AllergyWatch®

A Synopsis of Allergy and Asthma Literature, Resulting from an Unbiased, Comprehensive Review of Nineteen Major Medical Journals.

A Publication of The American College of Allergy, Asthma & Immunology

Volume 15, Number 6 November - December 2013

'Strikingly Low' Rates of Persistence with SCIT and SLIT

SUBCUTANEOUS and sublingual immunotherapy (SCIT and SLIT) are effective treatments for allergic rhinitis, but require at least 3 years of treatment to achieve long-term benefits. Studies have reported high rates of treatment noncompliance and nonpersistence. This study evaluated "real-life" compliance and treatment rates, along with associated predictors.

The retrospective analysis included Dutch pharmacy data on 6,486 patients who started immunotherapy for house dust mite, grass pollen, or tree pollen between 1994 and 2009. In the Netherlands, SCIT and SLIT can be initiated and administered by general practitioners or specialists and immunotherapy drugs are distributed at community pharmacies. The analysis included 2,796 SCIT patients and 3,690 SLIT patients. Time to treatment discontinuation was analyzed, along with independent predictors of persistence and compliance. The study also estimated the costs of premature treatment discontinuation.

Just 18% of patients achieved at least 3 years of immunotherapy: 23% with SCIT and 7% with SLIT. Median durations were 1.7 and 0.6 years, respectively. Patients prescribed immunotherapy by their general practitioner had longer treatment persistence than those prescribed by specialists. Other factors associated with better persistence and compliance were treatment with a combination of allergens (in the first year only), older patient age, and higher socioeconomic status.

Fifty-six percent of patients who persisted with immunotherapy were never late in picking up their drugs from the pharmacy. Direct costs of immunotherapy among nonpersistent patients increased from about €1,000 per patient for those who discontinued in the first year to €3,800 for those who discontinued in the third year.

This study confirms the "strikingly low" rates of treatment compliance and persistence with SCIT and especially SLIT. Prescriber- and patient-related factors that may be associated with higher or lower immunotherapy discontinuation rates are identified. The researchers cite the "urgent need for further➤➤

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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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identification of potential barriers and measures that will enhance persistence and compliance."

COMMENT: *This report provides an interesting perspective on the use of allergen immunotherapy in the Netherlands, where patients receive their immunotherapy directly from pharmacies. That may play a role in the fact that overall compliance and persistence for SCIT and SLIT are lower than rates we generally see in the United States. Interestingly, persistence for SCIT from general practitioners was greater than that for specialists. The authors suggest that the 4-mile distance from specialists compared to the 0.7 mile from general practitioners are "notable distances" and could contribute to the lower compliance in the specialist's office. How can we help our suburban "soccer moms" encourage compliance with immunotherapy, considering their busy lifestyles?*
S.M.F.

Kiel MA, Röder E, Gerth van Wijk R, et al: Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy.
J Allergy Clin Immunol. 2013;132:353-360. ♦♦

FOCUS ON FOOD ALLERGY

In this issue of *AllergyWatch*, we highlight some interesting new papers on peanut, egg, and milk allergy.
A.M.

Home Is Where the Peanut Is

HOUSEHOLD peanut consumption may be an important indirect marker of environmental peanut exposure, and thus contribute to the development of peanut allergy. This study measured peanut protein levels in household dust and surfaces and evaluated potential routes of peanut transfer to the home environment.

In an initial comparative study, the Veratox polyclonal enzyme-linked immunosorbent assay showed 100% sensitivity and specificity for assessing peanut protein levels in the home environment, with a low coefficient of variation. This assay was used to measure peanut concentrations in dust and air; on household surfaces, bedding and furnishings, and hand wipes; and in saliva. Samples were obtained from the homes of 45 infants seen at pediatric allergy clinics.

Within homes, levels of peanut protein in dust were highly correlated with the levels detected in household surface wipes. In a number of simulated scenarios, airborne peanut levels were below the detection level of the study assay--exception for a brief period directly above an area where peanuts were being deshelled. Peanut protein was detected on hands and in saliva up to 3 hours after peanuts were consumed. Cleaning with detergent completely eliminated peanut protein from granite tables, but not from laminate and wooden table surfaces or from pillows and sofa covers.

Significant levels of peanut protein are found in dust and on surfaces in homes, suggesting that peanut spreads easily in the home environment. Peanut protein can persist for hours after consumption and may be difficult to eliminate with usual cleaning methods. Transfer of peanut protein likely occurs by means of hands and saliva, but not by aerosols.

SINCE most children with peanut allergy react to their first oral exposure, initial sensitization must occur some other way. This study analyzed the association between reported household peanut consumption and measured levels of peanut protein in household dust, along with the biologic activity of peanut in the home environment.

The study included dust and wipe samples from the homes of 45 infants recruited from pediatric allergy clinics. The Veratox polyclonal peanut ➤➤

ELISA was used to measure peanut protein levels. Environmental peanut exposure was then compared with household peanut consumption, based on a food frequency questionnaire and other clinical and household variables. A basophil activation assay was used to assess the biologic activity of peanut protein in household dust.

Household peanut consumption over 1 month and 6 months was significantly and positively correlated with peanut protein levels in the infant's bed, crib rail, and play area. Parental peanut consumption was associated with peanut protein in both the parents' and infants' beds, even if the infant was not eating peanut.

On multivariate analysis, household peanut consumption was the factor most strongly related to peanut levels in the infant's bedding and play area. Household dust samples with high levels of peanut allergen induced dose-dependent activation of basophils from peanut-allergic children.

Household peanut consumption likely explains environmental exposure to peanut in infants. Peanut in household dust shows biologic activity, and thus may be responsible for early peanut sensitization in infants before oral ingestion. The authors call for "further prospective environmental population studies" of this issue.

COMMENT: *These two articles are from the same institution as part of the U.K. LEAP food allergy study. In the first paper, samples of various surfaces and fabrics were analyzed for peanut allergenicity. No significant peanut protein was found with aerosolization, unless there was active deshelling. However, there was a surprising level of peanut protein on certain surfaces even after cleaning. This could be due to the fact that peanut protein persisted on hands and saliva even 3 hours after consumption.*

In the second study, the researchers found that peanut protein levels in the homes of infants were positively correlated with family members' ingestion of peanut (household peanut consumption). In fact, peanut protein found in the infant's crib correlated with peanut protein found in parent's bedding. Peanut in dust is biologically active, which suggests that we should advise our families with peanut-allergic children to avoid having peanuts at home--and particularly not to eat them in bed!

S.M.F.

Brough H, Makinson K, Penagos M, et al: Distribution of peanut protein in the home environment.
J Allergy Clin Immunol. 2013;132:623-629

Brough H, Santos AF, Makinson K, et al: Peanut protein in household dust is related to household peanut consumption and is biologically active.
J Allergy Clin Immunol. 2013;132:630-638. ♦♦

Should We Be Training Nut-Allergic Patients to Identify Different Nuts?

ALLERGEN avoidance can be critical for patients with nut allergies. Previous studies have shown that nut-allergic patients and their guardians perform poorly at identifying peanuts and different types of tree nuts. This study compared allergists and the caregivers of nut-allergic children for their ability to identify various kinds of nuts.

The researchers made a sealed and locked "nut box" containing samples of various tree nuts and peanuts, both shelled and unshelled. Guardians of children with food allergies and allergists attending a national specialty meeting were evaluated for their ability to identify different types of nuts.

The allergists performed better in identifying the various types of nuts, compared to the guardians of allergic children: 13 vs 10 out of 14. Performance was no better for the guardians of nut-allergic children vs guardians of children with other food allergies. Better-educated parents performed better at nut identification. Allergy/immunology trainees did not perform as well as specialists who had completed their training.

Nut-allergic patients and their caregivers need education in the correct identification and avoidance of different kinds of tree nuts and peanuts. The authors suggest that a nut identification box like the one used in their study is a simple and effective training tool.

COMMENT: *With growing numbers of patients with food allergy, avoidance of the food allergen is essential. Nut allergy is particularly challenging in that many nuts look similar and are hard to differentiate. This study investigated whether guardians of children with peanut or tree nut allergy--as well as allergists--were able to properly identify different nuts. The authors suggest that making a box with different nuts labeled with an example of the nut and the name could help educate guardians of patients with peanut and tree nut allergy who may want their children to avoid specific nuts.*

V.H.-T.

Kao L, Bhangoo PS, Roy L, Bird JA: Identification of peanuts and tree nuts: Are allergists smarter than their patients?
Ann Allergy Asthma Immunol. 2013;111:282-285. ♦♦

Early Regular Egg Ingestion May Lower Egg Allergy Risk

IN the past, avoidance of egg and other allergenic foods was recommended for primary prevention of food allergies. However, recent studies have suggested that early regular exposure to allergenic foods might actually reduce the risk of food allergy. Early regular ingestion of egg was tested as a means of reducing the risk of egg allergy in high-risk infants.

The randomized, double-blind trial included 86 infants with a history of eczema, which is a risk factor for food allergies. Infants were assigned to receive a once-daily, 1-teaspoon dose of pasteurized raw whole egg powder or rice powder. At 8 months, both groups had an observed feeding followed by introduction of cooked egg. Rates of IgE-mediated egg allergy--based on observed pasteurized raw egg challenge and skin-prick testing--were compared between groups after 12 months. ➤➤

Thirty-one percent of infants assigned to receive early regular egg exposure had an allergic reaction, and did not continue egg powder administration. Of infants who continued in the study, 36% had egg-specific IgE levels of greater than 0.35 kU_A/L at age 4 months--before they had any known egg ingestion.

Because of funding issues, the study had to be stopped before full planned enrollment. At 12 months, the rate of diagnosed IgE-mediated egg allergy was non-significantly lower in infants assigned to early regular egg ingestion: 33% versus 51%. The early egg ingestion group had significantly higher egg-specific IgG_4 levels at both 8 and 12 months.

With limited statistical power, the study suggests that early regular egg exposure may induce immune tolerance pathways and reduce the risk of egg allergy in infants with eczema. The substantial rate of sensitization before any known egg ingestion highlights the need for caution when initially exposing these high-risk infants to egg. Earlier introduction of egg does not appear to increase the risk of developing egg allergy.

COMMENT: *In this well-designed prospective study, the authors suggest that immune tolerance to egg protein can be induced by regular oral feedings starting at 4 months in infants with eczema. A high number of infants had significant reactions to the initial ingestion with egg, although at 12 months fewer children receiving regular egg feedings were allergic to egg compared to controls receiving rice feedings. Unfortunately, the study was stopped prior to enrolling sufficient numbers to show statistical significance.*

S.M.F.

Palmer D, Metcalfe J, Makrides M, et al: Early regular egg exposure in infants with eczema: a randomized controlled trial.

J Allergy Clin Immunol. 2013;132:387-392. ♦♦

Muffin Testing: A Practical Approach to Egg Allergy

MANY children with IgE-mediated egg allergy can tolerate foods containing baked egg, suggesting that complete egg avoidance may not be necessary. However, other than food challenges, there is no reliable way to determine which children can tolerate baked egg. Skin prick testing (SPT) to baked egg and ovomucoid was evaluated as a predictor of tolerance to baked-egg challenge.

The prospective study included 143 egg-allergic children, based on a recent history of immediate allergic reactions to egg and confirmatory SPT or specific IgE levels (or test results with very high positive predictive value in children without such a history). All children underwent SPT to egg white, ovomucoid, and fresh muffin, followed immediately by baked-egg (muffin) challenge.

Sixty-three percent of egg-allergic children were able to tolerate food challenge with a muffin containing 1 g of egg protein. The remaining 53 children had positive challenges, including 8 with respiratory or cardiovascular symptoms. Among children with negative food challenges, median SPT diameters were 4.0 mm for muffin and 5.0 for ovomucoid, compared to 6.0 and 7.5 mm, respectively, for those with positive food challenges.

On receiver operating characteristic curve analysis, area under the curve was 0.68 for baked egg and 0.67 for ovomucoid. Children with a muffin SPT of less than 2 mm were likely to tolerate baked egg challenge: negative predictive value 88%. In contrast, those with an ovomucoid SPT of 11 mm or greater were very unlikely to tolerate baked egg: positive predictive value 100%.

Skin prick testing to fresh muffin and ovomucoid may help in predicting tolerance of baked-egg food challenges in children with egg allergy. Even children with a history of anaphylaxis to egg may tolerate muffin challenge. The researchers are testing an in-hospital, nurse supervised oral food challenge protocol for children defined as "low-risk" on muffin SPT.

COMMENT: *Egg allergy is one of the most common food allergies in children. Several studies have suggested that most egg-allergic children can tolerate baked egg products, thus expanding their dietary choices. The best marker to predict tolerance to a baked-egg challenge remains unclear. Most egg-allergic children passed the muffin challenge, including 74% of those with prior anaphylactic reactions to eggs. Severe reactions occurred in 15% of positive muffin challenges; all but 1 of these children had muffin SPT of 7 mm or larger. This study adds to the growing literature regarding the practical utility of baked-egg challenges, although future studies are needed to identify the best markers for tolerance.*

D.A.K.

Tan JW-L, Campbell DE, Turner PJ, et al: Baked egg food challenges--clinical utility of skin test to baked egg and ovomucoid in children with egg allergy.

Clin Exp Allergy. 2013;43:1189-1195. ♦♦

For Milk-Allergic Infants, Which Formula Leads to Faster Tolerance?

CURRENT guidelines call for the use of substitute "hypoallergenic" formulas in infants with cow's milk allergy (CMA). However, there are few data on how different products affect the acquisition of cow's milk tolerance. This study compared tolerance outcomes of five different substitute formulas in infants with CMA.

The open, nonrandomized trial included 262 otherwise healthy infants with CMA. The median age was 5.92 months; 42.7% of patients had IgE-mediated CMA. Formulas used for management were extensively hydrolyzed casein formula (EHCF) in 55 infants, EHCF plus *Lactobacillus rhamnosus* GG (EHCF-GG) in 71, hydrolyzed rice formula (RHF) in 46, soy formula in 55, and amino acid-based formula in 33. After 12 months, food challenge studies were performed to compare acquisition of tolerance between groups.

Oral tolerance of cow's milk was achieved in 43.6% of children with EHCF and 78.9% with EHCF-GG. By comparison, tolerance rates were 32.6% with RHF, 23.6% with soy formula, and 18.2% with amino acid-based formula. On binary regression analysis, the ➤➤

likelihood of achieving tolerance with 12 months was affected by the presence of IgE-mediated CMA, odds ratio 0.12; and by the use of EHCF or EHCF-GG, odds ratio 1.48 and 3.35, respectively.

For infants with CMA, use of EHCF may be associated with faster development of tolerance. This effect appears stronger with the use of EHCF plus *L. rhamnosus* GG. Further studies are needed to evaluate tolerance induction and other outcomes of EHCF-GG for young children with CMA.

COMMENT: *Once the diagnosis of CMA is made, a number of alternative substitute formulas are available. This study attempted to tease out the degree of induction of tolerance to cow's milk in allergic infants fed five different formulas. The total number of infants enrolled in this study is impressive--all of the 260 children had positive challenge tests, 96 had positive skin-prick tests, and 97 had positive allergy patch tests. The use of EHCF or EHCF-GG was associated with tolerance after 12 months. Amino acid formula was not associated with induction of tolerance. True, CMA in infants has a good prognosis; but identifying the appropriate formula, with or without probiotic, to speed induction of tolerance would be important. Even with its significant design flaws, this study should lay the groundwork for future blinded, randomized studies.*
S.F.W.

Canani RB, Nocerino R, Terrin G, et al: Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: a prospective multicenter study.
J Pediatr. 2013;163:771-777. ♦♦

The 12% BDR Cutoff: Is It Accurate in Children?

BRONCHODILATOR response (BDR) is a useful adjunct diagnostic tool for assessing the reversibility of airflow obstruction. A BDR cutoff of 12% or greater change in FEV_1 has been cited, but some reports have questioned the validity of this definition in children. Data from three large pediatric cohort studies were used to assess the diagnostic accuracy of the 12% BDR cutoff.

The analysis included 1,041 children with mild to moderate asthma enrolled in the Childhood Asthma Management Program, along with two population-based cohorts of control children without asthma or wheezing. Spirometry data were analyzed by receiver operating characteristic curve analysis to assess the diagnostic performance of different BDR cutoff values.

Baseline FEV_1 percent predicted values were similar between groups, but mean BDRs were 10.7% in the asthmatic children versus 2.7% in nonasthmatic controls. Testing of BDR was moderately accurate in differentiating asthmatic from nonasthmatic patients: area under the curve 73.3%.

A BDR cutoff of 12% had specificity of 89.5%, but sensitivity of only 35.6%. Performance was better at a BDR cutoff of 8%: specificity of 76.5% and sensitivity of 54.4%. On sensitivity analysis, the BDR test was more accurate for asthmatic subjects with an initial FEV_1 percent predicted value of less than 80%.

The recommended 12% cutoff value for BDR shows poor sensitivity in the diagnosis of asthma in children. These findings in asthmatic children and controls suggest better performance with an 8% BDR cutoff. The authors conclude that because of variability, however, "it might be not be appropriate to choose a specific BDR cutoff as a criterion for the diagnosis of asthma."

COMMENT: *We all know that the gold standard for asthma diagnosis is improvement in FEV_1 by at least 12% after bronchodilator. These authors used data from three large pediatric cohorts to analyze bronchodilator responses in asthmatic children. They found that the 12% reversibility was not particularly sensitive at predicting asthma, compared to lower cutoff values. Although they recommend an 8% cutoff, the authors caution that even that shouldn't be considered a "standard," since the bronchodilator response should only be used as an adjunctive assessment in our diagnosis of asthma in children.*
S.M.F.

Tse SM, Gold DR, Sordillo DR, et al: Diagnostic accuracy of the bronchodilator response in children.
J Allergy Clin Immunol. 2013;132:554-559. ♦♦

Parent Plus Physician Data Identifies Kids with 'Persistent Troublesome Wheezing'

PREVIOUS studies, based on parent-reported symptoms, have suggested that different phenotypes of childhood wheezing may exist. The use of physician-reported data might help to overcome the limitations of parent data. This study used a joint modeling approach incorporating data from medical records and parent reports to define the presence and severity of childhood wheezing disorders.

The researchers analyzed parental reports and medical records data from a population-based birth cohort of 1,184 children enrolled in the Manchester Asthma and Allergy Study. Follow-up data to age 8 included parental reports of current wheezing at four times as well as physician-recorded wheezing. These data were used to identify groups of children with differing "wheeze trajectories." The groupings were validated by association with lung function and other objective outcome measures, asthma medication use, and severe exacerbations.

The model was best described by defining five groups with different wheeze trajectories: no wheezing, 53.3% of children; transient early wheezing, 13.7%; late-onset wheezing, 16.7%; persistent controlled wheezing, 13.1%; and persistent troublesome wheeze (PTW), 3.2%. The five groups differed significantly in terms of atopy and lung function.

In particular, the PTW trajectory was associated with decreased lung function and increased airway hyperreactivity, along with higher rates of exacer-➤➤

bations, hospital admissions, and unscheduled visits. Odds ratios for exacerbation risk for children in the PTW group were 3.58 compared to children with persistent controlled wheezing, 15.92 compared to those with late-onset wheezing, and 12.24 compared to those with transient early wheezing.

Joint modeling of parentally reported and medical records data identifies children with different wheezing trajectories. This includes a group of children with persistent troublesome wheezing, who have high rates of exacerbations and other adverse events. The study identifies variables that may permit early identification of children with the PTW phenotype.

COMMENT: *In an effort to clarify the variety of phenotypes of early childhood asthma, these British researchers analyzed data from parent-reported and physician-documented wheezing in a large birth cohort. The interesting finding was that, within the well-recognized phenotype of persistent wheezing, there were really two distinct patterns of illness. The children who were the most difficult to control where labeled as persistent troublesome wheezing (PTW). Notably, this group could be identified early since they were highly atopic with larger allergy skin tests, had more frequent exacerbations with reduced lung function, and also tended to have eczema. One wonders if more rigorous therapeutic intervention early in this PTW phenotype could potentially improve the outcomes for these children.*

S.M.F.

Belgrave DCM, Simpson A, Semic-Jusufagic A, et al: Joint modeling of parentally reported and physician-confirmed wheeze identifies children with persistent troublesome wheezing.

J Allergy Clin Immunol 2013;132:575-583. ♦♦

Early NO_2 Exposure Is a Risk Factor for Childhood Asthma

AIR pollution has been shown to be an asthma trigger, linked to short-term outcomes such as reduced lung function and emergency hospital admission. Less is known about the possible association between early-life exposure to air pollutants and the incidence of developing asthma in children. Data from two case-control studies of minority children were used to study air pollution exposure in early life as a risk factor for childhood asthma.

The analysis included data on 3,343 Latino children enrolled in the "Genes-environments and Admixture in Latino-Americans" (GALA II) study and 977 African American children from the "Study of African Americans, Asthma, Genes and Environments" (SAGE II). The GALA II sample included 1,688 asthma cases while the SAGE II sample included 603 case subjects.

Air monitoring data were used to estimate average annual residential exposure to ozone, nitrogen dioxide, sulfur dioxide, and particulate matter not greater than 10 and 2.5 μm in diameter. Exposure over the first 3 years of life was analyzed for association with the subsequent diagnosis of asthma.

Early-life exposure to nitrogen dioxide was independently associated with asthma. With adjustment for confounders, for each 5 ppb increase in average NO_2 exposure during the first year of life, the odds ratio for physician-diagnosed asthma was 1.17. There were some significant region-specific effects, including an association with exposure to PM_{10} in Chicago and associations with PM_{10} and sulfur dioxide in Puerto Rico.

Early-life exposure to NO_2 is associated with an increased risk of later asthma in Latino and African American children. The study adds strength to previous results identifying traffic-related air pollutants as a causal factor of childhood asthma. The authors also note that asthma risk is significant despite NO_2 levels within current U.S. air quality standards.

COMMENT: *This very large, comprehensive study of gene-environment interaction in Latinos and African Americans shows that exposure to higher levels of NO_2 during infancy is associated with increased risk of developing asthma. This supports the growing body of knowledge that traffic-related air pollution is a major risk factor, and one that appears more significant in urban, less-affluent populations.*

B.E.C.

Nishimura KK, Galanter JM, Roth LA, et al: Early-life air pollution and asthma risk in minority children: The GALA II and SAGE II studies.

Am J Respir Crit Care Med. 2013;188:309-318. ♦♦

Are Asthma Phenotypes Stable Over Time?

CLUSTERING approaches have been used to identify different asthma phenotypes based on multiple disease features. Few studies have evaluated the stability of these disease phenotypes over time. This 10-year follow-up study assessed long-term phenotypic transitions in a large group of adult asthma patients.

The research analyzed data on 3,320 adult asthma patients, drawn from three large European epidemiologic cohort studies. Extensive evaluations performed at baseline and at 10 to 12 years' follow-up were used to assess the stability of cluster-based asthma phenotypes over time.

A cluster-based latent transition analysis model identified seven asthma phenotypes, with prevalence values ranging from 8.4% to 20.8%. Key factors in defining these phenotypes were the severity of asthma symptoms, rated low, moderate, or high; allergic status; and pulmonary function. Patterns of transition and stability differed among phenotypes--the likelihood of being in the same phenotype at baseline and follow-up ranged from 54% to 88%. Nonallergic phenotypes were more likely to show transitions toward increased asthma symptoms, compared to allergic phenotypes. Allergic status remained consistently stable.

Adult asthma phenotypes identified by cluster analysis show differing patterns of transition over time. Patients with nonallergic phenotypes appear more likely to developed increased asthma symptoms over a decade's follow-up. Further longitudinal studies ➤➤

may help in understanding asthma variability over time, and may identify phenotypes at higher risk of worsening.

COMMENT: *This study advances our understanding of cluster analyses in the longitudinal evaluation of patients with asthma. Allergic patients tended to have a more stable course, and in general, had consistency in cluster assignment over a 10-year period. The striking feature is the increase in the severity of asthma seen in nonallergic phenotypes. These findings suggest there may be a continuum of patients with nonallergic asthma, rather than discrete nonallergic phenotypes. (See also the editorial by Moore:*
Am J Respir Crit Care Med. 2013;188:521-522.)
B.E.C.
Boudier A, Curjuric I, Basagana X, et al: Ten-year follow-up of cluster-based asthma phenotypes in adults: A pooled analysis of three cohorts.
Am J Respir Crit Care Med. 2013;188:550-560. ♦♦

Is Real-World Adherence Better with Once-Daily ICS Dosing?

POOR adherence to inhaled corticosteroid (ICS) therapy is a common problem, and is linked to worse asthma outcomes. Studies of other chronic diseases have shown improved adherence with simplified dosing regimens. This study evaluated the effects of once-daily ICS dosing on adherence and clinical outcomes in patients with asthma.

The researchers analyzed 6 years of pharmacy claims data linked to prescription records from a large health maintenance organization. Patients were followed up from their first filled prescription for ICS until they filled their last prescription during the observation period, switched ICS dosing regimen, or started on ICS plus long-acting β-agonist therapy.

A continuous multiple-interval model of medication availability was used to compare adherence for patients on once-daily ICS regimens versus those taking ICS twice daily or more frequently. The analysis included 1,302 patients, ranging from 16 to 52 years old.

Seventeen percent of asthma patients were on once-daily ICS; the rest were on prescribed ICS at least twice daily. Once-daily ICS therapy was associated with better adherence: 61%, compared to 41% for more frequent dosing. Once-daily dosing did not compromise clinical efficacy; the difference in adherence persisted after adjustment for demographic factors and asthma severity. Patients on once-daily ICS were also more likely to be more than 75% adherent: 40.7% vs. 17.3%.

These real-world data suggest that once-daily ICS dosing is associated with improved treatment adherence by asthma patients. The association remains significant in subgroups defined by sex, race/ethnicity, and asthma severity. Once-daily ICS dosing is a "practicable therapeutic option" to improve adherence while maintaining clinical efficacy.

COMMENT: *Adherence to once-a-day inhaled steroid dosing for asthma would logically seem better than more frequent dosing, but is it as effective? This large, real-world study—within the limits of its HMO environment—finds that once-a-day ICS therapy improves adherence without compromising clinical efficacy.*
C.C.R.
Wells KE, Peterson EL, Ahmedani BK, Williams LK: Real-world effects of once vs greater daily inhaled corticosteroid dosing on medication adherence.
Ann Allergy Asthma Immunol. 2013;111:216-220. ♦♦

Beta-Agonist Use and Asthma Outcomes: More Is Worse

OVERUSE of β-agonists has been linked to poor asthma control. Few studies have evaluated direct measures of β-agonist use and measures as predictors of the risk of future asthma events. This relationship was assessed using data from a randomized trial of asthma treatment, which included measurement of actual salbutamol use.

The researchers analyzed data from a randomized trial comparing a single maintenance and reliever therapy (SMART) regimen versus standard therapy. The SMART regimen consisted of a combination budesonide/formoterol inhaler; standard therapy consisted of fixed-dose salbumatol as a reliever. Electronic monitoring was used to measure actual medication use. Measurements of salbutamol use over a 2-week baseline period were evaluated as predictors of future adverse outcomes, including severe asthma exacerbations, poor asthma control, and "extreme" salbutamol overuse.

High measured salbutamol use predicted an increased risk of future severe asthma exacerbations. Risk was increased for higher mean daily salbutamol use, odds ratio (OR) 1.24 per 2 salbutamol actuations per day; more days of salbutamol use, OR 1.15 per 2 days of salbutamol use over a 2-week period; and higher maximal 24-hour use, OR 1.09 per 2 actuations per day. The risk of future poor asthma control was higher for patients with higher mean daily salbutamol use: OR 1.13. The risk of future extreme salbutamol overuse was predicted by higher mean daily salbutamol use, OR 2.72; more days of use, OR 1.46; and maximum daily use, OR 1.57.

The results show that several measures of actual salbutamol use are significant predictors of future adverse outcomes in patients with asthma. Average daily salbutamol may be the most useful predictor in clinical practice, as it predicts severe exacerbations, poor asthma control, and extreme salbutamol overuse.

COMMENT: *Overuse of β-agonists has been known to predict poor outcomes for several decades, although there remains some debate as to whether the drug actually causes problems or is merely a marker of poor control. This post hoc analysis of data from a 24-week open-label trial comparing on-demand ICS/LABA with fixed-dose LABA revealed that the mean frequency of albuterol rescue use was a stronger predictor of adverse outcomes than number of days of albuterol use or maximum number of rescue doses per day.*
S.A.T.

➤➤

Patel M, Pilcher J, Reddel HK, et al: Metrics of salbutamol use as predictors of future adverse outcomes in asthma.
Clin Exp Allergy. 2013;43:1144-1151. ♦♦

Dust Mites Invade China

CHINA has experienced rising rates of asthma and allergic disease over the last few decades. In previous studies the authors found that, while multiple sensitizations were common, house dust mite HDM was the allergen most frequently implicated in Chinese cases of asthma or rhinitis. This 15-year follow-up study evaluated changes in asthma and allergic sensitization in Chinese schoolchildren over 15 years.

The study included 6,928 children, aged 13 to 14 years, from secondary schools in the city of Guangzhou, China. The schools were the same as those from which children were recruited for Phase I and Phase III of the International Study of Asthma and Allergic Disease in Childhood (ISAAC)--performed in 1994-95 and 2001-02, respectively. For the new study, children were studied using the ISAAC Phase III protocol, including skin prick testing for seven common aeroallergens in 2,531 children.

The prevalence of any history of asthma increased from 3.9% in 1994, to 4.6% in 2001, to 6.9% in 2009. Rates of current wheezing increased from 3.4%, to 4.8%, to 6.1%, respectively. Children in the follow-up study had significantly higher rates of skin responses to HDM and cat, compared to children in ISAAC Phase III. The atopic index was also significantly increased.

There was no increase in the prevalence of wheezing among children who were not sensitized to the tested allergens, including HDM. However, wheezing prevalence was significantly increased among children sensitized to HDM, particularly *Dermatophagoides pteronyssinus*. The prevalence of allergen sensitization was four to five times higher than the prevalence of wheezing. On multivariate analysis, high degrees of sensitization to HDM and high atopic index were associated with physician-diagnosed asthma.

The results show a significant increase in aeroallergen sensitization and current wheezing among Guangzhou schoolchildren since the mid-1990s. House dust mite sensitization appears to be an important contributor to the increased prevalence of wheezing. The authors discuss climate and socioeconomic factors potentially associated with the increase in HDM sensitization.

COMMENT: *Following the ISAAC Phase III protocol, these investigators identified an increase in both aeroallergen sensitization and asthma in Guangzhou, China. Dust mite sensitization was a strong predictor of wheezing, similar to the situation in developed countries in the West. The authors speculate that both the increase in urbanization of China and its warmer and more humid climate over time have contributed to the increased importance of dust mites.*
S.A.T.
Li J, Wang H, Chen Y, et al: House dust mite sensitization is the main risk factor for the increase in prevalence of wheeze in 13- to 14-year-old schoolchildren in Guangzhou city, China.
Clin Exp Allergy. 2013;43:1171-1179. ♦♦

Should We Consider Omalizumab for Chronic Refractory Urticaria?

SEVERAL studies have suggested that omalizumab may be an effective treatment for patients with refractory chronic urticaria. Especially with the high cost of this anti-IgE antibody, it's important to identify subgroups more likely to respond to omalizumab therapy. This retrospective study explored whether some chronic urticaria phenotypes are associated with a better response to omalizumab.

The researchers analyzed 3 years' experience with omalizumab in 19 patients with refractory chronic urticaria seen at a university allergy clinic. Most patients had either treatment failure or toxic side effects to treatment with immunomodulators. The overall response rate was 89%, including complete responses in 47% of patients and partial responses in 42%. Responses to omalizumab appeared similar for "autoimmune positive" vs "autoimmune negative patients." There was also no significant difference in response among subgroups defined by patient age and sex, IgE levels, or omalizumab dosing regimen.

This specialist clinic experience shows a high response rate to omalizumab among patients with refractory chronic urticaria. No specific patient subgroup, disease phenotype, or dosing protocol appears to be associated with a better response to omalizumab. The authors hope past reports and future randomized trials will lead to approval of omalizumab as a new treatment alternative for refractory chronic urticaria.

COMMENT: *Since patients with chronic urticaria are often difficult to treat, the authors looked at a subset of patients who were refractory to traditional treatment. All except 1 patient required a burst of oral steroids within 6 months of starting the study. Almost 90% had some response to omalizumab, and nearly half had a complete response. Patients responded well whether or not they tested positive for autoimmune markers. The authors comment that it would be important to study how 6 to 12 months of treatment would affect long-term response and efficacy of treatment. This study lends support to others showing that omalizumab is useful in the treatment of some subsets of patients with chronic idiopathic urticaria.*
V.H.-T.
Viswanathan RK, Moss, MH, Mathur SK, et al: Retrospective analysis of the efficacy of omalizumab in chronic refractory urticaria.
Allergy Asthma Proc. 2013;34:446-452. ♦♦

Are Patients with Venom Allergy Getting Proper Care After ED Discharge?

CURRENT guidelines for patients with stinging insect anaphylaxis include prescription of an epinephrine autoinjector and referral to an allergist. Previous studies have shown a need for improvement in clinical management of patients with anaphylaxis. This study analyzed disposition and follow-up care in ➤➤

patients with an emergency department (ED) visit or hospitalization for stinging insect anaphylaxis.

Using the MarketScan Database, the researchers identified 954 patients who had an ED visit or hospitalization for stinging insect anaphylaxis between 2002 and 2008. Fifty-nine percent of patients were men; the mean age was 46 years, with 13% of patients being younger than 18 years. More than three-fourths of cases occurred from June through September.

Eighty-five percent of patients were discharged directly from the ED. For hospitalized patients, mean length of stay was 1 day. However, one-half of hospitalized patients spent time in the ICU and more than one-fourth had cardiorespiratory failure. Sixty-nine percent of patients filled at least one epinephrine autoinjector prescription, but only 14% visited an allergist/immunologist. Factors associated with preventive anaphylaxis care during follow-up included higher household income, no previous ED visit for any reason, and no cardiorespiratory arrest or failure in the hospital.

The results highlight some deficiencies of care for patients with stinging insect anaphylaxis, including a low rate of follow-up care from an allergist. Failure to refer patients for potentially curative venom immunotherapy places them at risk of recurrent anaphylaxis.

COMMENT: *Proper treatment and long-term management of patients with anaphylaxis are essential. This study looked at patients with anaphylaxis to stinging insects who presented to an ED or were hospitalized. No deaths occurred. In the ED, only 6% were treated with epinephrine. Almost 90% of patients were discharged home, and almost 70% filled a prescription for an epinephrine autoinjector. Just 4% had another ED visit in the next year, but nearly half of these occurred the day after presentation for anaphylaxis. Only 14% were seen by an allergist after discharge. As the authors state, a limitation of this study is that patients were required to have medical and prescription coverage for 1 year, thus limiting the generalizability of the results. The study reminds us that, since immunotherapy can be curative in most patients with venom allergy, there's an opportunity to improve patient care by increasing referrals to the allergist.*
V.H.-T.

Rudders SA, Clark S, Wei W, Camargo CA Jr: Longitudinal study of 954 patients with stinging insect anaphylaxis.
Ann Allergy Asthma Immunol. 2013;111:199-204. ♦♦

Is SPT to Pollen the Best Test on Which to Base Immunotherapy?

In addition to grass, olive is a major cause of pollen allergy in southern Spain. In parallel pollination such as grass and olive, the disease-causing allergen cannot be identified by skin prick test (SPT) only. In this real-world study, a predetermined IgE molecular profile was compared with other tests of sensitization.

The study included 175 patients with springtime seasonal pollen-allergic rhinoconjunctivitis or asthma at the authors' center, located in the southernmost part of the Iberian peninsula. All patients underwent SPT using *Olea europaea* (olive) and *Phleum pratense* (grass), along with palm profilin and peach peel. In addition, in vitro study was performed using a specific recombinant IgE protocol including major olive and grass allergens (nOle e1 and rPhl p1-5b) along with three cross-reactive recombinant allergens (rPhl p12, rPhl p7, and rPru p3). Immunotherapy choices based on the two test methods were compared.

The results showed high sensitization to both nOle e1 and rPhl p1-5b. The cross-reactive allergens did not contribute to the differential diagnosis of olea and/or grass pollen sensitization. Based on the molecular profile, the immunotherapy prescription changes in 55% of patients. In most cases, the change was from both pollens to only grass or olive pollen.

Molecular diagnosis can increase the accuracy of diagnosis of parallel pollen allergy, compared to traditional methods. The authors conclude that component-resolved diagnostics is useful in establishing individual sensitization patterns in an area with overlapping pollen seasons, thus improving patient selection for immunotherapy.

COMMENT: *Various diagnostic modalities for patients with seasonal allergic rhinitis exist. This study looked at the utility of specific IgE molecular evaluation of olive and grass pollen, compared to SPT, in patients with seasonal pollen-associated asthma or rhinoconjunctivitis. In more than half of these patients, immunotherapy was changed based on the molecular evaluation. The study raises interesting questions regarding the way we currently diagnose and treat patients with pollen allergy. The authors recommend consideration of component-resolved diagnostic testing to improve the treatment of our patients with pollen allergy.*
V.H.-T.

Letrán A, Espinazo M, Moreno F: Measurement of IgE to pollen allergen components is helpful in selecting patients for immunotherapy.
Ann Allergy Asthma Immunol. 2013;111:295-297. ♦♦

Exhaled NO Monitoring: Recommended But Not Helpful

Exhaled nitric oxide is a potential useful biomarker for use in predicting asthma exacerbations. Current American Thoracic Society (ATS) guidelines include a strong recommendation for exhaled NO monitoring in patients with asthma, while acknowledging the low quality of the supporting evidence. This study evaluated exhaled NO as a predictor of asthma-related health-care use in an inner-city population.

The prospective study included 138 children, mean age 11 years, with persistent asthma. The children were predominantly black and living in low-income households. Ninety percent were atopic, with one or more positive skin-prick tests. Exhaled NO, lung function, and asthma-related health-care use were evaluated at baseline and every 3 months. ➤➤

During 1 year of follow-up, the children had high levels of asthma-related health care use, including 237 health care visits, 105 unscheduled doctor visits, 125 emergency department visits, and 7 hospitalizations. Exhaled NO was not a significant predictor of health-care outcomes, before or after adjustment for age, sex, and lung function. At various cutoff points, positive predictive value for acute health-care use was no higher than 33%. In contrast, lung function was a significant predictor of health-care use within the subsequent 3 months.

Following the ATS algorithm, exhaled NO is not a useful predictor of asthma-related health-care use in urban minority children with asthma. The results are in addition to previous "equivocal" findings on the utility of exhaled NO monitoring in children, adolescents, and adults. The authors call for further evidence to support the routine use of exhaled NO monitoring in clinical asthma care.

COMMENT: *Noninvasive monitoring for airway inflammation in asthma remains the "Holy Grail." Measurement of exhaled NO has been studied with largely negative results as to its added utility in managing asthma. This study of a cohort of inner-city children with asthma found that exhaled NO was not a predictor of asthma-related health-care use, and that applying the ATS's suggested algorithm for "significant" change in exhaled NO was also not predictive. Lung function was a better predictor. Although this cohort may not be representative of all asthma patients, the burden of proof lies with demonstrating that implementing exhaled NO measurement into asthma management is truly beneficial. While the ATS recommendation is "strong," the evidence remains weak.*
D.A.K.

McCormack MC, Aloe C, Curtin-Brosnan J, et al: Guideline-recommended fractional exhaled nitric oxide is a poor predictor of health-care use among inner-city children and adolescents receiving usual asthma care.
Chest. 2013;144:923-929. ♦♦

Maternal Asthma Linked to a Wide Range of Diseases in Children

ASTHMA during pregnancy is associated with an increased risk of adverse obstetric outcomes, but less is known about the possible long-term health risks for the child. Maternal asthma was evaluated as a risk factor for diseases in offspring.

The analysis included prospective data on 66,712 mother-child pairs, including 4,145 pairs in which the mother had asthma during pregnancy. Maternal asthma was evaluated as a risk factor for various diseases in the children at a median age of 6.2 years, using information from Danish national registries.

Maternal asthma was associated with increased risk of several different disease categories, including infectious and parasitic diseases, hazard ratio (HR) 1.34; nervous system diseases, HR 1.43; ear diseases, HR 1.33; respiratory system diseases, HR 1.43; and skin diseases, HR 1.39. Initial associations with endocrine and metabolic disorders, digestive diseases, and malformations were not confirmed in secondary analyses. There were no associations with neoplasms, mental disorders, blood or immune diseases, and diseases of the circulatory, musculoskeletal, and genitourinary systems.

The results suggest that children born to mothers with asthma during pregnancy are at increased risk of a wide range of diseases. While the causes of these associations remain unknown, the findings re-emphasize the need for careful monitoring of the mother and child during pregnancies where asthma is present.

COMMENT: *This large prospective study explored associations between asthma during pregnancy and diseases in offspring. Children born to mothers with asthma were at increased risk of a variety of disorders. Even more reason for careful monitoring of women with asthma during pregnancy!*
C.D.

Tegethoff M, Olson J, Schaffner E, Meinlschmidt G: Asthma during pregnancy and clinical outcomes in offspring: a national cohort study.
Pediatrics. 2013;132:483-491. ♦♦

I'll Have a Grande Probiotics-- Without *L. acidophilus,* Please

SOME evidence suggests that probiotics can reduce asthma and atopy risk in children, although the limited clinical trials have yielded conflicting results. The results of previous trials of probiotics for prevention of atopy and allergic disease were pooled for meta-analysis.

The meta-analysis included data on 4,031 participants from 25 randomized, placebo-controlled trials of early-life probiotic administration with outcomes relevant to atopy and asthma. Probiotics were associated with a significant reduction in total IgE: mean -7.59 U/mL. On meta-regression, the effect on IgE was more pronounced with longer follow-up.

Probiotics were associated with a significant reduction in the risk of atopic sensitization, given prenatally or postnatally: relative risk 0.88 and 0.86, respectively. Risk of atopy was higher for infants receiving *L. acidophilus,* compared to other strains. There was no evidence of effect on asthma/wheezing risk.

The assembled evidence suggests that prenatal or early-life probiotic supplementation can reduce the risk of atopic sensitization and lower total IgE levels in children. Further well-designed studies of probiotics for allergy prevention are needed, especially in high-risk infants.

COMMENT: *The role of the intestinal microbiome and the effect of early-life probiotic administration on the development of allergies and asthma in childhood are unclear. This meta-analysis of randomized, placebo-controlled trials demonstrated that administration of probiotics in early life may reduce total IgE and protect against atopic sensitization. Administration of* L. acidophilus, *compared to other strains, was associated with an increased risk of sensitization. Probiotics did not seem to protect against asthma/wheezing.* ➤➤

Future trials on this issue should include carefully selected probiotic strains and longer follow-up.
C.D.Elazab N, Mendy A, Gasan J, et al: Probiotic administration in early life, atopy, and asthma: a meta-analysis of clinical trials.
Pediatrics. 2013;132:e666-e676. ♦♦

Majority of Childhood Asthma Does Not Remit

REPORTED remission rates of childhood asthma vary widely. The course of asthma during adolescence is dynamic, with high rates of both remission and relapse. This study assessed asthma remission and persistence rates during follow-up from school age through adolescence.

Through questionnaires distributed to the parents of 7- to 8-year old children in northern Sweden, the researchers identified 248 children with asthma. Annual evaluations were performed through age 19 in 205 participants. The primary outcome was the rate of asthma remission, defined as no wheezing and no use of asthma medication for at least 3 years.

At follow-up, asthma was in remission for 21% of participants. Asthma was periodic in 38% of participants and persistent in 41%. Remission was more common in males, adjusted odds ratio (OR) 2.53. Factors associated with a lower remission rate were sensitization to furred animals, OR 0.14; and an asthma score of 2 or higher in childhood: OR 0.19. Eighty-two percent of adolescents with the latter two factors had persistent asthma.

This long-term follow-up study suggests that 80% of most children with asthma at age 7 or 8 have persistent or periodic asthma at age 19. The chances of remission are lower for females, patient sensitized to furred animals, and those with more severe asthma as children. These groups may benefit from closer clinical management and follow-up.

COMMENT: *In a large study, school-age children with asthma in northern Sweden were followed annually till age 19. The 83% patient retention rate was impressive. Only one out of five children was in remission at age 19. As has been reported in the past, remission was more common in boys and less common in those sensitized to furred animals and greater baseline severity of asthma. It is to be noted that the dominant allergens in the study area are pollen and furred animals; dust mites are inhibited by the cold and dry climate.*
C.D.
Andersson M, Hedman L, Bjerg A, et al: Remission and persistence of asthma followed from 7 to 19 years of age.
Pediatrics. 2013;132:e435-e442. ♦♦

CLINICAL TIDBITS

Childhood Asthma Admissions Fall, but Hospital Costs Rise

FEW recent studies of childhood asthma have evaluated trends in hospitalization, which is a serious and potentially preventable outcome. Changes in pediatric asthma hospitalizations and associated outcomes from 2000 to 2009 were assessed.

Using the Kids' Inpatient Database, the researchers analyzed national discharge data on a total of 592,805 weighted childhood asthma hospitalizations for 2000, 2003, 2006, and 2009. The results showed a 13% decrease in pediatric asthma hospitalizations from 2000 to 2009: from 21.1 to 18.4 per 10,000 person-years. With adjustment for confounders, mortality decreased significantly: odds ratio 0.37 in 2009 vs 2000.

Use of mechanical ventilation increased by 28%, from 0.8% to 1.0%. Hospital charges increased by 26%, from $1.27 to $1.59 billion. This mainly reflected a 42% increase in geometric mean hospital charges per discharge: from $5,940 to $8,410.

The results show continued progress in reducing hospitalizations for childhood asthma, but a continued high asthma burden with substantial rates of adverse outcomes. The authors call for further research to bridge gaps in childhood asthma care and to develop more cost-effective management approaches.

COMMENT: *The good news: hospitalizations for asthma are down. The bad news: hospital costs are up, mechanical ventilation is up. It appears that providers are doing a good job keeping kids out of hospitals, but there is an unmet need to identify those high-risk patients who actually are admitted. Again, another reason for specialty referral.*
S.F.W.
Hasegawa K, Tsugawa Y, Brown DFM, et al: Childhood asthma hospitalizations in the United States, 2000-2009.
J Pediatr. 2013;163:1127-1133. ♦♦

Can We Predict Which Patients With Chronic Sinusitis Will Improve After Surgery?

FOR patients with refractory chronic rhinosinusitis (CRS), it can be challenging to predict the outcomes of sinus surgery. A modified Sino-Nasal Outcome Test (SNOT) was evaluated as a predictor of improvement after surgery for CRS.

The SNOT-22 was created by adding questions addressing "nasal obstruction" and "loss of smell and taste" to the SNOT-20. Baseline SNOT-22 score was then evaluated for association with symptom improvement after sinus surgery in 104 patients with refractory CRS.

Functional endoscopic sinus surgery was "extremely effective," with a 51% overall improvement in SNOT-22 score. On multivariate analysis, an item addressing "runny nose" was directly correlated with improvement, while items on "sadness" and "cough" were negatively related to improvement. Items relevant to nasal or ear symptoms were "uniquely associated" with postoperative improvement. Improvement was unrelated to CT score, total IgE level, or absolute eosinophil count.

Certain items on the SNOT-22 may help in predicting symptomatic improvement after surgery for refractory CRS. The authors add, "This study begins to define important questions that must be asked before surgical intervention" for chronic sinusitis. ➤➤

COMMENT: *Patients with refractory CRS may require surgical intervention. Outcome measures such as the SNOT-20 may be useful in determining which patients will benefit from surgery. The authors added two questions to make the SNOT-22. All patients had postoperative improvement; those who had no prior sinus surgery did better. Questions addressing "runny nose" correlated with improvement, whereas patients with "cough" or "sadness" had less improvement. Further studies would be useful to support the test's utility in clinical practice.*
V.H.-T.
Kennedy JL, Hubbard MA, Huyett P, et al: Sino-nasal outcome test (SNOT-22): A predictor of postsurgical improvement in patients with chronic sinusitis.
Ann Allergy Asthma Immunol. 2013;111:246-251. ♦♦

New Congenital Neutrophil Defect Syndrome

GENETIC disorders affecting neutrophils predispose affected patients to severe infections, and lend insights into the mechanisms underlying vesicular trafficking, hematopoiesis, and innate immune function. A novel congenital immunodeficiency syndrome caused by mutations of *VPS45* is reported.

The researchers studied 7 children from 5 families with neutropenia, neutrophil dysfunction, bone marrow fibrosis, and nephromegaly. All children had one of two homozygous mutations of *VPS45*: Thr224Asn in one ethnic group and Glu238Lys in another. Affected patients had decreased levels of VPS45 protein, with a reduced level of β1 integrin on the surface of VPS45-deficient neutrophils and fibroblasts. Impaired motility and increased apoptosis of VPS45-deficient fibroblasts were corrected by transfection of patient cells with nonmutated *VPS45*. Five children died, and two were awaiting hematopoietic stem cell transplantation.

Biallelic mutations of *VPS45* leading to defective endosomal intracellular protein trafficking are identified as the cause of a previously unrecognized immunodeficiency syndrome with impaired neutrophil function. Based on the observed cellular defects, impaired vesicle trafficking could cause other immunodeficiency disorders.

COMMENT: *Vilboux et al describe biallelic mutations in* VPS45 *as the cause of a new immunodeficiency syndrome involving impaired neutrophil function. Affected children had homozygous mutations in* VPS45, *which encodes a protein regulating membrane trafficking through the endosomal system.* VPS45*-deficient fibroblasts demonstrated impaired motility and increased apoptosis. Transfection of patient cells with nonmutated* VPS45 *corrected the migration defect and decreased apoptosis.*
C.D.
Vilboux T, Lev A, Malicdan MCV, et al: A congenital neutrophil defect syndrome associated with mutations in VPS45.
N Engl J Med. 2013;369:54-65. ♦♦

REVIEWS OF NOTE

COMMENT: *This paper provides an excellent review of leukotrienes in treatment of lung disease.*
B.E.C.
Scott JP, Peters-Golden M: Antileukotriene agents for the treatment of lung disease.
Am J Respir Crit Care Med. 2013;188:538-544. ♦♦

COMMENT: *Here's a thorough review of interstitial lung disease (ILD) in children. Although ILD is not primarily seen by allergists, it must be considered in selected patients.*
B.E.C.
Kurland G, Deterding RR, Hagood JS, et al: An official American Thoracic Society clinical practice guideline: Classification, evaluation, and management of childhood interstitial lung disease in infancy.
Am J Respir Crit Care Med. 2013;188:376-394. ♦♦

COMMENT: *As allergists, we are seeing more patients with chronic obstructive pulmonary disease (COPD). Depression or anxiety occurs in about 40% of COPD patientsm and these diagnoses are associated with poor outcomes. This systematic review evaluated the effects of depression/anxiety on COPD and, conversely, the effects of COPD on depression/anxiety. Depression or anxiety confers an increased risk for COPD adverse outcomes and possibly death. Interestingly, COPD increased the risk of developing depression.*

Since these comorbid conditions are common, allergists need to be aware of the reported associations. They may wish to consider using some simple screening tools for depression, such as asking these two questions: During the past month, have you often been bothered by feeling down, depressed, or hopeless? During the past month, have you often been bothered by little interest or pleasure in doing things? An answer of yes to either question suggests the possibility of depression.
D.A.K.
Atlantis E, Fahey P, Cochrane B, Smith S: Bidirectional associations between clinically relevant depression or anxiety and COPD: A systematic review and meta-analysis.
Chest. 2013;144:766-777. ♦♦

COMMENT: *This fascinating review article highlights the asthma susceptibility gene* ORMDL3, *located on chromosome 17q21, which appears to have a major role in sphingolipid metabolism. Alterations in sphingolipid metabolism have been associated with airway hyperreactivity and with changes in lung magnesium homeostasis. This may explain the clinically variable response observed with the use of intravenous magnesium for asthma exacerbations. Although these findings are preliminary, they enhance understanding of asthma pathobiology and may catalyze discovery of new potential therapeutic targets.*
C.D.
Levy BD: Sphingolipids and susceptibility to asthma.
N Engl J Med. 2013;369:976-978. ♦♦