# 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 4 July - August 2011


## FOCUS ON ALLERGY RISK FACTORS

THIS issue of *AllergyWatch* highlights new research on risk factors for the development of asthma and allergies in children.

## 'To Feed or Not to Feed'

COMPLEMENTARY feeding refers to early introduction to solid food or cow's milk--before 4 months of age--with the goal of reducing later allergy risk. The benefits of such dietary manipulation remain unclear. This birth cohort study evaluated the effects of early complementary feeding on the risk of food sensitization by age 2 years.

The study included 594 maternal-infant pairs in Detroit, Mich. The mothers averaged 30 years of age, and more than 60% were African-American. Infant feeding was assessed at age 1, 6, and 12 months. At age 2 years, blood samples were obtained for measurement of IgE to egg, milk, and peanut; the study definition of sensitization was IgE levels of 0.35 IU/mL or higher.

Forty percent of the mothers reported introducing complementary food before age 4 months. At age 2, rates of IgE sensitization were 23.9% for egg, 30.6% for milk, and 11.4% for peanut. The effects of early complementary feeding on sensitization were modified by parental history of asthma or allergy. On adjusted analysis, infants with a parental history of allergy who were exposed to early feeding were less likely to be sensitized to peanut: odds ratio 0.2. At an IgE cutoff point of 0.70 IU/mL or higher, early complementary feeding also protected against egg sensitization: odds ratio 0.5. For infants without a parental history, early feeding had no protective effect.

Early introduction of complementary foods may reduce the risk of peanut (and possibly egg) sensitization by age 2 to 3. However, this protective effect is apparent only in children with a parental history of allergy. Further study of modifiable risk factors for food sensitization is needed.

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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*®.

*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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**COMMENT:** *Analyzing data from the large birth cohort in Detroit, this report suggests that infants exposed to peanut protein by 4 months were five times less likely to develop peanut allergy. However, this was statistically significant only for infants with a family history of allergy or asthma. Interestingly, early milk or egg exposure did not provide significant protection. The recommendations for earlier introduction of potentially allergenic foods in infants have changed in recent years. More large cohort studies will help to better define the optimal age for the introduction of these foods.*
*S.M.F.*

*Joseph CLM, Ownby DR. Havstad SL, et al: Early complementary feeding and risk of food sensitization in a birth cohort.*
**J Allergy Clin Immunol**. 2011;127:1203-1210. ♦♦

## Allergen Exposure and TV Watching Linked to Higher eNO in Kids

MEASUREMENT of exhaled nitric oxide (eNO) has become a useful tool for asthma monitoring. However, there are few data on the association between eNO and allergic sensitization and allergen exposure. The effects of sedentary behavior--a lifestyle factor related to asthma--on eNO are also unclear. These questions were addressed in a birth cohort study with long-term follow-up.

The study included 430 children enrolled with a parental history of allergy or asthma. Children were enrolled in the birth cohort between 1994 and 1996 and followed up to age 12. Exposure to allergens was measured in bed dust samples, with sensitizations assessed mainly by specific IgE measurement. Questionnaires were used to assess current asthma and allergic symptoms and hours of television viewing or video game playing.

The children also underwent spirometry and eNO measurement. The relationship between eNO and exposure to specific allergen was assessed in sensitized versus unsensitized children. The association between eNO and sedentary behavior was examined as well.

Children with current asthma, wheezing, or rhinitis had higher eNO levels: 32.2, 27.0, and 23.2 ppb, respectively. Sensitization to cat, dog, and dust mite allergen predicted higher eNO levels, explaining one-third of the variability in eNO. Children who were sensitized and exposed to dust mite had the highest eNO levels.

Television viewing was also associated with eNO: children who watched more than 10 hours of TV on weekdays had a 0.64-log increase in eNO, after controlling for allergen exposure, body mass index, and sensitization.

Exposure to indoor allergens and sedentary behavior may be associated with increased eNO in children at risk of allergy and asthma. The findings highlight the contribution of allergic sensitization when evaluating the effects of allergen exposure on airway inflammation. The association between eNO and television viewing or video game playing remains significant after adjusting for other factors.

**COMMENT:** *Using a birth cohort of children at risk for allergies and asthma, this unique study investigated the effect of home exposures to allergens and sedentary home behaviors on eNO levels. The findings suggest possible subclinical effects of environmental allergen exposures. Sedentary lifestyle may also result in higher eNO and potential airway inflammation. We need to encourage our families of allergic children to continue with allergen avoidance at home and to support physical activities for their children.*
*S.M.F.*

*Sordillo JE, Webb T, Kwan D, et al: Allergen exposure modifies the relation of sensitization to fraction of exhaled nitric oxide levels in children at risk for allergy and asthma.*
**J Allergy Clin Immunol**. 2011;127:1165-1172. ♦♦

## Is There a 'Gender Switch' in Childhood Rhinitis?

SEVERAL studies have reported a "gender switch" in asthma, from male predominance in childhood to female predominance in adolescence. In light of the strong comorbidity between asthma and rhinitis, a similar change might be suspected for rhinitis. This study assessed the effects of gender and atopy on the natural history of rhinitis through childhood and adolescence.

The analysis included 1,456 participants from the Isle of Wight birth cohort, recruited in 1989. Nasal symptoms were assessed at age 1, 2, 4, 10, and 18 years. Skin prick tests for atopy were assessed at age 4, 10, and 18 years. In addition to 12-month period prevalence, the investigators assessed changes in rhinitis disease status, stratified by gender and atopic status.

The prevalence of rhinitis increased from 5.4% at age 5 to 35.8% at age 18. The prevalence of atopic rhinitis increased from 3.4% at age 4 to 27.3% at age 18. Atopic rhinitis showed a greater positive transition in boys between age 10 and 18, and was more frequent in boys at 18. In contrast, girls had a greater positive transition for nonatopic rhinitis from age 10 to 18, with a higher prevalence at 18. Nonatopic rhinitis was more likely to go into remission during the early childhood years, and less so in later childhood and adolescence.

Gender and atopic status affect the prevalence of rhinitis during childhood and adolescence. From age 10 to 18, boys are more likely to develop atopic rhinitis, while girls are more likely to develop nonatopic rhinitis. The findings suggest some differential effect of pubertal factors; further study of the relevant mechanisms is needed.

**COMMENT:** *Gender differences in the prevalence of atopy have been recognized for many years. This fascinating study uses a birth cohort to help us understand the dynamics of changes in the prevalence of rhinitis birth to adolescence. Not surprisingly, the prevalence of allergic rhinitis increased significantly from birth to age 18. Surprisingly, there was a persistent male predominance of allergic rhinitis at age 18. There was no gender difference in nonallergic rhinitis at age 2, whereas females were much more likely to have nonallergic rhinitis at age 18.*
*S.A.T.*

*Kurukulaaratchy RJ, Karmaus W, Raza A, et al: The influence of gender and atopy on the natural history of rhinitis in the first 18 years of life.*
**Clin Exp Allergy**. 2011;41:851-859. ♦♦

## Allergen Plus Nonallergen Exposures Increase Asthma Risk

THE contribution of allergen exposure to the development of asthma remains unclear. Whereas most studies of asthma risk factors focus on individual exposures, in reality children are exposed to many different potential risk factors. This study examined the effects of combined exposure to dog and environmental tobacco smoke (ETS) in children at high risk of asthma.

The birth cohort study included 380 children with a family history of asthma or allergic disease. Cord blood cotinine was measured as an indicator of ETS exposure around the time of birth. Atopy, exposure to Can f 1 and indoor nitrogen dioxide, and urinary cotinine were measured during the first year of life. At age 7, the children were assessed for asthma and bronchial hyperresponsiveness. The effects of Can f 1 and ETS exposure were assessed by stepwise multiple linear regression.

Children exposed to Can f 1 and $NO_2$ or Can f 1 and perinatal ETS were at increased risk of asthma. Odds ratios were 4.8 for Can f 1 plus $NO_2$ and 2.7 for Can f 1 plus cotinine measured in cord blood, compared to neither exposure. The results were similar on analysis of dog ownership rather than Can f 1 exposure. The effects of early exposures appeared greater in children with atopy--among atopic children, the odds ratio for bronchial hyperresponsiveness with cotinine measured in cord blood was 3.1.

Among children at high genetic risk, the incidence of asthma is elevated for those with early co-exposure to dog allergen, indoor $NO_2$, or ETS. The increase in risk associated with ETS is significantly higher for children with atopy.

**COMMENT:** *For children at high risk of asthma, co-exposure to a dog in the house with gaseous or particulate pollutants appears to increase the risk of asthma. The atopic state appears to increase risk when exposure to ETS occurs. These data support the need for close environmental control of childhood exposures.*
*B.E.C.*

*Carlsten C, Brauer M, Dimich-Ward H, et al: Combined exposure to dog and indoor pollution: incident asthma in a high-risk birth cohort.*
**Eur Respir J**. 2011;37:324-330. ♦♦

## Extreme Prematurity May Confer Higher Asthma Risk in Adults

PRETERM infants are at increased risk of chronic lung disease and childhood asthma symptoms. However, as increasing numbers of preterm infants reach adulthood, their longer-term risk of asthma remains unclear. This issue was addressed using nationwide registry data.

Using the Swedish national birth register, the investigators identified 622,616 singleton infants born from 1973 through 1979. Pharmacy data were used to assess prescription of asthma medications to these individuals in 2005-07. The relationship between preterm birth and prescription of asthma medications in young adulthood was assessed. To increase positive predictive value for asthma, the analysis focused on prescriptions for both an inhaled beta-2 agonist and glucocorticoid and for products containing a beta-2 agonist plus other drugs for obstructive airway diseases.

The analysis identified 165 individuals with a history of extremely preterm birth: between 23 and 27 weeks' gestation. These young adults were more than twice ➤➤

as likely to receive a prescription for asthma medications, compared to those with term birth: adjusted odds ratio 2.4. Later preterm birth--from 28 to 32 weeks or 33 to 36 weeks--was unrelated to prescription of asthma drugs.

This very large birth cohort study suggests that extreme prematurity is a risk factor for asthma in young adulthood. Recognition of this association may lead to better detection and treatment of susceptible patients--especially as more individuals with extreme preterm birth enter adulthood. Preterm birth at 28 weeks' gestation or later is unrelated to adult asthma risk.

**COMMENT:** *Infants born prematurely have lowered lung volumes and maturity, and corresponding increased risks for respiratory problems in childhood. Those early risks have been thought to resolve with growth, in tandem with pulmonary function increases and maturity. Or--contrary to our conventional thinking--could those issues actually persist longer? This cohort study challenges the notion that prematurity-related pulmonary effects are confined to childhood, at least when considering extreme preterm birth.*
*K.R.M.*
*Crump C, Winkleby MA, Sundquist J, Sundquist K: Risk of asthma in young adults who were born preterm: a Swedish national cohort study.*
**Pediatrics**. 2011;127:e913-e920. ♦♦

## Low Birth Weight, Maternal Smoking and Childhood Asthma

PRENATAL exposure to tobacco smoke is associated with an increased risk of low birth weight (LBW). Low birth weight is also independently associated with decreased lung function. This study assessed the independent and joint effects of prenatal smoking and LBW on childhood asthma risk.

The study included 3,389 children who participated in a survey study on allergy and asthma in 1996, when they were 7 to 8 years old. Follow-up data obtained at age 11 to 12 included skin-prick testing in 2,121 children. Associations between prenatal smoking, LBW, and self-reported physician-diagnosed asthma were assessed.

Birth weight was significantly lower among children exposed to prenatal smoking: mean 3,360 g, compared to 3,571 g in nonexposed children. Prenatal smoking greatly increased the risk of asthma among LBW children, compared to a relatively modest increase in normal birth weight children: risk ratio 8.8 versus 1.3. On its own, LBW was not an independent predictor of childhood asthma. The associations remained unchanged on multivariate analysis, including a highly significant interaction between LBW and smoking.

The results suggest nearly a 9-fold increase in the risk of physician-diagnosed asthma among LBW children exposed to prenatal smoking. This synergistic interaction persists after adjustment for other known risk factors, including allergic sensitization. One possible mechanism is that airway inflammation from prenatal smoke more readily causes obstructive symptoms in the underdeveloped airways of LBW children.

**COMMENT:** *Intrauterine growth is reduced by maternal smoking during pregnancy; pulmonary function is affected in infants with low birth weight. These are known factors. What is not known is the degree to which those factors might act synergistically to increase asthma risk in school-aged children. The study was not initiated until these children were at least age 7, so a large potential confounding variable would be ongoing exposure to environmental tobacco smoke throughout early childhood in study homes. Still, the findings are compelling.*
*K.R.M.*
*Bjerg A, Hedman L, Perzanowski M, et al: A strong synergism of low birth weight and prenatal smoking on asthma in schoolchildren.*
**Pediatrics**. 2011;127:e905-e913. ♦♦

## Obese Patients with Wheezing Have Lower eNO

ALTHOUGH several studies have reported an association between asthma and obesity, the specific mechanism of this link is unclear. One question is the relationship of obesity with airway inflammation, as reflected by exhaled nitric oxide (eNO), and atopy. This population-based study compared the phenotype of obese versus nonobese patients with asthma.

The analysis included 2,187 Swedish men and women, aged 25 to 74, from a previous population cohort. Assessments included body mass index (BMI), body composition, eNO, lung function, IgE measurement, and respiratory symptoms. Associations of eNO with obesity (BMI 30 or over) and other factors were analyzed.

Wheezing was associated with increased eNO and atopy in nonobese subjects. Among participants with wheezing, eNO was significantly lower for those who were obese: 16.1 versus 19.1 ppb. There was no significant difference in atopy: 25.0% and 20.7%, respectively. Among subjects with wheezing, eNO was negatively associated with waist-to-hip ratio and body fat content, as well as BMI. These associations were not present in subjects without respiratory symptoms.

Wheezing is associated with lower eNO values in obese subjects, compared to the positive association seen in nonobese subjects. This finding suggests a possible body-weight-related difference in asthma phenotype. Wheezing associated with obesity may be related to other inflammatory processes or mechanical effects, rather than eosinophilic airway inflammation.

**COMMENT:** *Obesity is epidemic. It is comorbid with a variety of chronic conditions, including asthma. The nature of the relationship between obesity and asthma is complex. This study notes discordancy between eNO, a measure of airway inflammation, and wheezing. Although the study has some issues, this finding implies that either "obesity-related asthma" may be different than asthma in nonobese individuals, or that wheezing in obese individuals may not result from airway* ➤➤

*inflammation. There is probably overlap between these conditions, which will need to be teased out.*
*S.F.W.*
*Berg CM, Thelle DS, Rosengren A, et al: Decreased fraction of exhaled nitric oxide in obese subjects with asthma symptoms: data from the population study INTERGENE/ADONIX.*
**Chest**. 2011;139;1109-1116. ♦♦

## Omalizumab for Severe Uncontrolled Asthma: 7-Year Follow-Up

ANTI-IgE therapy with omalizumab represents a new approach to treatment of severe allergic asthma. In a previous study, the authors linked improvements in severe persistent asthma with omalizumab to increased expression of Foxp3, a regulator of inflammation; and to reduced expression of the inflammatory mediator interleukin-8 (IL-8). This study reports on the outcomes of 7 years of omalizumab therapy in patients with severe uncontrolled asthma.

The study included 7 corticosteroid-dependent patients with severe, persistent allergic asthma. All required daily treatment with inhaled corticosteroids, dose 3,000 μg of beclomethasone dipropionate equivalent, and long-acting $\beta_2$ agonists, as well as short-acting $\beta_2$ agonists as needed. Outcomes were assessed after 7 years of open-label add-on therapy with omalizumab.

Long-term omalizumab therapy was well tolerated by all patients, with no adverse events. Mean $FEV_1$ increased from 53% predicted at baseline to 71% predicted at 7 years. The ratio of $FEV_1$ to forced vital capacity increased from 52% to 65% predicted. Reductions in severe exacerbations and asthma symptom score achieved with 4 years of treatment were even more evident at 7 years. Use of medications decreased as well, including antibiotics, nebulized steroids, bronchodilators, and oral corticosteroids.

This experience supports the benefits of long-term omalizumab therapy for patients with severe uncontrolled asthma. The clinical and lung function benefits observed at 4 years are maintained or even increased at 7 years. Omalizumab is safe and effective as long-term add-on therapy for this challenging group of patients.

**COMMENT:** *This provocative study argues for longer-term omalizumab therapy in severe uncontrolled asthma. Such longer therapy--beyond 4 years and up to 7 years--leads to progressive, continued statistically and clinically significant reductions in exacerbations of asthma, use of oral and nebulized steroids, bronchodilators and antibiotics. Extended therapy also yields improvements in $FEV_1$ and $FEV_1$/FVC. Omalizumab is uniquely positioned as an immune modulator to enhance Foxp3 regulatory T cells and decrease IL-8: a major mediator of chronic severe asthma that is uncontrolled with conventional therapy, including steroids.*
*C.C.R.*
*Pace E, Ferraro M, Bruno A, et al: Clinical benefits of 7 years of treatment with omalizumab in severe uncontrolled asthmatics.*
**J Asthma.** 2011; 48:387-392. ♦♦

## High Rate of Cardiovascular Symptoms in Older Patients with Anaphylaxis

FEW studies have focused on the characteristics and management of older adults presenting to the emergency department (ED) with anaphylaxis. An ED series of older patients with anaphylaxis is analyzed, including comparison with younger patients.

The study included 220 patients with anaphylaxis presenting to a busy ED over 27 months. All met current diagnostic criteria for anaphylaxis. Nearly one-fourth of the patients (24.5%) were 50 years of age or older, including 12.7% who were 65 years or older.

Foods were the suspected cause of anaphylaxis for less than 15% of patients aged 50 or older, compared to about 40% of younger patients. Older patients were more likely to present with cardiovascular symptoms: 55.6% of those aged 50 years or older and 64.3% of those aged 65 or older, compared to about one-third of younger patients. Older patients were less likely to be discharged home directly from the ED: 35.2% for patients aged 50 or older and 32.1% of those aged 65 or older, compared to more than half of younger patients. The older age groups were also less likely to receive a prescription for self-injectable epinephrine: 40.7% of patients aged 50 or older and 32.1% of those aged 65 or older.

The study highlights some important differences in ED presentation among older adults with anaphylaxis. Most patients aged 50 or older have cardiovascular symptoms at presentation. The authors call for a multicenter, prospective study to clarify the characteristics and management of older adults with anaphylaxis.

**COMMENT:** *This provocative study concludes that in older patients presenting to the emergency room with anaphylaxis there is decreased probability of food-related but an enhanced probability of medication-related anaphylaxis, compared to younger patients. Older patients have an increased probability of presentation with cardiovascular symptoms but a decrease in direct discharge home and in prescriptions for self-administered epinephrine. These results argue for better recognition of anaphylaxis in the elderly. Lack of recognition and diagnosis in this age group is likely related to confounding comorbidities and the lack of a standardized diagnostic format.*
*C.C.R.*
*Campbell RL, Hagan JB, Li JTC, at al: Anaphylaxis in emergency room department patients 50 or 65 years or older.*
**Ann Allergy Asthma Immunol**. 2011;106:401-406. ♦♦

## Allergies to Antibiotics in Children

STUDIES of adverse drug reactions (ADRs) in adults find that most penicillin-related ADRs are not true allergic reactions, and that these patients can safely receive the antibiotic in question. It would be useful to have data on the rates and characteristics of antibiotic allergy in children. The outcomes of skin testing in ➤➤

a series of children with ADRs to antibiotics are reported.

Chart review at a U.S. children's hospital from 2004 to 2009 identified 96 children who underwent skin testing and/or graded challenge testing after an ADR to antibiotics. Implicated drugs were penicillin in 52 patients, azithromycin in 24, cephalosporins in 7, and clindamycin in 4. Along with the outcomes of testing, the researchers analyzed demographic and atopic factors potentially associated with positive challenges.

The provocative drug challenges were tolerated by 90.6% of children overall. The remaining 9.4% had a positive skin test result or failed challenge and were advised to avoid the implicated drug. Of these 9 patients, 8 had a positive skin or challenge test to penicillin. One patient had a positive skin test to clindamycin; none of the azathioprine or cephalosporin challenges were positive. Atopy was present in 55% of children in the study cohort and was associated with positive challenge outcomes.

In this series, less than 10% of children tested for ADRs to antibiotics had true antibiotic allergy. Similar to studies in adults, the results suggest that appropriate challenge testing can avoid unnecessary treatment with alternative antibiotics in nearly 90% of patients.

**COMMENT:** *This study in children supports data in adults that true antibiotic allergy is rare. The study supports others showing that the majority of patients with a history of adverse drug reaction will have negative skin test or negative oral challenge to that antibiotic. All patients challenged to azithromycin and cephalosporins tolerated the medications. This emphasizes the importance of the allergist in evaluating patients with suspected antibiotic allergy and preventing unnecessary overuse of alternative antibiotics.*
*V.H.-T.*

*Kamboj S, Yousef E, McGeady S, Hossain J: The prevalence of antibiotic skin test reactivity in a pediatric population.*
**Allergy Asthma Proc**. 2011;32:99-105. ♦♦

## Local Anesthetic Allergy--Do We Test or Not?

ADVERSE reactions to local anesthetics are common. Although true IgE-mediated reactions are rare, the distinction can be difficult to make and there are no clear guidelines for doing so. A large experience with skin testing for diagnosis of local anesthetic allergy is presented.

Chart review identified 178 patients undergoing skin testing with local anesthetics at the Mayo Clinic between 1992 and 2008. All underwent skin prick and intradermal testing followed by incremental subcutaneous challenge. An additional chart review evaluated clinical responses to local anesthetics after open subcutaneous challenge in the allergist's office.

A total of 227 local anesthetic skin tests were performed. Lidocaine was the most commonly tested agent, followed by bupivacaine, procaine, and mepivacaine. Overall, 97% of the tests were negative. In addition, 97% of the negative tests were associated with negative results or probable non-IgE-mediated events on challenge. Three patients, with a total of six negative skin tests, had local reactions on open subcutaneous challenge.

Seven tests in five patients met criteria for positive skin test results. One patient with an equivocal local reaction to subcutaneous challenge had no systemic reaction to open challenge. Subcutaneous challenges were negative in 3 patients; the fifth patient did not undergo open challenge. Clinical administration of local anesthetics after open challenge was tolerated by 98% of patients. Local anesthetic skin testing had a negative predictive value of 97%.

This large experience finds a low rate of positive results on local anesthetic skin tests. Patients with negative skin test results are highly likely to tolerate clinical administration of the tested anesthetic. The authors call for further studies to evaluate skin test-only protocols for local anesthetic allergy.

**COMMENT:** *The workup of patients for local anesthetic reactions is hazy. Most patients in this study of local anesthetic evaluation had negative testing and negative challenge results. The negative predictive value was very high, which supports the utility of testing for reactions to these medications. It certainly gives us food for thought. I agree that studies looking at skin test-only protocols would provide useful information.*
*V.H.-T.*

*McClimon B, Rank M, Li J: The predictive value of skin testing in the diagnosis of local anesthetic allergy.*
**Allergy Asthma Proc**. 2011;32:95-98. ♦♦

## Skin Prick Testing--How Long Is Too Long to Read?

IMMEDIATE reactions to skin-prick tests (SPTs) are usually assessed within 15 to 20 minutes. However, because of competing clinical responsibilities, allergists may not be available to read the results within this time. This study evaluated the reliability of reading skin test results before or after 15 to 20 minutes.

The prospective study included 53 patients with allergy symptoms undergoing routine aeroallergen SPTs. In addition to allergen extracts, patients were tested with histamine and a negative control solution. Wheal-and-flare reactions at 10, 30, and 40 minutes were compared with the standard 20-minute assessments. All SPTs were placed and read by a single investigator.

For both wheal and flare measurements, there was excellent agreement between paired measurements made at 20 versus 30 minutes. At 10 versus 20 minutes, agreement was moderate and good, respectively. At 40 versus 20 minutes, agreement was good for both measurements.

The results suggest that allergy SPT results can be read at 30 minutes, with no significant loss of reliability compared to 20 minutes. Results can still be read at 40 minutes, though with decreased reliability. The findings allow the allergist some time flexibility in reading the results of SPTs. ➤➤

**COMMENT:** *I have wondered what to do when I have an emergency in one examination room and am unable to read skin test results within 20 minutes. These authors show that SPT reactions can be read at up to 40 minutes, but are more reliable within 20 to 30 minutes. This is important information to avoid unnecessarily repeating tests, and gives us reassurance that we can read SPTs in a longer period than we would routinely, and still obtain reliable results.*
*V.H.-T.*
*Seibert SM, King TS, Kline D, et al: Reliability of skin test results when read at different time points.*
**Allergy Asthma Proc**. 2011;32:203-205. ♦♦

## Can a Genetic Test Predict Hospital Admission in Asthmatics?

GENE-environment interactions are thought to affect the course of childhood asthma. A specific single-nucleotide polymorphism of the chitinase 3-like 1 gene (*CHI3L1*) gene, rs4950928, has been linked to increased asthma susceptibility in adults. This gene variant was evaluated for association with asthma exacerbations in a large sample of asthmatic children and young adults.

The study included a population-based sample of 1,071 Scottish children and young adults with physician-diagnosed asthma. Genotyping of *CHI3L1* was performed in saliva samples. Logistic regression analysis was performed to evaluate the association between rs4950928 and the risk of asthma exacerbations.

About 60% of the sample patients were homozygous for the risk allele. Of this group, nearly 40% had a reported asthma exacerbation within the past 6 months. On logistic regression analysis, children and young adults with the minor -131G allele were at lower risk of asthma-related hospitalization: odds ratio 0.62. There was no association with other measures of exacerbation (ie, oral steroid treatment or school absences) and no evidence of a gene-dosage effect.

The *CHI3L1* rs4950928 polymorphism is significantly associated with the risk of asthma-related hospitalization in children and young adults. The results suggest the possibility of screening to identify asthmatic children with high-risk genotypes. Even a small reduction in asthma hospitalizations might offset the costs of the screening program.

**COMMENT:** *This study looked at the presence of polymorphisms at* CHI3L1 *and their effects on asthma severity. This may be an opportunity to answer the common question, "Is my patient at risk of severe asthma?" This genetic test may help "convince" families that their children are at risk, and provide support to health care providers in explaining the need for preventive medications. The results will be of interest as we further explore genotype-phenotype correlation for allergic disease.*
*V.H.-T.*
*Cunningham J, Basu K, Tavendale R, et al: The* CHI3L1 rs4950928 *polymorphism is associated with asthma-related hospital admissions in children and young adults.*
**Ann Allergy Asthma Immunol**. 2011;106:381-386. ♦♦

## Treatment for HAE--Still Suboptimal

HEREDITARY angioedema (HAE) is a rare, potentially life-threatening autosomal dominant condition. Over the last few years, new specific treatments have been approved, including pasteurized plasma-derived human C1 esterase inhibitor and the plasma kallikrein inhibitor ecallantide. American physicians were surveyed regarding current management of HAE.

Responses to an Internet survey were obtained from 172 physicians who treated patients with HAE. Respondents were asked about their patients' clinical characteristics, current diagnostic approaches to HAE, use of short- and long-term prophylactic therapies, treatments for acute HAE events, and factors affecting choice of treatments.

Nearly three-fourths of physicians reported treating no more than five patients with HAE. Laboratory tests were considered most important for establishing the diagnosis of HAE, followed by the presenting symptoms. The most frequent treatments for HAE events were fresh-frozen plasma and C1 esterase inhibitors; nearly half of physicians prescribed C1 esterase inhibitors for acute attacks. Eighty percent used androgens for long-term prophylaxis. About half of respondents knew about and were likely to use recently approved treatments for HAE. Adverse effects were an important factor affecting choice of treatment for both physicians and patients; additional factors included efficacy for physicians and costs for patients.

These survey results show wide variation in clinical management of patients with HAE. Despite the availability of new, specific treatments, many patients are still receiving androgens and fresh frozen plasma. The authors note that their survey was performed shortly after the recent approvals; follow-up studies will be useful in assessing changing patterns of HAE therapy.

**COMMENT:** *This survey looked at treatment of patients with HAE by physicians. Physicians may not be aware of newer agents used in the treatment of HAE, as fresh-frozen plasma continues to be used in acute attacks. Androgens were the most frequent treatment of choice for long-term prophylaxis. This is of concern. It will be important to repeat the survey over time to ensure that patients with HAE receive the best current medications for treatment and prophylaxis.*
*V.H.-T.*
*Riedl M, Gower RG, Chrvala C: Current medical management of hereditary angioedema: results from a large survey of US physicians.*
**Ann Allergy Asthma Immunol**. 2011;106:316-322. ♦♦

## Bronchoconstriction Alone Induces Airway Remodeling

EOSINOPHILIC inflammation is thought to be an important contributor to airway remodeling in asthma. Recent in vitro studies suggest that compressive mechanical forces associated with bronchoconstriction may induce remodeling, independent of the effects of inflammation. An experimental study was designed ➤➤

to evaluate the independent effects of repeated bronchoconstriction on airway structural changes in human patients with asthma.

Forty-eight asthma patients were randomly assigned to four inhalation challenge groups, in which they underwent a series of three challenges with a single inhaled agent at 48-hour intervals. One group was challenged with dust mite allergen, which induces both bronchoconstriction and eosinophilic inflammation; and another group with methacholine, which induces bronchoconstriction without inflammation. The other two groups received control challenges with saline alone or albuterol followed by methacholine. Bronchial biopsy specimens were obtained to assess indicators of airway remodeling.

Dust mite allergen and methacholine induced similar levels of bronchoconstriction. Both active challenges were associated with significant airway remodeling, which was not seen after the control challenges. Evidence of structural changes included increased subepithelial collagen band thickness (by a median of approximately 2 μm) and increased periodic acid-Schiff staining of the epithelium (approximately 2 percentage points). These changes were not significantly different between the allergen and methacholine groups.

Bronchoconstriction induces airway structural changes in patients with asthma, even in the absence of inflammation. This result highlights the importance of preventing bronchoconstriction in asthma management --particularly in patients with more severe asthma for whom inhaled glucocorticoids don't normalize bronchial hyperresponsiveness.

**COMMENT:** *Bronchial airway remodeling is thought to be the pathway for long-term and irreversible obstruction in asthma. Remodeling consists of goblet-cell hyperplasia, thickening of the basement membrane, and smooth muscle hypertrophy. Anti-inflammatory corticosteroids have greatly enhanced the control of clinical asthma, but surprisingly they do not prevent long-term lung function changes. This study shows that the strictly mechanical effects of repeated bronchoconstriction--regardless of whether it's induced by allergen or nonspecific stimulus (methacholine)--result in indistinguishable remodeling. Thus bronchodilators may be as important as steroids to the long-term health of bronchi.*
*R.J.M.*

*Grainge CL, Lau LCK Ward JA, et al: Effect of bronchoconstriction on airway remodeling in asthma.*
**N Engl J Med**. 2011;364:2006-2015. ♦♦

## Maternal ICS Treatment 'Unlikely' to Harm Fetus

CURRENT asthma treatment recommendations call for continued use of inhaled corticosteroids (ICS) during pregnancy. There is a need for more data on the systemic effects of corticosteroids on the mother, placenta, and fetus. This study evaluated the effects of maternal ICS treatment on glucocorticoid-regulated pathways throughout pregnancy.

The study included two groups of pregnant women: 156 with and 51 without asthma. In each trimester, blood samples were collected for measurement of maternal plasma cortisol, estriol, osteocalcin, and corticotropin-releasing hormone levels. The effects of ICS use and dosage on these maternal hormone concentrations were assessed, including possible differences by fetal sex.

Asthma per se did not influence the maternal hormone levels. However, all levels were significantly inhibited by ICS in dose-dependent fashion. The changes differed by fetal sex: when the fetus was female, ICS was inversely related to maternal cortisol in the first trimester and inversely related to maternal osteocalcin in the second and third trimesters.

When the fetus was male, ICS dose was unrelated to maternal cortisol, estriol, or osteocalcin levels. However, ICS use was associated with increased maternal corticotropin-releasing hormone during the first trimester.

In pregnant women with asthma, treatment with ICS seems to affect maternal glucocorticoid-regulated pathways only when the fetus is female. Regardless of sex, fetal adrenal function appears unaffected by ICS. The results suggest that maternal ICS therapy is unlikely to adversely affect fetal growth and development.

**COMMENT:** *This reassuring study finds no effect on the fetus with inhaled corticosteroid given for maternal asthma. Fetal growth and adrenal function are not affected. Inhibition of maternal glucocorticoid-responsive pathways were seen in a differential manner, primarily in pregnancies with female fetus. The accompanying editorial* (Am J Respir Crit Care Med. 2011;183:687-688) *gives more historical perspective on this problem.*
*B.E.C.*

*Hodyl NA, Stark MJ, Osei-Kumah A, et al: Fetal glucocorticoid-regulated pathways are not affected by inhaled corticosteroid use for asthma during pregnancy.*
**Am J Respir Crit Care Med**. 2011;183:716-722. ♦♦

## Exercise Improves Asthma Control

AMONG patients with asthma, those who are physically active use less health care. Although some exercise intervention studies have yielded promising results, they have yet to demonstrate a direct association between asthma control and exercise. This trial evaluated the effects of a supervised exercise program on asthma control.

In the nonrandomized trial, 21 adults with partially controlled asthma took part in a 12-week supervised exercise program. The program consisted of three sessions per week, emphasizing aerobic training with some strength training; it was followed by 12 weeks of self-administered exercise. Changes in asthma control and aerobic fitness were compared with those of 15 matched controls.

The supervised exercise program was associated with significant improvements in asthma control. At week 12, patients in the exercise group had a 0.5 increase in Asthma Control Questionnaire score, compared to ➤➤

controls. Asthma quality of life was also improved. At 24 weeks, the improvement in asthma control was well-maintained, and was accompanied by an improvement in aerobic fitness.

In motivated patients with asthma, a 12-week supervised exercise program yields significant improvements in asthma control and quality of life. These benefits are maintained through an additional 12 weeks of self-administered exercise. With further research, exercise could become an "essential adjunct" to asthma management.

**COMMENT:** *A 6-month exercise period led to improvement in asthma control and fitness level. This was not supported by changes in measures of airway obstruction. Thus nonpharmacologic management may be helpful and does not require prior authorization or a copay.*
*B.E.C.*
*Dogra S, Kuk JL, Baker J, Jamnik V: Exercise is associated with improved asthma control in adults.*
**Eur Respir J**. 2011;37:318-323. ♦♦

## Oral Food Challenges in Children Diagnosed with Food Allergy (by Serum Test!)

SERUM food-specific IgE tests are now commonly used to diagnose food allergy in children--particularly those with moderate to severe atopic dermatitis (AD). Based on this diagnosis, many children are prescribed elimination diets to avoid the food to which they are "allergic." The authors report the results of oral food challenges in a series of children referred for evaluation of AD and food allergy.

The retrospective study included 125 children, median age 4 years, undergoing specialist evaluation for suspected food allergy. Ninety-six percent of the children had active AD--mainly moderate to severe. Evaluation included clinical history skin-prick testing, and serum allergen-specific IgE testing.

Forty-four children underwent oral food challenges for foods they were avoiding on the basis of previous immunoassay and skin-prick results. Based on the results, children were able to resume consumption of 84% to 93% of the implicated foods. In many cases, children were avoiding foods for reasons other than previous test results. Of the total 131 oral food challenges performed, only 11 were positive.

The results show a very high rate of negative oral food challenges in children who have been diagnosed with food allergy diagnosed on the basis of specific IgE testing. Except in children with a history of anaphylaxis, foods should not be eliminated on the basis of specific IgE only. Particularly in patients with AD, oral food challenges are recommended to confirm the diagnosis.

**COMMENT:** *How often in practice do we see a child's diet limited, based on the results of serum IgE testing alone? Unfortunately, this scenario is all too common. Practitioners of allergy/immunology are well aware that a single test in isolation does not "diagnose" any allergic condition, as a clinical history is essential! This reasoned concept is--once again--borne out by study results.*
*K.R.M.*
*Fleischer DM, Bock A, Spear GC, et al: Oral food challenges in children with a diagnosis of food allergy.*
**J Pediatrics**. 2011;158:578-583. ♦♦

# CLINICAL TIDBITS

## At Last, a Test for Diagnosis of Radiocontrast Media Allergy?

THE diagnosis of immediate hypersensitivity reactions to radiocontrast media (RCM) continues to pose a challenge in allergy practice. This study evaluated the basophil activation test (BAT) for diagnosis of immediate RCM reactions.

The BAT was performed in 26 patients with a history of immediate RCM reactions, as well as in 43 healthy volunteers. The optimal activated basophil percentage for diagnosis of RCM hypersensitivity was calculated by receiver operating characteristic curve analysis.

Incubation of blood with RCM produced higher activated basophil percentages in patients with RCM reactions compared to controls: 13.11% versus 2.71% at a 1:100 dilution and 19.23% versus 3.73% at a 1:10 dilution. Either the percentage of activated basophils or the stimulation index (SI) performed well in the diagnosis of RCM hypersensitivity. Using SI as the diagnostic criterion with a 1:100 dilution of RCM, the area under the curve was 0.79, with specificity of 88.4% to 100%.

The BAT is a promising test for diagnosis of immediate RCM hypersensitivity. Additional research will be needed to clarify test accuracy and assess predisposing factors.

**COMMENT:** *This study looked at the utility of the BAT in patients with suspected immediate RCM hypersensitivity. This test has been used in patients with other medication allergies. In patients with RCM hypersensitivity, the BAT was higher than in controls. Larger studies are needed to confirm its utility in confirming the diagnosis of RCM hypersensitivity.*
*V.H.-T.*
*Pinnobphun P, Buranapraditkun S, Kampitak T, et al: The diagnostic value of basophil activation test in patients with an immediate hypersensitivity reaction to radiocontrast media.*
**Ann Allergy Asthma Immunol**. 2011;106:387-393. ♦♦

## Why Do Egg-Allergic Children Tolerate Baked Eggs?

MOST egg-allergic children can tolerate baked egg ingestion. A series of experiments were performed to identify the mechanisms for reduced allergenicity of egg allergens after heating.

After oral sensitization to ovalbumin (OVA) or ➤➤

ovomucoid, mice were challenged with native or heated egg proteins. After heating, neither OVA nor ovomucoid caused symptoms of anaphylaxis. In both proteins, heat treatment did not completely destroy IgE-binding capacity. In an in vitro assay, digestibility of OVA increased after heating. For both allergens, digestion was associated with reduced mediator release in a rat basophil leukemia assay and a human basophil assay. After heating, the allergens could no longer be transported across human intestinal epithelial cells in a form capable of producing basophil or T-cell activation.

Heating of the major egg white proteins alters their digestion and absorption in the human digestive tract, thus reducing their allergenicity. This helps to explain why most patients with egg allergy can tolerate ingestion of eggs after heating. The findings highlight the potential to alter the ability of food proteins to trigger allergic reactions, even without interfering with IgE binding.

**COMMENT:** *Using a carefully designed in vitro model and sensitized mice, these researchers attempted to find the reason that 70% to 80% of children with egg allergy can tolerate foods with baked egg. Although heating did not completely destroy the IgE binding capacity of OVA or ovomucoid, it prevented allergen transport across in vitro intestinal epithelial cells, which could potentially trigger basophils and anaphylactic reactions. Therefore food processing can alter the ability of food allergens, not necessarily by interfering with IgE binding, but possibly by altering their absorption and degradation within the GI tract.*
*S.M.F.*

*Martos G, Lopez-Exposito I, Bencharitiwong R, et al: Mechanisms underlying differential food allergy response to heated egg.*
**J Allergy Clin Immunol**. 2011;127:990-997. ♦♦

## A Link Between Allergies and Suicide?

SEVERAL lines of evidence, including seasonal peaks in suicide, suggest a possible association between allergy and suicidality. A population-based study was performed to clarify this association, including the possible confounding or modifying effect of mood disorder.

A total of 27,096 completed suicides from the Danish population were matched to 467,571 living controls. Records showed hospital contacts for allergy in 1.17% of suicides versus 0.79% of controls. On conditional logistic regression, the association was limited to allergy leading to inpatient treatment: incidence rate ratio 1.59. The association was weakened, but still significant, after adjustment for personal psychiatric history and socioeconomic status. The effect was nonsignificantly stronger in women, and stronger for older individuals.

There was also a significant interaction between allergy and mood disorder. Whereas allergy increased suicide risk in subjects with no history of mood disorder, it eliminated risk for those with a history of mood disorder.

These population-based data add to the suggested association between allergy and suicide risk. Further study is needed, including the potential mediating--or even antagonizing--effect of mood disorder.

**COMMENT:** *Allergic rhinitis has a well-known association with certain psychiatric disturbances, and there has been speculation that seasonal increases in completed suicide may be due to symptoms resulting from allergen exposure. This Danish study focused on suicide victims, performing a nested case-control comparison to live controls. The authors found that having prior inpatient allergy treatment was associated with completed suicide. Interestingly, suicide victims with a history of mood disorder were not more likely to have allergies.*
*S.A.T.*

*Qin P, Mortensen PB, Waltoft BL, Postolache T, et al: Allergy is associated with suicide completion with a possible mediating role of mood disorder--a population-based study.*
**Allergy**. 2011;66:658-664. ♦♦

## Some Restaurants Think 'A Little Bit' of Allergen Is OK

MOST deaths from food-related anaphylaxis are caused by foods purchased outside the home. Restaurant staff share some responsibility for allergen avoidance. Restaurant workers were surveyed regarding their knowledge of food allergy.

A telephone interview was conducted with a staff member at 90 English restaurants. Most respondents were managers or waiters. Ninety percent reported receiving foodservice training, while 33% said they had specific food allergy training.

Eighty-one percent of respondents were confident in their ability to serve a safe meal to a customer with food allergies. However, 38% thought that drinking water would dilute food allergens during a reaction, while 23% believed it was safe to eat a small amount of allergen. Twenty-one percent thought allergenic foods could simply be removed from the cooked meal and 16% thought cooking prevented allergic reactions. Twelve percent were unaware that allergic reactions to foods could be fatal.

Patients need to know that restaurant workers may have gaps in knowledge about food allergies. The authors call for "more rigorous and accessible" food allergy training for foodservice workers.

**COMMENT:** *These authors administered a very straightforward questionnaire to restaurant workers in England. Although more than 80% of respondents were confident that they provide safe meals to food allergic customers, many also were mistaken regarding the risks posed by meals contaminated by small amounts of food allergen. Given the high prevalence of food allergy in England, these results are astonishing. They point to the need for more education in the restaurant industry.*
*S.A.T.*

*Bailey S, Albardiaz R, Frew AJ, Smith H: Restaurant staff's knowledge of anaphylaxis and dietary care of people with allergies.*
**Clin Exp Allergy**. 2011;41:713-717. ♦♦

## Tacrolimus Leads to Inhalant Allergy in Kidney Transplant Patients

ORGAN transplant recipients commonly develop type I allergies, despite receiving T cell-targeted immunosuppressive drugs. This study explored a possible link between the calcineurin inhibitor tacrolimus and the occurrence of allergies after transplantation.

The cross-sectional study included two groups of 100 kidney transplant recipients: one group receiving tacrolimus and one group receiving cyclosporin A. Based on skin-prick testing or specific IgE measurement, the prevalence of sensitization was 34% in the tacrolimus group versus 20% in the cyclosporin group. Rates of clinically relevant allergy were 15% versus 8%, respectively. On logistic regression analysis, no other factor affected the risk of allergic sensitization or disease.

Kidney transplant patients receiving tacrolimus appear to be at increased risk of IgE-mediated sensitization, and possibly allergic disease. The findings suggest a differential effect of tacrolimus on Th2-mediated immune responses.

**COMMENT:** *Most of us are familiar with case reports of severe allergies in transplant recipients, presumably due to introducing memory immune cells from an allergic donor. However, an evolving literature suggests a paradoxical effect of calcineurin inhibitors--particularly tacrolimus--leading to new allergic sensitization in transplant recipients. This report identifies a significant increase in allergic sensitization among kidney transplant patients treated with tacrolimus, compared to those receiving cyclosporin. This difference was observed for both food and inhalant allergies and was independent of the patient's age. The mechanism for these findings is unclear, but allergists should be aware of this issue, especially when consulted about refractory allergies in transplant patients.*
*S.A.T.*
*Gruber S, Tiringer K, Dehlink E, et al: Allergic sensitization in kidney-transplanted patients prevails under tacrolimus treatment.*
**Clin Exp Allergy**. 2011;41:1-8. ♦♦

## How Do Kids Describe Their Asthma Symptoms?

CONSIDERABLE research has been done to explore the language used to describe symptoms of dyspnea in adults. This study sought to determine whether children and adolescents use similar terms to describe breathlessness.

Questionnaires regarding asthma descriptors were administered to 100 children, aged 8 to 15 years, with moderate to severe persistent asthma. The patients were consistent in their choice of descriptors on two study occasions. Two of the most commonly endorsed descriptors were "My chest feels tight" and "I cannot get enough air in." Children with greater self-reported asthma severity endorsed a higher number of terms to describe their breathing discomfort. The choice of descriptors was unaffected by anthropometric or demographic variables, including race.

Asthma patients as young as 8 use consistent descriptors to describe their symptoms of dyspnea. Many of the terms endorsed by children are the same as those endorsed by adults in previous studies.

**COMMENT:** *Evaluating asthma begins with history taking. Children often need surrogates to perform this function. However, this study demonstrated that children (8 to 15 years of age) describe their breathlessness similar to the way adults do. Empowering this group of children to express their feelings is important.*
*S.F.W.*
*Harver A, Schwartzstein RM, Kotses H, et al: Descriptors of breathlessness in children with persistent asthma.*
**Chest**. 2011;139;832-838. ♦♦

## Some Childhood Asthma Features Linked to GER

CHILDREN with asthma have an increased prevalence of gastroesophageal reflux (GER), although the nature of this association is unclear. This study evaluated the relationship between the intensity of esophageal acid exposure and the clinical features of asthma.

Sixty-six children, mean age 10 years, with persistent asthma symptoms underwent 24-hour esophageal pH monitoring. They also answered a detailed questionnaire addressing a wide range of asthma, environmental, and family variables. Forty-two percent of the children had abnormal results on pH monitoring.

Age at asthma onset was significantly younger for children with abnormal pH results: 3.63 versus 5.77 years. Esophageal acid was more intense for children without atopy compared to those with atopy: Boix-Ochoa score 28.19 versus 18.26. Children with higher-intensity acid exposure also had more frequent or difficult-to-control nocturnal asthma attacks.

In children with persistent asthma, some clinical features are associated with intensity of esophageal acid exposure. The nature of the associations raises the possibility that some asthmatic children may have coexisting GER in need of treatment.

**COMMENT:** *These authors contend that there are variations in the clinical presentation of asthma in children associated with the intensity of esophageal acid exposure. Symptoms of asthma in nonatopic children with early onset and intractable nocturnal asthma episodes should suggest the possibility of simultaneous clinically related GER.*
*C.C.R.*
*Kwiecien J, Machura E, Halkiewicz F, et al: Clinical features of asthma in children differ with regard to the intensity of distal gastroesopheal acid reflux.*
**J Asthma**. 2011;48:366-373. ♦♦

## ACEIs plus DDP-4Is May Increase Angioedema Risk

ANGIOTENSIN-converting enzyme inhibitors (ACEIs) are likely an important cause of hospitalization for angioedema. The dipeptidyl peptidase IV inhibitors (DDP-4Is) are a new class of antidiabetic medications that are commonly used along with ACEIs. The authors discuss the potential for synergistic increases in angioedema risk among patients taking this combination of drugs.

A recent meta-analysis found an overall 0.51% rate of angioedema among patients taking an ACEI in combination with the DDP-4I vildagliptin. Other lines of evidence support this association, including an interactive hemodynamic effect between the two medication classes. At least one case of angioedema has been reported in a patient taking an angiotensin receptor blocker and a DDP-4I.

The mechanism of angioedema related to ACEIs and DDP-4Is may involve generation of bradykinin. Mammalian target of rapamycin inhibitors--rapamycin or sirolimus--may also cause angioedema, with or without ACEIs. Some studies have provided clues about the mechanisms by which concurrent ACEI and DDP-4I therapy may increase angioedema risk.

Health care providers should be aware of this potential risk and be "judicious" when prescribing DDP-4Is to patients with a history of angioedema. More research is needed to clarify these risks.

**COMMENT:** *This concerning perspective piece provides compelling evidence that a progressive increase in the development of angioedema is likely with concomitant use of DDP-4Is and ACEIs in the context of type 2 diabetes. The ACEIs and DDP-4Is are first-line therapy for hypertension and type 2 diabetes, respectively, and are likely to be used in the treatment of increasingly prevalent type 2 diabetes. ACEIs already account for 1 in 4 hospitalizations for angioedema, so concomitant use of DPP4Is is likely to enhance the potential for life-threatening angioedema.*
*C.C.R.*
*Byrd JS, Minor DS, Elsayed R, Marshall GD: DDP-4 inhibitors and angioedema: a cause for concern?*
**Ann Allergy Asthma Immunol**. 2011;106:436-438. ♦♦

## REVIEWS OF NOTE

**COMMENT:** *This review is a reminder of the importance of T lymphocytes in allergic disease. As we learn more about the role of cells, such as Th22 and regulatory T lymphocytes, and cytokines, we gain a better understanding of the diseases we treat. These are interesting prospects for the future treatment of allergic rhinitis and asthma.*
*V.H.-T.*
*Wisniewski JA, Borish L: Novel cytokines and cytokine-producing T cells in allergic disorders.*
**Allerg Asthma Proc** 2011;32:83-94. ♦♦

**COMMENT:** *Here's an excellent review of the assessment of problematic severe asthma in children.*
*B.E.C.*
*Lødrup Carlsen KC, Hedlin G, Bush A, et al: Assessment of problematic severe asthma in children.*
**Eur Respir J**. 2011;37:432-440. ♦♦

**COMMENT:** *This is an excellent review regarding the pathogenesis of cough. Especially of interest is the section dealing with gastroesophageal reflux as a possible cause of chronic cough.*
*B.E.C.*
*Birring ss: Controversies in the evaluation and management of chronic cough.*
**Am J Respir Crit Care Med.** 2011;183:708-715. ♦♦

**COMMENT:** *How effective are the "10 warning signs"--promoted in the United Kingdom for screening purposes--at identifying primary immunodeficiency? Family history of immunodeficiency, use of intravenous antibiotics for sepsis, and failure to thrive seem to be the most predictive of the ten signs.*
*K.R.M.*
*Subbarayan A, Colarusso G, Hughes SM, et al: Clinical features that identify children with primary immunodeficiency diseases.*
**Pediatrics**. 2011;127:810-816. ♦♦

**COMMENT:** *This overview highlights the importance of considering STAT-5b deficiency in children with both significant growth failure and chronic infection. The numerous functions of STAT-5b, with evidence from human and animal research, are thoroughly detailed.*
*K.R.M.*
*Nadeau K, Hwa V, Rosenfeld RG: STAT5b deficiency: an unsuspected cause of growth failure, immunodeficiency, and severe pulmonary disease.*
**Pediatrics**. 2011;158:701-708. ♦♦