analyzed.

The percentage of asthmatic children receiving preventive medications increased from 17.8% in 1988-94 to 34.9% in 2005-08. The increase was significant after adjustment for age, sex, race/ethnicity, and health insurance status: adjusted odds ratio 2.6.

On multivariate analysis of children in all three periods, minority children were less likely to receive preventive medications: odds ratio 0.5 for African American and 0.6 for Mexican American children. Preventive medication use was also less likely for adolescents aged 12 to 19 (compared to children aged 1 to 5) and for uninsured children.

The study shows a significant increase in the use of preventive medications by U.S. children and adolescents with asthma. These medications remain underused in certain groups, including adolescents, minorities, and uninsured children. Further studies are needed to increase adherence to guidelines and reduce disparities in preventive asthma medication use.

**COMMENT:** Since the advent of the NHLBI Asthma Guidelines in 1991, there has been a significant and nearly continuous campaign to educate primary care providers and the public about the importance of preventive asthma management. Perhaps another positive impact of this campaign can now be seen, albeit with variable results by ethnic group—or dependent on insurance status. Steady gains in preventive medication use over the course of this 20-year study are certainly encouraging!

K.R.M.

Kit BK, Simon AE, Ogden CL, Akinbami LJ: Trends in preventive asthma medication use among children and adolescents, 1988-2008.

*Pediatrics.* 2012;129:62-69. ♦♦

## Acetaminophen Use and Childhood Asthma

**P**REVIOUS studies have shown a strong link between acetaminophen exposure and asthma, raising the possibility that this drug could be a contributor to the rising prevalence of childhood asthma. The author dis-

cusses the evidence on the association between acetaminophen and asthma, along with the clinical implications.

A number of cross-sectional epidemiologic studies show significant associations between asthma and acetaminophen in children and adults. For example, some studies have reported up to a threefold increase in asthma risk among children who take acetaminophen at least once monthly. However, these associations are subject to several potential confounders, including confounding by indication, reverse causation, or preferential use of acetaminophen for children at highest risk of asthma.

These issues can only be resolved by controlled trials. The two prospective studies reported to date—including a randomized trial in febrile children—both support the association between acetaminophen and asthma. Population-attributable risks for asthma prevalence and severity have been estimated at 20% to 40%.

Any such association is obviously of high clinical relevance, opening the possibility that a relatively simple change in practice could reduce asthma risk for many children. Pending further studies, Dr. McBride writes, "I will recommend avoidance of acetaminophen by all children with asthma or those at risk for asthma."

**COMMENT:** Without a randomized controlled trial, it is difficult to know with certainty whether acetaminophen may itself increase asthma risk, or is rather a marker for increased risk related to viral/bacterial infections. Additionally, there are a number of potential candidates that have occurred broadly over the same time frame: increased obesity, deficiency of vitamin D/indoor lifestyle, increased antibiotic use, increased cesarean section rate, etc. We know ASA and non-steroidal anti-inflammatory drugs may exacerbate asthma. Now if acetaminophen is to be withheld, what should any child be given for fever or pain?

K.R.M.

McBride JT: The association of acetaminophen and asthma prevalence and severity.

Pediatrics. 2011;128:1181-1185. ♦♦

## There Is Trouble Outside and Inside the House

**S**EVERAL lines of evidence suggest that airborne particulates are linked to asthma-related outcomes in children, including urinary leukotriene E<sub>4</sub> (LTE<sub>4</sub>) levels and albuterol use. However, these studies have not accounted for the effects of concurrent exposures, such as environmental tobacco smoke (ETS). The combined health effects of exposure to ambient particulate matter and ETS were evaluated in a group of urban schoolchildren with asthma.

The study included 82 children, aged 6 to 15, attending one school in Denver. Over 3 consecutive school years, the children underwent monitoring of albuterol use and urinary LTE<sub>4</sub> levels. Air quality data were used to monitor exposure to particulate matter less than 2.5 µm in aerodynamic diameter (PM<sub>2.5</sub>). Repeated measurements of urine cotinine were made to assess ETS exposure.

On days with low urine cotinine levels (less than 10 ng/mL/mg creatinine), albuterol use and LTE<sub>4</sub> were significantly associated with morning maximum PM<sub>2.5</sub> levels. On these days, each 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> was associated with a 5% or 6% increase in albuterol use or urine LTE<sub>4</sub>.

In contrast, the associations with PM<sub>2.5</sub> were not significant on days with high urine cotinine levels—even though albuterol use and LTE<sub>4</sub> were higher on those days. Models suggested a nonlinear dose-response relationship between PM<sub>2.5</sub> exposure and airway mediators of asthma, with a "flatter" relationship at higher particulate levels.

Exposure to ETS appears to limit the effects of airborne particulates on asthma-related outcomes in children. On days with higher exposure to secondhand smoke, children show lesser effects of particulate exposure. It may be important to consider the impact of ETS when assessing the potential health effects of exposure to ambient air pollution.

**COMMENT:** This is the first study to clearly link exposure to secondhand smoke and particulate matter in the outdoor environment as risk factors for asthma severity in children 6 to 15 years of age. Both LTE<sub>4</sub> and albuterol use were higher on the days of high outdoor ambient PM<sub>2.5</sub> concentrations, and this was stronger when there was exposure to secondhand smoke. These data are important in helping us continue our quest to understand the environmental determinates for asthma. See the accompanying editorial by Baccarelli and Kaufman (Am J Respir Crit Care Med. 2011;184:1325-1327).

B.E.C.

Rabinovitch N, Silveira L, Gelfand EW, Strand M: The response of children with asthma to ambient particulate is modified by tobacco smoke exposure.

Am J Respir Crit Care Med. 2011;184:1350-1357. ♦♦

## FOCUS ON VITAMIN D

### What's the Evidence on Vitamin D and Asthma?

**V**ITAMIN D deficiency and asthma share several risk factors, including living in an urban area, obesity, and African American race. The authors summarize recent research on the potential association between vitamin D and asthma.

Epidemiologic data suggest that the U.S. prevalence of vitamin D deficiency has increased as a result of less time spent outdoors and dietary factors. Although questions remain about the effects of vitamin D in the immune system, there is evidence that it plays an immune-modulatory role. Vitamin D may affect asthma pathogenesis via modulation of T-regulatory cells. Although a causal association has yet to be demonstrated, low maternal intake of vitamin D during pregnancy or low cord blood levels have been linked to childhood wheezing.

Several observational studies have suggested promising effects of vitamin D in protecting against asthma morbidity and asthma exacerbations. At least seven clinical trials are being performed to evaluate the ►►

effects of vitamin D supplementation on asthma or asthma morbidity. Evidence supports several possible mechanisms, including antiviral properties, enhanced steroid responsiveness, and down-regulation of atopy, among others.

Pending the results of clinical trials, it is too early to give a recommendation for (or against) vitamin D supplementation for the prevention or treatment of asthma. Serum vitamin D measurement seems appropriate for children and adults in high-risk groups, including African Americans and Mexican Americans, obese people, and those with limited sun exposure. However, supplementation is currently recommended only for patients with serum 25(OH)D levels less than 20 ng/mL, which may adversely affect musculoskeletal health.

**COMMENT:** *This article provides a very complete pulmonary perspective regarding the interactions of vitamin D with asthma.*

B.E.C.

Paul G, Brehm JM, Alcorn JF, et al: Vitamin D and asthma.

Am J Respir Crit Care Med. 2012;185:124-132. ♦♦

## More about Vitamin D in Severe Asthma

**L**OW vitamin D levels have been linked to poor disease control and other adverse outcomes in children with mild to moderate asthma. This study evaluated vitamin D status in a group of children with severe, therapy-resistant asthma.

The researchers measured serum 25-hydroxyvitamin D [25(OH)D<sub>3</sub>] in 86 children, mean age 11.3 years, who had persistent severe asthma despite inhaled corticosteroids and other controller medications. Vitamin D status was also assessed in 26 children with moderate asthma and 24 nonasthmatic controls. Associations between 25(OH)D<sub>3</sub> and the asthma control test (ACT), spirometric findings, corticosteroid use, and exacerbations were evaluated.

Median 25(OH)D<sub>3</sub> levels were 28 nmol/L in children with severe, therapy-resistant asthma versus 42.5 nmol/L in children with moderate asthma and 56.6 nmol/L in controls. In all three groups, 25(OH)D<sub>3</sub> was significantly and positively related to percent predicted FEV<sub>1</sub> and FVC. In both groups of asthma patients, vitamin D status was positively associated with ACT score and inversely associated with exacerbations and inhaled steroid dose.

Twenty-two of the children with severe, therapy-resistant asthma underwent bronchoscopy. In this group, 25(OH)D<sub>3</sub> was inversely related to airway smooth muscle mass, but not to epithelial shedding or reticular basement membrane thickness. Airway smooth muscle mass was positively correlated with bronchodilator reversibility and inversely correlated with ACT score.

Children with severe, therapy-resistant asthma have reduced serum vitamin D levels, even compared to children with moderate asthma. In these patients, low vitamin D is related to decreased lung function, poor disease control, and increased exacerbations and med-

ication use. The link between vitamin D and airway smooth muscle mass may be an important underlying mechanism.

**COMMENT:** *This study shows us that in patients with severe therapy-resistant asthma, lower serum vitamin D levels are associated with lower lung function, poor asthma control, increased medication use and asthma exacerbations, compared to controls and patients with moderate asthma. It also, very interestingly, shows us that the serum vitamin D level is inversely correlated with airway smooth muscle mass. These data reinforce our need to measure vitamin D levels and potentially optimize these at all levels of asthma severity. See the accompanying editorial by Gerber and Sutherland (Am J Respir Crit Care Med. 2011;184:1324-1325).*

B.E.C.

Gupta A, Sjoukes A, Richards D, et al: Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma.

Am J Respir Crit Care Med. 2011;184:1342-1349. ♦♦

## Vitamin D as a Predictor of Allergy and Asthma

**T**HERE is evidence linking vitamin D with atopy and disease phenotypes in children with established asthma. However, there are few data on the role of vitamin D in asthma development at the community level. The relationship between vitamin D and development of childhood asthma phenotypes was evaluated in a birth cohort study of children in southwestern Australia.

The researchers measured serum vitamin D levels in 989 6-year-old and 1,380 14-year-old children. The children were drawn from the West Australian Pregnancy Cohort study; 689 were studied at both ages. Vitamin D status was evaluated as a risk modifier for respiratory and allergic disease outcomes at both ages, based on previously reported asthma phenotypes. In addition, vitamin D levels at age 6 were evaluated as a predictor of clinical phenotypes at age 14.

At both ages, serum vitamin D levels were inversely associated with allergic phenotypes. The associations were significant only for males. Boys without sufficient vitamin D had higher rates of bronchial hyperresponsiveness, atopy, and house dust mite sensitization, with trends toward increased asthma risk and decreased lung function. Children with vitamin D insufficiency at age 6 were more likely to have atopy- and asthma-associated phenotypes at age 14.

These findings in an unselected community cohort suggest that children with inadequate vitamin D levels are at increased risk of a clinical phenotype involving the development of atopy, bronchial hyperresponsiveness, and asthma. More research is needed to clarify how vitamin D status at all stages of childhood affects the risk of allergic disease and asthma.

**COMMENT:** *This prospective study of over 2,000 children from an unselected community population shows that inadequate vitamin D at 6 years of age,*



*especially in males, predicts subsequent atopy and asthma phenotypes at age 14. This is the first study to demonstrate such an association, which has previously been seen in early-life birth cohorts. It extends the observation that vitamin D deficiency, which is rampant in the population, is an important risk factor for the development of chronic allergic respiratory disease. See the accompanying editorial by Weiss and Litonjua (Eur Respir J. 2011;38:1255-1257).*

*B.E.C.*

*Hollams EM, Hart PH, Holt BJ, et al: Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study.*

*Eur Respir J. 2011;38:1320-1327.* ♦♦

## New Tools Help Predict Adverse Outcomes in Asthma

**I**DENTIFICATION and treatment of high-risk patients is essential for preventing asthma morbidity and mortality. The severity of asthma (SOA) score is a new, validated questionnaire for identifying asthma patients at risk of adverse clinical outcomes, without the need for pulmonary function test data. The SOA score was compared with other asthma assessment tools for prediction of clinical outcomes in a large group of asthma patients.

The study included 2,878 patients with moderate to severe persistent asthma and reactivity to perennial aeroallergens. The patients were participating in a clinical trial of omalizumab, but did not receive anti-IgE therapy. Baseline SOA scores were compared with the asthma control test (ACT), the work productivity and impairment index-asthma (WPAI-A), and FEV<sub>1</sub> percent predicted for prediction of adverse outcomes. The predictive ability of baseline and 1-year data was evaluated by logistic regression analysis, area under the receiver operating characteristic curve (AUCROC), and classification and regression tree (CART) analysis.

The SOA score was the only tool to make a significant contribution in all models of adverse clinical outcomes: in the full logistic regression model, the range of AUCROC values was 0.689 to 0.783. On its own, the SOA score predicted 4 out of 5 outcomes of interest: exacerbations, hospitalizations, unscheduled physician visits, and steroid bursts (but not ED visits), with AUCROC values of 0.689 to 0.773. On CART analysis, the SOA was the most important predictive variable for all five outcomes.

The SOA score performs well in predicting a range of adverse clinical outcomes in children with moderate to severe asthma. This score appears useful not only as a research tool, but also for identifying patients at risk of adverse asthma-related outcomes.

**I**MPAIRMENT, including current symptoms, and the risk of future exacerbations are both important domains of asthma control. However, the association between impairment and risk are unclear. This study evaluated three asthma impairment questionnaires for their ability to predict future exacerbations.

The study included 2,680 patients with persistent asthma, who completed the Asthma Control Test (ACT), the mini-Asthma Quality of Life Questionnaire (mAQLQ), and the Asthma Impact Survey (AIS). History of exacerbations over the past year was evaluated as well. Data on responses to questions in all three tools were included in a factor analysis. The tools and the factors derived from them were evaluated for ability to predict exacerbations in the following year.

All three tools provided information on the risk of future exacerbations, beyond the risk associated with exacerbations in the previous year: relative risk (RR) 1.3. In a model including previous exacerbations, the three tools provided similar and overlapping information; thus the mAQLQ was the only tool included in the model. Factor analysis identified three factors associated with future exacerbations: symptoms, activity, and bother. Of these, only activity was independently related to future exacerbations.

The findings demonstrate the association between asthma impairment and future exacerbation risk. However, the three tools evaluated in this study do not provide independent information from each other. In assessing asthma exacerbation risk, it seems particularly important to assess interference with activities.

**COMMENT:** Predicting risk in the form of asthma exacerbations has important implications in terms of identifying at risk asthmatics and allocating resources. The SOA instrument was compared to other commonly used questionnaires in a population of moderate to severe asthmatics. Interestingly, two questions of the thirteen--previous intubation and hospitalization--accounted for one third of the score.

Underscoring the need to identify asthmatics at risk, the ACT, mAQLQ and AIS-6 were found to equally identify subjects at risk for exacerbation during the following year of observation. In this prospective survey, if a history of previous exacerbation in the past year was captured, the sensitivity increased more than 13%. With potential fragmentation of acute care, it is important to assess risk as well as impairment per current guidelines.

*S.F.W.*

*Eisner MD, Yegin A, Trzaskoma B: Severity of asthma score predicts clinical outcomes in patients with moderate to severe persistent asthma. Chest. 2012;141:58-65. Schatz M, Zeiger RS, Yang S-J, et al: The relationship of asthma impairment determined by psychometric tools to future asthma exacerbations.*

*Chest. 2012;141:66-72* ♦♦

## No Increase in Tachycardia Risk with $\beta_2$ -Agonists

**T**ACHYCARDIA and tachyarrhythmias are common problems in critically ill adults, and are linked to increased morbidity and mortality. The nebulized bronchodilators albuterol and ipratropium have the potential to contribute to these rhythms; it has been suggested that levalbuterol may have fewer side effects. A randomized trial compared these agents for their

effects on heart rate and arrhythmias in adult ICU patients.

The study included 70 critically ill adults receiving nebulized bronchodilator therapy. Patients were assigned to receive nebulized albuterol alternating with levalbuterol every 4 to 6 hours. In group A, albuterol 2.5 mg alternated with levalbuterol 0.63 mg; in group B, albuterol alternated with levalbuterol 1.25 mg. Nebulized ipratropium bromide was given with each treatment.

In group A, heart rate increased by a mean of 4.5 beats/min after albuterol versus 0.85 beats/min after levalbuterol. In group B, heart rate decreased by 0.16 beats/min after albuterol, but increased by 1.4 beats/min after levalbuterol. In a total of 836 treatments, there was a 0.6% rate of arrhythmias. Four out of these five events were occasional premature ventricular contractions. One patient had a five-beat run of ventricular tachycardia leading treatment to be stopped—a rate of 1.4%.

Neither nebulized albuterol nor ipratropium causes problematic tachycardia or tachyarrhythmias in critically ill adults, the results suggest. Thus there is no need to use levalbuterol in place of albuterol to prevent these adverse rhythm changes. At the authors' hospital, eliminating levalbuterol resulted in significant cost savings.

**COMMENT:** *This study adds to the literature affirming the cardiac safety of nebulized  $\beta_2$ -agonists. Two points are derived from this study. Severely ill, ICU-treated patients did not experience clinically relevant increases in heart rate, and there was no relevant difference between levalbuterol and albuterol. One patient, out of seventy who received  $\beta_2$ -agonist, experienced ventricular tachycardia that necessitated discontinuation of the drug.*

S.F.W.

*Khorfan FM, Smith P, Watt S, Barber KR: Effects of nebulized bronchodilator therapy on heart rate and arrhythmias in critically ill adult patients.*

*Chest.* 2011;140:1466-1472. ◆◆

## Chinese Herbal Medicine for Food Allergy Is Safe

**N**EW treatments for food allergy are urgently needed. In previous studies, a Chinese herbal medicine called food allergy herbal formula-2 (FAHF-2) blocked peanut anaphylaxis in a mouse model. An acute phase 1 study showed that FAHF-2 was safe and well-tolerated in patients with food allergy. The results of an extended phase 1 clinical trial are reported.

The open-label trial included 18 children and adults with food allergies. All were treated with FAHF, 3.3 g (six tablets) three times daily for 6 months. Fourteen patients completed the study; none dropped out because of serious adverse events. Close monitoring showed no significant treatment-related changes in laboratory test results, pulmonary function parameters, or electrocardiographic findings.

At the end of the 6-month treatment period, CCR3/CD63 staining and flow cytometry studies showed

a significant reduction in basophil CD63 expression in response to ex vivo stimulation. Treatment with FAHF-2 was also associated with a trend toward reduced eosinophil and basophil counts.

The initial clinical trial supports the safety and tolerability of FAHF-2 treatment for patients with food allergy. In vitro studies suggest a significant inhibitory effect on basophil numbers. A placebo-controlled, phase 2 efficacy trial of FAHF-2 is planned, along with studies of its mechanism of action.

**COMMENT:** *The FAHF-2 formula containing 9 Chinese herbs has been reported to block food allergic reactions in mice. This report is a 6-month extension of the FDA phase 1 trial in humans with food allergy. Remarkably, there were no significant adverse side effects in patients using this preparation orally three times a day for 6 months. There was a reduction of basophil numbers and CD63 expression in vitro, suggesting that FAHF-2 has significant immunologic benefit. It will be interesting to see how patients respond to food challenges with this product.*

S.M.F.

*Patil SP, Wang J, Song Y, et al: Clinical safety of food allergy herbal formula-2 (FAHF-2) and inhibitory effect on basophils from patients with food allergy: extended phase I study.*

*J Allergy Clin Immunol.* 2011;128:1259-1265. ◆◆

## Latex Allergy--Is There a Serologic Test to Help Us Make the Diagnosis?

**T**HERE is no U.S. Food and Drug Administration (FDA)-approved extract for skin testing in patients with latex allergy. Thus allergists must use the patient history and serologic assays to make the diagnosis. An FDA-cleared antilatel IgE serology test (the CAP assay) and an enzyme-linked immunosorbent assay (ELISA) were evaluated for diagnostic performance in a sample at risk of latex allergy.

The study included an unselected population of 792 healthcare workers. All underwent serologic testing with the CAP assay (using antigen k82) and ELISA (using four different latex antigens) for latex-specific IgE. Performance was assessed by comparison with the results of skin prick tests (SPTs).

There was a 5% rate of positive SPTs. The CAP assay had a sensitivity of 35%, specificity of 98%, and positive and negative predictive value of 48.3% and 96.6%, respectively. The ELISA showed similar diagnostic performance. In multivariable logistic regression models using categorical values for the serologic tests yielding 98% or 99% specificity, the odds of a positive SPT were significantly increased with positive CAP assay and ELISA results with powdered glove extract.

The IgE serologic test for latex allergy evaluated in this study appears to have lower diagnostic sensitivity than previously reported. An experimental ELISA also has low performance. Although the CAP assay may be useful in patients with a clinical history, it is not appropriate for use as a screening test in populations with a low prevalence of latex allergy.

**COMMENT:** In the absence of an FDA-approved extract to perform skin prick testing for patients, the authors investigated the use of the existing serologic tests in making the diagnosis of latex allergy. The study demonstrated a low sensitivity by CAP testing to latex, reminding us that we should not use this as a screen for latex allergy in the general population. The dilemma in diagnosing latex allergy remains; having an FDA-approved SPT extract would be useful for screening purposes.

V.H.-T.

Acceta Pedersen DJ, Klancik M, Elms N, et al: Analysis of available diagnostic tests for latex sensitization in an at-risk population.

Ann Allergy Asthma Immunol. 2012;108:94-97. ♦♦

## Can Patients Truly Be Allergic to More Than "a Few" Medications?

**P**ATIENTS with intolerance of three or more unrelated medications may be classified as having multiple drug intolerance syndrome (MDIS). The word "allergies" is often applied to the varying intolerances, whether or not they are IgE mediated. This paper reports on the prevalence, clinical characteristics, and management of MDIS.

Analysis of electronic medical records of nearly 2.4 million members of a large Southern California health plan found that about 20% had one or more reported "allergies." Patients with a higher incidence of "allergies" had a higher incidence of new "allergies," as did females in general. The drug classes with the highest population-based incidence of "allergies" (excluding the category "other antibiotics") were penicillins, narcotics, angiotensin-converting enzyme inhibitors, lipid regulators, proteins, and nonsteroidal anti-inflammatory drugs.

As defined above, 2.1% of members had MDIS. These patients were older and heavier than the average plan member, with an age of 62.4 years and body mass index of 29.3. Nearly 85% were female. Patients with MDIS had high rates of health care utilization and medication use, as well as a higher incidence of new drug "allergies." The presence of MDIS was associated with seeking care for common, "not particularly morbid" problems. This group of patients appeared to have high rates of anxiety, but not atopy, acute life-threatening conditions, or serious mental illness.

In this large health plan population, about 2% of members meet criteria for MDIS. This problem is most common in older women with high rates of health care and medication use, with a high rate of new drug "allergies." The authors view MDIS as "partially an iatrogenic condition," which may be reduced by efforts to address polypharmacy.

**COMMENT:** This review identified a subset of patients who may have the multiple drug intolerance syndrome (MDIS). Medications that were non-antibiotics were seen increasingly in the elderly female population. As allergists, we are reminded to recommend avoidance of polypharmacy. Drug challenges may help

to dispel the belief that these forms of adverse reactions are allergic in nature.

V.H.-T.

Macy E, Ho NJ: Multiple drug intolerance syndrome. Ann Allergy Asthma Immunol. 2012;108:88-93. ♦♦

## Finally--Support to Help Us Convince Patients Hypoallergenic Pets Don't Exist!

**M**OST U.S. households have pets, and 17% of cat owners and 5% of dog owners are sensitized to their pets. Many patients are interested in "hypoallergenic" pets, and some companies are charging very high prices for breeds claimed to meet this description. This article reviews the scientific evidence on hypoallergenic dogs and cats.

One company (Allerca) claims to have bred dogs and cats selected for a "divergent gene" associated with lower allergenic quantities of dander. The company's website features physician endorsements and claims of unpublished supporting data. However, leading allergy associations refute those claims, finding no published evidence that hypoallergenic pets exist. One study reported no difference in allergen shedding by hypoallergenic dogs versus other dogs.

Even if selective breeding could affect major pet allergens, patients could still be sensitized to a variety of minor allergens. In contrast to the lack of evidence supporting hypoallergenic pets, extensive evidence shows the health effects of exposure to cat and dog allergen in sensitized individuals. Although removing the pet is the most effective treatment for pet allergy, many families refuse this step. In this situation, lifestyle modifications may be tried to reduce exposure to allergenic dander. Measures like extensive housecleaning may be impractical, and show only modest benefits. Regular bathing of the pet may help to reduce allergen levels, especially in dogs.

Contrary to marketing claims, patients should be educated that there is no scientific evidence to support the concept of hypoallergenic pets. Instead, patients should be advised to follow "more established practices" to preventing pet allergies and the resulting health effects.

**COMMENT:** This brief article provides us further support as we try to explain that no pet is truly "hypoallergenic." Scientific evidence for pets that are hypoallergenic does not exist, so patient education regarding the morbidity associated with allergies and asthma from pets is essential.

V.H.-T.

Butt A, Rashid D, Lockey RF: Do hypoallergenic cats and dogs exist?

Ann Allergy Asthma Immunol. 2012;108:74-76. ♦♦



## Are TRUE Patch Test Panels Accurate Enough to Diagnose Contact Dermatitis?

**T**HE "Thin-Layer Rapid-Use Epicutaneous" (TRUE) test is a commercially available patch test system using a limited panel of 28 allergens. Few studies have evaluated the use of patch testing in allergy practice. This study evaluated the TRUE test system in allergy practices, including diagnostic performance versus more extensive patch testing panels.

The 5-year retrospective study included data on 427 patients undergoing patch testing at three separate allergy practices. The patients' mean age was 49.8 years; 82% were female and 54% had a reported history of atopy. The patch test results were analyzed to determine the percentage of patients with positive results to at least 1 of the 28 allergens included in the TRUE test. The study sought to determine whether the use of the limited TRUE test panel would miss a significant number of positive results that might be detected with expanded or supplementary panel allergens.

The allergens with the highest rates of positive results were nickel sulfate, fragrance mix I, p-phenylenediamine, thimerosal, and cobalt chloride. Overall, 56.9% of patients tested positive for at least 1 TRUE test panel allergen. This included a 25.6% rate of positive results for both a TRUE test allergen plus a supplemental allergen.

However, 12.5% of patients had no positive results to TRUE test allergens but did test positive to a supplemental allergen. The findings were consistent with published data on patch testing at allergy practices. The final diagnosis included contact allergic dermatitis in 60.6% of patients, irritant contact dermatitis in 18.5%, and other dermatoses in 13.1%.

In allergy practice, patch testing using the TRUE test alone would miss the causative allergen in 1 out of 8 patients. In addition, 1 out of 4 would be only partially evaluated. While the TRUE test may be an adequate screening tool, a more extensive panel is needed for full evaluation of contact dermatitis.

**COMMENT:** The TRUE test is widely utilized in allergy practice for diagnosis of contact dermatitis. The authors of this multi-center retrospective study of patch testing in allergy practices find that positive testing for allergens would not be defined in 12.5% of patients using TRUE tests and approximately 26% would be partially evaluated or identified. The results are similar for dermatology practices. The take-home message is that TRUE tests are sufficient screening test for allergy practice, but a more extensive panel is necessary to fully assess for contact dermatitis.

C.C.R.

Camacho-Halili M, Axelrod S, Michelis S, et al: A multi-center, retrospective review of patch testing for contact dermatitis in allergy practices.

Ann Allergy Asthma Immunol. 2011;107:487-492. ♦♦

## Risk Factors for Montelukast Treatment Failure in Step-Down Management

**L**EUKOTRIENE receptor antagonist therapy with montelukast can be used as part of step-down therapy for patients with mild asthma that is adequately controlled by low-dose inhaled corticosteroids. Data from a large randomized trial were used to identify risk factors for failure of montelukast step-down therapy.

The researchers analyzed data on 165 patients who were stepped down from low-dose ICS to montelukast during the Leukotriene Modifier or Corticosteroid or Corticosteroid-Salmeterol (LOCCS) trial. Baseline variables associated with treatment failure were identified, and incorporated into a clinical index to predict the risk of failed step-down therapy with montelukast.

Independent risk factors for montelukast treatment failure were asthma onset before age 10, and odds ratio (OR) 2.39; need for steroid burst therapy in the past year, OR 2.39; and lower prebronchodilator FEV<sub>1</sub>, OR 1.44 per 10% reduction in FEV<sub>1</sub>% predicted. A clinical index consisting of these variables identified groups at low and high risk of treatment failure: less than 20% and greater than 60%, respectively.

Three distinct clinical variables affect the risk of montelukast failure in step-down treatment for asthma. The montelukast failure index reported in this study may help in assessing this risk before starting step-down therapy for asthma that is controlled on low-dose ICS.

**COMMENT:** The risk factors from the LOCCS trial of the Asthma Clinical Research Network that predict failure of montelukast step-down therapy include early asthma onset before 10 years of age, exacerbating asthma in the last year requiring steroid burst, and lower prebronchodilator FEV<sub>1</sub>. Montelukast had a higher failure rate (30%) than inhaled steroids (approximately 20%). The literature supports the superior efficacy of inhaled steroids in terms of pulmonary function, symptom assessment, exacerbations requiring oral steroids, and pharmacoeconomic cost. The authors provide a failure index for montelukast to assess probability of failure before therapy, with scores less than zero predicting low risk and scores greater than 5 predicting high risk. These risk factors are probable indices for more severe and typically atopic asthma, which has been demonstrated to be uncontrolled with montelukast, requiring inhaled steroids.

C.C.R.

Drummond BM, Peters SP, Castro M, et al: Risk factors for montelukast treatment failure in step-down therapy for controlled asthma.

J Asthma. 2011;48:1051-1057. ♦♦

## FDA Approval of Indacaterol for COPD--Why Only 75 µg?

**T**HE long-acting beta-agonist (LABA) indacaterol was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic



obstructive pulmonary disease (COPD). However, approval was for a dosage of 75 µg once daily—lower than the doses approved in Europe. Risk/benefit issues relevant to the FDA's approval decision are reviewed.

The manufacturer's original new drug application proposed once-daily doses of 150 and 300 µg for indacaterol. However, the data showed no evidence that these doses had higher efficacy than the 75 µg dose. In the light of reports linking LABAs to asthma exacerbations and asthma-related deaths, a safety review suggested that the proposed doses—geared to show higher efficacy than formoterol or tiotropium—were higher than necessary. The FDA requested new dose-ranging studies in patients with asthma.

The results suggested that doses higher than 75 and 150 µg initially showed greater efficacy. However, these differences lessened by week 2, consistent with a plateau in the bronchilator effect. Confirmatory studies in COPD patients showed that indacaterol 75 µg was superior to placebo, but no further improvement at higher doses. Model-based analyses did not support approval of a 150 µg dose in terms of efficacy. There were no safety signals at either the 75 or 150 µg dose.

Based on this balance of efficacy data and safety concerns, indacaterol was approved for COPD only at the 75 µg once-daily dose. The FDA believes this dose will maximize benefits without unnecessary safety risks.

**COMMENT:** *Arcapta Neohaler (indacaterol maleate powder), a long-acting beta-agonist (LABA), was approved on July 1, 2011, as a bronchodilator for patients with COPD at a dose of 75 µg once daily. This same medication was approved for use by the European Medicines Agency at doses of 150 and 300 µg in 2009. Dr. Badrul Chowdhury, the Director of the Division of Pulmonary, Allergy, and Rheumatology Products, and his colleagues from the Center for Drug Evaluation and Research, Food and Drug Administration outline the FDA's rationale. They cite a combination of safety and efficacy concerns aimed at ensuring "maximal benefit without posing unnecessary safety risks." This "must-read" article provides excellent insight into the thought process of the FDA.*

C.D.

*Chowdhury BA, Seymour SM, Michele TM, et al: The risks and benefits of indacaterol—the FDA's review. NEJM. 2012;365:2447-2249* ♦♦

## Grandma Was Right--Brussels Sprouts (Ugh!) Are Good for You

**R**ECENT studies suggest that dietary components found in vegetables have important immune effects via interaction with intestinal immune receptors. Given that high vegetable intake may protect against inflammatory bowel disease (IBD), these dietary factors might act to prevent inflammation in the gastrointestinal tract. The author reviewed recent evidence on immunomodulatory compounds in foods.

Two recent studies provide insights on the aryl hydrocarbon receptor (AhR), a ubiquitous transcription factor activated by various environmental ligands.

Once AhR has bound to its dimerization partner, the heterodimer activates many genes with effects on immunity and inflammation. Cruciferous vegetables like broccoli, cabbage, and brussels sprouts include AhR ligands and thus affect the host cells involved in gastrointestinal immunity and defense.

The findings raise the possibility of dietary recognition factors linking diet with intestinal immunity, and suggest that AhR ligands may have implications for prevention and treatment of diseases—including IBD. Studies show down-regulation of AhR in intestinal tissues from IBD patients, while AhR ligands are linked to beneficial increases in interleukin-22 and the production of mucus and defensins.

The preliminary findings raise many questions, including whether there is some "inflammatory diet" that interferes with the immune system. There is also the potential for involvement in antitumor immune responses. Studies to identify other foods with similar immunomodulatory components are underway.

**COMMENT:** *This thought-provoking review sheds light on how diets high in vegetable fiber may play a role in immunomodulation of gastrointestinal disorders, and evokes the exciting possibility of dietary pattern recognition receptors linking food and intestinal immunity. Specific components of cruciferous vegetables of the Brassicaceae family (eg, broccoli, cabbage, and brussels sprouts) are physiologic ligands of AhR, a transcription factor universally expressed in vertebrate cells. Activation of AhR by these ligands impacts development of certain lymphoid cells, interleukin-22 cytokine expression, and synthesis of defensins and other mediators of local immunity that influence microbial flora. Aryl hydrocarbon receptor ligands are additionally postulated to exert health benefits both in disease prevention (eg, in persons at risk for IBD) and treatment (eg, for IBD and the metabolic syndrome). C.D.*

*Tilg H: Diet and intestinal immunity.*

*NEJM. 2012;366:181-183.* ♦♦

## Triple Whammy: Cold Urticaria, Autoimmunity, and Immunodeficiency

**T**HERE are several different types of cold urticaria although mast cells are clearly involved, the processes leading to cell degranulation are unclear. This paper reports on the genetic findings in three families with an unusual syndrome of cold urticaria plus immune defects.

The three families of European ancestry had lifelong cold urticaria beginning at a very young age. In contrast to typical cold urticaria, results were negative on skin testing with cold-water immersion but positive for evaporative cooling and general exposure to cold air. Almost all affected subjects had immunologic abnormalities, including antibody deficiency in 75% of subjects. Other findings included antinuclear antibody positivity, symptomatic allergic disease, and recurrent sinopulmonary infections. Symptomatic autoimmune disease was ►►

present in 26% of patients and common variable immunodeficiency in 11%.

Genetic studies were performed to identify the cause of this dominantly inherited syndrome. Abnormalities were detected in an interval on chromosome 16q including the gene *PLCG2*—which encodes the signaling molecule phospholipase  $C\gamma_2$ , expressed in B cells, natural killer cells, and mast cells. Further studies identified three separate in-frame deletions, which produced proteins with constitutive phospholipase activity. In functional studies, cells expressing the *PLCG2* mutations had increased signaling at subphysiologic temperatures.

The inherited syndrome of cold urticaria, immunodeficiency, and autoimmunity in these families related to genomic deletions of *PLCG2*. The resulting gain in  $PLC\gamma_2$  function is responsible for multiple leukocyte signaling abnormalities, thus leading to a syndrome with both excessive and deficient immune function.

**COMMENT:** Mendelian analysis of three families with a dominantly inherited complex of cold-induced urticaria, antibody deficiency, and autoimmunity identified three distinct in-frame *PLCG2* genomic deletions resulting in protein products with constitutive phospholipase activity. These mutant *PLCG2*-expressing cells encoding phospholipase  $C\gamma_2$  ( $PLC\gamma_2$ ) demonstrated enhanced signaling at subphysiologic temperatures, which explains the cold urticaria that occurred in all affected subjects. Paradoxically, there was decreased  $PLC\gamma_2$ -dependent signaling and function in B cells, natural killer cells resulting in immunodeficiency. This novel disorder is therefore labeled "phospholipase  $C\gamma_2$ -associated antibody deficiency and immune dysregulation" (PLAID).

C.D.

Ombrello MJ, Remmers EF, Sun G, et al: Cold urticaria, immunodeficiency, and autoimmunity related to *PLCG2* deletions.

N Engl J Med. 2012; 366:330-338. ♦♦

## Infant Gut Microflora: Link with Atopy

**C**HANGES in the intestinal microbiota during the first few years of life have an important impact on immunologic maturation and systemic immune responses. Patterns of gut microbial colonization from birth through age 2 were analyzed for association with allergen-specific IgE and atopic eczema in infants.

The prospective study included 94 unselected infants from a population-based study in Trondheim, Norway. Fecal samples were obtained at the ages of 10 days, 4 months, and 1 and 2 years, and analyzed by quantitative real-time polymerase chain reaction for the presence of 12 different bacteria. Blood samples at age 2 were tested for specific IgE to 12 different allergens. Patterns of gut microflora over time were compared for infants who tested positive versus negative for specific IgE—42 and 52 infants, respectively. Associations with the phenotype of atopic asthma were evaluated as well.

Children positive for specific IgE at age 2 had lower levels of *Escherichia coli* in 4-month and 1-year fecal

samples. They also had higher levels of *Bifidobacterium longum* at age 1 and lower levels of *Bacteroides fragilis* at age 2. The sensitization-related differences in *E. coli* and *B. longum* were no longer apparent at age 2. No significant differences in colonization were noted for the other bacterial species studied. There were no significant associations between gut microflora and atopic eczema.

Children with specific IgE sensitization at age 2 show some distinct patterns of gut microbial colonization at younger ages. It is unclear whether the associations are causal in nature, or whether reduced gut microbial diversity has implications for the development of atopy.

**COMMENT:** The interaction between the immune system and gut microflora early in life has become widely recognized as a possible determinant of atopy risk. This population-based prospective study from Norway found an association between the pattern of intestinal bacterial colonization and allergen-specific IgE, but not with a diagnosis of atopic dermatitis.

S.A.T.

Storrø O, Øien T, Langsrud Ø, et al: Temporal variations in early gut microbial colonization are associated with allergen-specific immunoglobulin E but not atopic eczema at 2 years of age.

Clin Exp Allergy. 2012;41:1545-1554. ♦♦

## CLINICAL TIDBITS

### CRS Pathophysiology: Link between *S. aureus*, Biofilms, and Th2 Inflammation

**A**MID ongoing debate over the pathogenesis of chronic rhinosinusitis (CRS), biofilms have been suggested as a possible environmental trigger. Specifically, *Staphylococcus aureus* biofilms may predict severe disease resistant to current treatments. This study examined adaptive immune responses in patients with CRS associated with *S. aureus*-resistant biofilms.

Analysis of sinonasal mucosa from 53 patients with CRS found a significant association between *S. aureus* biofilms and staphylococcal superantigens. Thus the biofilms may serve as a nidus for superantigen-eluting bacteria. In patients with CRS of varying severity, *S. aureus* biofilms were linked to eosinophilic inflammation, in the presence of the Th2-skewed host adaptive immune response. This was distinct from the superantigen effect leading to induction of IgE.

The findings add new evidence linking *S. aureus*-biofilms and a skewed immune response to the development of CRS. The associations are independent of the superantigen pathway, suggesting a direct link between the micro-organism and host.

**COMMENT:** Chronic eosinophilic inflammation in the sinuses—independent of known allergen sensitivity—has been a difficult concept for us to accept, let alone understand. Fortunately, recent advances in our understanding of biofilm pathophysiology have opened

the door to an understanding of the mechanisms involved. This study describes a link between eosinophilic inflammation and *S. aureus* found in biofilms that is independent of the classic staph super-antigen concept.

S.A.T.

Foreman A, Holtappels G, Psaltis AJ, et al: Adaptive immune responses in *Staphylococcus aureus*-biofilm-associated chronic rhinosinusitis.

Allergy. 2012;66:1449-1456. ◆◆

## Low-Dose, Long-Term Azithromycin Is Not Effective for CRS

**L**ONG-TERM treatment with low doses of macrolide antibiotics has been suggested as an option for patients with chronic rhinosinusitis (CRS) that does not respond to conventional treatment. Long-term azithromycin was compared with placebo in patients with recalcitrant CRS.

The randomized trial included 60 patients with CRS, with or without nasal polyps, who had not responded to optimal medical and in most cases surgical treatment. One group received azithromycin, 3 days at 500 mg followed by 500 mg/wk for 11 weeks. Controls received placebo.

There was no significant difference in outcomes on a wide range of measures, including the Sino-Nasal Outcome Test-22, visual analog scale scores, and the Short Form-36. There was also no difference in the nasal endoscopic findings, smell test, or microbiology results.

At least with the 3-month treatment regimen evaluated here, azithromycin is not efficacious for patients with recalcitrant CRS. Further studies are needed, including other macrolides, other dosages, and different treatment periods.

**COMMENT:** Given azithromycin's broad spectrum, low cost, good safety profile, and convenient dosing schedule, one might suspect it would be an ideal agent to improve symptoms in patients with chronic sinusitis. This study suggests otherwise.

S.A.T.

Videler WJ, Badia L, Harvey RJ, et al: Lack of efficacy of a long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial.

Allergy. 2012;66:1457-1468. ◆◆

## EPIT Patch Therapy Reduces Hay Fever Symptoms

**E**PICUTANEOUS allergen-specific immunotherapy (EPIT)—with allergen applied to the skin using patches—has been proposed as a needle-free alternative for allergy treatment. This technique was evaluated for use in patients with grass pollen allergy causing rhinoconjunctivitis.

Patients were randomly assigned to grass pollen EPIT, at three different doses, or placebo. Before and

during pollen season, each group received six weekly patches. Symptoms and other outcomes were assessed 4 to 5 months after treatment in 110 patients, and the following year during pollen season (without treatment) in 93 patients.

For patients in the high-dose EPIT group, in-season hay fever symptoms were reduced by more than 30% during the treatment year and by 24% the following year, compared to placebo. Symptom response in the follow-up year depended on treatment dose. Adverse events—mainly pruritus, erythema, wheal, or eczema—were more frequent in patients receiving higher allergen doses. There was an 8.3% rate of adverse events leading to study dropout, but no serious adverse events.

This trial supports the safety and efficacy of EPIT in patients with grass pollen allergy. At higher doses, a significant reduction in hay fever symptoms is produced by a course of just six weekly patches.

**COMMENT:** EPIT is a novel approach to allergen immunotherapy that is particularly appealing to "needle-phobic" patients. Previous reports used scarification to enhance antigen absorption transdermally. In this study, adhesive tape was used to pretreat the skin for the allergen patch, which was applied for only 8 hours each time. Although the results of patient reported outcomes were impressive in the group receiving the higher doses, there was no significant change in conjunctival provocation or skin tests. It will be of interest to see future reports of this potential option of allergen administration.

S.M.F.

Senti G, von Moos S, Tay F, et al: Epicutaneous allergen-specific immunotherapy (EPIT) ameliorates grass pollen-induced rhinoconjunctivitis: a double-blind, placebo-controlled dose escalation study.

J Allergy Clin Immunol. 2012;129:128-135. ◆◆

## Appropriate Use of Allergen-Specific IgE Testing in Children

**S**PECIFIC IgE testing is widely available for assessment of suspected allergy in children. This clinical report seeks to provide guidance on the use of allergen-specific IgE tests in children.

Pediatricians commonly treat children with specific allergies causing diseases such as asthma, allergic rhinitis, atopic dermatitis, and anaphylaxis. Allergen-specific IgE tests, including in vitro assays or skin tests, may be performed to confirm an allergic trigger suspected by the clinical history. Identification of allergen-specific IgE and sensitization is valuable in eliminating allergic triggers and guiding specific immunotherapy. However, pediatricians should understand that children with a positive test for specific IgE do not necessarily have clinical allergy. They should also be aware that newer enzymatic assays have replaced the radioallergosorbent test.

The report addresses considerations in test selection and interpretation, issues specific to respiratory and food allergies, and other type of allergy. Pediatricians are also advised to consider consulting with a board-certified allergist/immunologist. ➤➤



**COMMENT:** Allergists understand that sensitization found during specific IgE testing does not equate to a diagnosis of allergy, in the absence of corresponding history. That this message has been clearly sent by the American Academy of Pediatrics Section on Allergy/Immunology to all pediatricians is terrific!

K.R.M.

Sicherer SH, Wood RA, et al: Allergy testing in childhood: using allergen-specific IgE tests.

Pediatrics. 2012;129:193-197. ♦♦

## Vocal Cord Dysfunction: Treatment Response in Children

**P**ATIENTS with paradoxical vocal-fold motion (PVFM) have inappropriate induction of the vocal cords with inspiration. A series of children with PVFM seen at a multidisciplinary pediatric airway center is reviewed.

The series included 59 children, mean age 13.64 years; three-fourths were girls. The diagnosis of PVFM was made on the basis of clinical history and exclusion of other pulmonary abnormalities, or with visualization of inappropriate vocal cord adduction on laryngeal fiberoptic examination.

Speech therapy was successful as initial treatment in 63% of patients after a mean of 3.7 sessions. Ten percent of children had a known psychiatric diagnosis at referral; a psychiatric diagnosis was eventually made in 30% of children overall. Speech therapy was less successful, and underlying psychiatric disorders more likely, in children with inspiratory stridor at rest. In these cases, psychiatric treatment had a 100% success rate, with a mean of 3 sessions over a 2-month period.

This large case series suggests that most children with PVFM are successfully treated with speech therapy. Children with PVFM at rest appear more likely to have underlying psychiatric diagnoses, for which appropriate treatment is helpful.

**COMMENT:** Vocal cord dysfunction, also known as paradoxical vocal fold motion, is a clinical problem frequently seen in allergy practice. Patients affected typically respond well to breathing exercises, and benefit from speech therapy evaluation or a multidisciplinary approach, in refractory cases.

K.R.M.

Maturo S, Hill C, Bunting G, et al: Pediatric paradoxical vocal-fold motion: presentation and natural history.

Pediatrics. 2012;128:e1443-1449. ♦♦

## REVIEWS OF NOTE

**COMMENT:** This review nicely summarizes the available treatments for hereditary angioedema, and the most recent advancements among these treatment options.

K.R.M.

Sardana N, Craig TJ: Recent advances in management and treatment of hereditary angioedema.

Pediatrics. 2011;128:1173-1180. ♦♦

**COMMENT:** Sharing the vast experience from the Brigham and Women's Hospital desensitization program, this is an excellent review of the state of the art in drug sensitization. It includes an overview of mechanisms and specific approaches to desensitization with antibiotics, biologicals, and chemotherapeutic agents.

S.A.T.

Liu A, Fanning L, Fernandez J, et al: Desensitization regimens for drug allergy: state of the art in the 21st century.

Clin Exp Allergy. 2012;41:1679-1689. ♦♦

**COMMENT:** Vitamin D deficiency is increasingly identified as a contributor to many disease states, including allergies and asthma. Younger subjects with allergies have lower levels of vitamin D. This study and review support the need to educate the general public on vitamin D intake. We should review our recommendations to allergic and asthmatic patients about the need to take vitamin D replacement, particularly if they are found to have low levels.

V.H.-T.

Frieri M, Valluri A: Vitamin D deficiency as a risk factor for allergic disorders and immune mechanisms.

Allergy Asthma Proc. 2011;32:338-444. ♦♦

**COMMENT:** This review of allergic rhinitis is best suited for generalists who relegate this condition to lower than 10 on their problem list. They should be made aware of its existence.

S.M.F.

Greiner AN, Hellings PW, Rotiroti G, Scadding GK: Allergic rhinitis. Lancet. 2011;378: 2112-2122. ♦♦