AllergyWatch®

"10th Anniversary Volume"

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

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Measles and Pertussis Vaccines: Much Maligned, but Not a Cause of Atopy

PARENTS commonly refuse vaccines because of concerns over perceived health risks, including an increased risk of asthma. Epidemiologic studies of this issue have had important limitations, with conflicting results. The relationship between pertussis vaccination and childhood wheezing disorders was evaluated in a large, population-based study.

The analysis included 6,811 children born in one U.K. county from 1993 to 1997. Questionnaire data on respiratory symptoms were linked to National Health Service data on vaccinations. Incidences of wheezing and asthma were compared for children with different pertussis vaccination status: complete, partial, and no pertussis vaccine coverage. Over 23,201 person-years of follow-up, new-onset wheezing developed in 2,426 children.

Rates of wheezing or asthma did not differ across pertussis vaccination groups. For children with complete vaccine coverage, estimated hazard ratios were consistently less than 1, compared to unvaccinated children. Sensitivity analyses, including analysis of exposure to other vaccines, yielded similar patterns.

In contrast to some previous reports, this population-based study shows no increase in wheezing or asthma among children receiving pertussis vaccine. The data suggest that, if there is any effect of routine childhood vaccinations on asthma risk, it is likely protective.

Spycher BD, Silverman M, Egger M, et al: Routine vaccination against pertussis and the risk of childhood asthma: a population-based cohort study. **Pediatrics**. 2009;123:944-950.

SOME studies have suggested an association between measles vaccine and allergic disease in children. Steiner school children--many of whom follow an anthroposophic lifestyle, with limited exposure to antibiotics and immunizations--have a reduced prevalence of allergic disease. The relationship between ➤➤

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

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

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measles vaccination or infection and allergic disease and atopy was studied in Steiner school children and other groups.

The analysis used data from the Prevention of Allergy Risk Factors for Sensitization in children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) project, a cross-sectional study included nearly 15,000 children, aged 5 to 13 years, from five European countries. Eighty-four percent of children had complete data on measles vaccination and measles infection. Rates of allergic disease and atopic sensitization were assessed by measles status for Steiner school children, children living on farms, and children from nonfarming households.

Across the three groups of children, measles infection was associated with a lower rate of atopic sensitization. A similar pattern was noted for measles vaccination. After exclusion of children with symptoms of wheezing and/or eczema during the first year of life, measles infection was associated with a lower rate of allergic symptoms or physician diagnosis of allergy. Measles vaccination was unrelated to any allergic disease outcome.

Measles vaccination does not appear to increase the risk of allergic disease or atopic sensitization in children, including Steiner school children. On analysis designed to reduce the chances of disease-related exposure modification, measles infection is associated with reduced rates of allergic disease. Prospective studies are needed to assess possible causal associations.

COMMENT: *Among parents in the developed world, there has been a growing drumbeat of concern regarding safety of childhood immunizations. Such alarm has led to reduced immunization rates, and unfortunately, occasional outbreaks of preventable diseases. One of the more salient questions on this subject, raised by previous research, has been whether such immunizations might contribute to increasing atopy vis-á-vis the hygiene hypothesis/reduction of childhood diseases. These two large-scale studies, respectively, report neither an association between measles vaccine and incidence of atopy, nor between pertussis vaccine and development of asthma. The data are reassuring and should allay vaccine-related parental anxiety, at least where development of atopy is concerned.*
K.R.M.
Rosenlund H, Bergström A, Alm JS, et al: Allergic disease and atopic sensitization in children in relation to measles vaccination and measles infection. **Pediatrics**. 2009;123:771-778. ♦♦

It Takes a Village — or a School System

NEW approaches are needed to increase adherence to inhaled corticosteroids among children with asthma. Directly observed therapy is one strategy shown to be effective in patients with tuberculosis or HIV infection. A school-based program of supervised asthma treatment for children was evaluated.

The randomized follow-up trial included 290 children with asthma at 36 participating schools. All children had persistent asthma for which they were taking daily controller medication; all were able to use a dry-powder inhaler and peak flowmeter. The mean age was 11 years; 57% of the children were boys and more than 90% were African American. Children in the intervention group received school-based, supervised therapy, with daily supervision provided by study staff members. Controls received usual care. School absences because of respiratory illness/asthma, using rescue medication more than twice weekly (excluding pre-exercise treatment), or one or more yellow or red peak flowmeter readings were assessed during baseline and follow-up periods in both groups.

The analysis included 240 study completers. In the usual care group, episodes of poor asthma control occurred at similar rates during the baseline and follow-up periods. In contrast, for the supervised therapy group, the odds of an experiencing an episode of poor asthma control during the baseline period were 1.57 higher than during the follow-up period. There was a marginally significant interaction between assigned group and ➤➤

time period, suggesting greater improvement in asthma control with supervised therapy. Both groups had low adherence rates during the baseline period. In the usual care group, adherence remained low during follow-up, despite the fact that both groups received inhaled steroids at no cost.

A school-based supervised medication program appears to improve asthma control for children with asthma. A coordinated approach to supervised therapy should be considered when poor asthma control in children may be related to medication nonadherence. In schools without nurses, this may involve training school personnel to supervise inhaled steroid use.

COMMENT: *With asthma controller compliance rates among schoolchildren reportedly less than 50%, anything that can be done to improve adherence in those most severely affected would be a boon. One possible strategy is to have medications administered regularly at school to the most vulnerable children. The downside: school nurses are already overtaxed, and nonmedical personnel may need training in administering medications. Not ideal, but these children may ultimately benefit.*
K.R.M.

Gerald LB, McClure LA, Mangan JM: Increasing adherence to inhaled steroid therapy among schoolchildren: randomized, controlled trial of school-based supervised asthma therapy.
Pediatrics. 2009;123:466-474. ♦♦

Pollution's Effect on Asthma: Is it Rapidly Reversible?

A growing body of evidence shows that exposure to air pollutants can promote airway inflammation, with adverse health effects in children with chronic respiratory disorders. It is unclear whether these changes would be reversible if air quality could be improved. Markers of airway inflammation and function were used to assess short-term responses to reductions in outdoor air pollution in children with allergic asthma.

Thirty-seven children with untreated mild allergic asthma were recruited from a children's hospital asthma clinic located in a highly polluted city environment. After baseline assessments, the children were taken for 1 week to a rural area with low levels of air pollution. Changes in noninvasive markers--including nasal eosinophils, exhaled nitric oxide, peak expiratory flow, and urinary leukotriene E_4--were assessed.

At the end of the study week, the children showed an average fourfold decrease in nasal eosinophils--in most subjects, upper airway eosinophils became almost undetectable. Children with high baseline levels showed a significant reduction in exhaled NO. Peak expiratory flow also decreased significantly; urinary leukotriene E_4 was unchanged.

In children with allergic asthma, moving from a polluted urban environment to a less-polluted rural environment leads to rapid reduction in airway inflammatory markers. The reduction in inflammation is accompanied by an increase in peak expiratory flow. Measures to improve air quality might improve health in children with respiratory diseases.

COMMENT: *A number of studies have made the connection between elevated air pollutant levels and increased risk of worsening asthma. But what happens if pollution exposure is subsequently reduced? Are effects on pulmonary health permanent or reversible? This small study attempts to tackle these not insignificant questions.*

Potential confounding variables exist, including the fact that study participants were all dust-mite allergic and lived at ~100 m elevations, whereas the rural locale where improvement occurred after 1 week was situated at 1,500 m. A reduction in dust mite exposure could also contribute to the changes noted during such a brief time; dust mite levels were not measured in either locale. A larger, better-constructed study is needed to more definitively answer the questions raised herein. But indeed, these are questions worth answering!
K.R.M.

Renzetti G, Silvestre G, D'Amario C, et al: Less air pollution leads to rapid reduction of airway inflammation and improved airway function in asthmatic children.
Pediatrics. 2009;123:1051-1058. ♦♦

New Data on Health Effects of Air Pollution in Asthma

SEVERAL studies have shown increases in asthma and asthma symptoms in children living near roads with heavy traffic. This study assessed the effects of traffic exposure on pulmonary function and health outcomes in adult asthma patients.

The study included 176 adults with asthma or rhinitis (145 with asthma). Geocoding was used to assess the distance from the subjects' home addresses to various types of roadways. Potential associations between traffic exposure and pulmonary function measures and general health status were assessed.

Distance from the nearest roadway and the nearest major roadway were significantly and positively associated for FEV_1--ie, pulmonary function was better for adults living farther from roadways. On adjusted analysis, an interquartile change in distance to roadway was associated with a 2.2% increase in FEV_1 percent predicted. Distances to roadways were unrelated to measures of health status or quality of life.

Consistent with studies of children, adult asthma patients living closer to roadways have reduced pulmonary function. Patients with asthma should be advised to avoid living near roadways, and especially near high-traffic roads, if possible.

Balmes J, Earnest G, Katz PP, et al: Exposure to traffic: lung function and health status in adults with asthma.
J Allergy Clin Immunol. 2009;123:626-631. ♦♦

A growing body of evidence suggests that exposure to air pollution affects respiratory outcomes. Proximity to oil refineries was evaluated as an indicator of the effects of exposure to petrochemical pollution on respiratory health in children.

Health questionnaires were completed by the parents of three groups of children in La Plata, Argentina: 282 children living near petrochemical plants, 270 living in an area with exposure to heavy traffic, and 639 living in an area with relatively low air pollution. Particulate pollutant levels were measured, along with outdoor and indoor volatile organic compounds. Lung function testing was performed in a random sample of 181 children.

Asthma was present in 24.8% of children living near petrochemical plants, compared to 10.1% of those exposed to traffic pollution and 11.5% of those living in less-polluted areas. Children living near oil refineries had more frequent asthma exacerbations: 6.7 per year, compared to 2.9 and 3.6 per year, respectively, in the comparison groups. Exposure to petrochemical pollution was also associated with increased respiratory symptoms and more than a 13% decrease in FEV_1 percent predicted. Length of residence in the study area was significantly associated with reduced lung function.

Exposure to pollution from petrochemical plants is associated with reduced lung function and increased asthma symptoms in Argentinean children. In contrast, the study finds no significant effects of exposure to heavy traffic. When considering the health effects of air pollution, the source of the pollution may be an important factor.

COMMENT: *These two studies report the effects of air pollution on patients with asthma. The Balmes report, from California, finds that adults with asthma had lower lung functions when they lived closer to roadways. The Wichmann study reports that Argentinean children living closer to an oil refinery with petrochemical pollutants had substantially greater prevalence of asthma with more symptoms than their counterparts in less-polluted areas. Taken together, these articles strengthen the evidence that air pollution has detrimental effects on our asthmatic patients and suggest that we should be recommending that they live far from roadways and refineries.*
S.M.F.

Wichman FA, Müller A, Busi LE, et al: Increased asthma and respiratory symptoms in children exposed to petrochemical pollution.
J Allergy Clin Immunol. 2009;123:632-638. ♦♦

Asthma Coaches Reduce Readmission in Inner-City Children

CONTACTS with community health workers have shown benefits for children with asthma from low-income families. Previous studies have reported reductions in acute care and urgent care. This study evaluated the effects of an asthma coach intervention on hospitalization rates in low-income children with asthma.

The randomized, controlled trial included 306 children hospitalized for asthma at an urban children's hospital. All were 2 to 8 years old, African American, and covered by Medicaid. Of 200 parents contacted, 191 were randomly assigned to intervention and control groups. Intervention families received sessions with peer asthma coaches, working toward a set of key behavioral objectives. The intervention was standardized yet flexible, with a planned contact schedule and a nondirective supportive style. The main outcome of interest was asthma rehospitalization over 2 years' follow-up.

About 90% of parents had at least one "substantive" contact with the asthma coach during the first 3 months of the intervention. Over the 2-year study, the average number of contacts was 21 per parent. Rehospitalization rates were 36.5% for children assigned to asthma coaches versus 59.1% in the usual care group. Relative risk of hospitalization in the intervention group was 0.61, controlling for parental education, child age and sex, and hospitalization in the year before enrollment. In evaluations, parents strongly favored a nondirective approach that was "encouraging and cooperative" rather than prescriptive.

An asthma coach intervention for families of low-income African American children reduces the risk of rehospitalization by 40%. The flexible, nondirective approach used in this intervention appears to be an important component of its success.

COMMENT: *The asthma coach model with home visitation once again is proven to be successful in reducing repeat hospitalization for pediatric asthma in this low-income, inner-city Medicaid population. Unfortunately this option is not readily reimbursable in our current reimbursement system.*
S.M.F.

Fisher E, Strunk R, Highstein GR, et al: A randomized controlled evaluation of the effect of community health workers on hospitalization for asthma.
Arch Pediatr Adolesc Med. 2009;163:225-232. ♦♦

Quality of ED Care for Acute Asthma Is 'Moderate'

EACH year, about 2 million emergency department (ED) visits for asthma are made in the United States. Few studies have evaluated the quality of care provided at these visits. Quality of care for acute asthma was evaluated in a large sample of ED visits.

The retrospective analysis included 4,053 patients, age 13 to 55, seen for acute asthma at 63 urban EDs in 23 states between 2003 and 2006. The median age was 34 years; 64% of patients were women and 47% were black. Concordance with National Institutes of Health asthma guidelines was assessed, with composite concordance scores (on a 0-to-100 scale) assigned for individual patients and EDs. Factors associated with higher concordance at the ED level were assessed, along with the association between concordance and hospital admission.

Median concordance score was 67 on the patient level and 71 on the ED level. On multivariate analysis, ED concordance scores were lower in southern states than in northeastern states. With adjustment for➤➤

asthma severity at presentation, hospitalization risk was reduced by 46% for patients receiving all recommended treatments. The results were unchanged on sensitivity analyses.

For adult patients seen for acute asthma at U.S. urban EDs, the concordance with guideline-based treatment recommendations is "moderate." The analysis shows significant variations in the quality of ED care for acute asthma, including geographic variations. Higher concordance with recommended treatments for acute asthma is associated with a lower risk of hospitalization.

COMMENT: *This report confirms that asthmatic patients receiving treatment in the ED which followed recommended guidelines had a significantly lower risk of hospitalization. Although these data were collected via a retrospective chart review and most of the sites appeared to be in the Northeast, the resulting low concordance with recommended guidelines--particularly in the South--is disconcerting. We need to do a better job educating ED medical personnel, particularly on the benefits of checking peak flow rates in asthmatics having exacerbations.*
S.M.F.

Tsai C-L, Sullivan AF, Gordon JA, et al: Quality of care for acute asthma in 63 US emergency departments.
J Allergy Clin Immunol. 2009;123:354-361. ♦♦

Probiotics Don't Prevent Allergies in High-Risk Infants

THERE is interest in the use of probiotics to alter the gut microflora in infants, thus modifying the later risk of allergic disease. Previous studies of this approach have yielded contradictory results. The preventive effects of probiotic and prebiotic supplementation on allergic disease risk in high-risk children were evaluated in a randomized trial.

The double-blind trial included 1,223 pregnant women whose fetuses were at high genetic risk of allergy. Mothers in the intervention group received a probiotic mixture consisting of two lactobacilli, bifidobacteria, and propionibacteria during the last month of pregnancy. After birth, the infants received the same mixture from birth to age 6 months, plus a prebiotic galactooligosaccharide. Controls received placebo. Rates of allergic disease and IgE sensitization were assessed through age 5 years.

Follow-up to age 5 was available for 891 children. The overall rate of allergic disease was 52.6% in the probiotic group and 54.9% in the placebo group. There was also no significant difference in the rate of IgE-associated allergic disease, 29.5% versus 26.6%; or sensitization, 41.3% in both groups. Rates of specific allergic diseases were similar as well.

However, there was a significant interaction between intervention and mode of delivery. Among children with cesarean delivery, the rate of IgE-associated allergic disease was 24.3% in the probiotic group, compared to 40.5% in the placebo group--odds ratio 0.47.

The probiotic/prebiotic supplementation regimen evaluated in this study does not reduce long-term rates of allergic disease or sensitization among high-risk infants. There is evidence of a possible preventive benefit of probiotics among children delivered by cesarean section.

COMMENT: *In this large, prospective, well controlled, birth-cohort study there was significant reduction in allergic disease when the mothers were given probiotics perinatally, but only in the cesarean-delivered children. The authors speculate that these children, deprived of the microbial load from vaginal delivery, may be more likely to benefit from the immunologic effects of the probiotics. With the increasing interest in alternative medicine and probiotics it is helpful to have data from well-controlled studies to evaluate effectiveness.*
S.M.F.

Kuitunen M, Kukkonen K, Juntunen-Backman K, et al: Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort.
J Allergy Clin Immunol. 2009;123:335-341. ♦♦

Environmental Exposure May Contribute to Peanut Allergy

AS many as 80% of children seen for peanut allergy react to their first known exposure. A number of routes of peanut exposure are possible, including environmental exposure. Some studies implicate cutaneous exposure as a possible route of sensitization. Routes of exposure leading to peanut allergy in children were investigated.

The study included 133 children with peanut allergy. Parents completed a detailed questionnaire regarding peanut consumption by all household members during pregnancy and the child's first year of life. The same questionnaire was completed for two groups of control children: a high-risk risk group of 160 children with egg allergy and a low-risk group of 150 nonallergic children.

Median weekly household peanut consumption was 18.8 g for cases of peanut allergy, compared to 1.9 g for high-risk controls and 6.9 g for nonallergic controls. Peanut consumption in infancy was similar across groups. There were some differences in maternal peanut consumption during pregnancy and breast-feeding, but these became nonsignificant after adjustment for total household peanut consumption. Environmental peanut exposure was significantly associated with the occurrence of peanut allergy--especially in households with high consumption of peanut butter. Where environmental peanut exposure was high, early oral exposure to peanut may have had a protective effect against the development of peanut allergy.

High environmental exposure to peanut in the household appears to be associated with sensitization to peanut in children. In children predisposed to atopy, low exposure to peanut may have a protective effect. Maternal peanut consumption during pregnancy or breast-feeding does not appear to be a contributing factor.

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COMMENT: *Does environmental exposure to peanut protein predispose infants to develop peanut allergy? These British researchers suggest that their questionnaire-based case-controlled study data supports the concept that environmental peanut exposure may increase the risk of peanut allergy in allergic infants. True environmental measurements of peanut protein need to be obtained before this hypothesis is confirmed.*
S.M.F.

Fox A, Sasieni P, et al: Household peanut consumption as a risk factor for the development of peanut allergy.
J Allergy Clin Immunol. 2009;123:417-423. ♦♦

Study Shows Variations in ED Management of Asthma

STUDIES conducted before the most recent Canadian guidelines for asthma management were issued showed variations in hospitalization rates for asthma in Ontario. This could reflect shortfalls in evidence-based management of acute asthma in the emergency department (ED). Variations in ED management of acute asthma in children and adults were analyzed, including the relationship between guideline adherence and admission and relapse rates.

The researchers analyzed data from a stratified sample of patients receiving ED care for acute asthma at 16 Ontario hospitals during 2001-02, including 2,761 patients under age 20 (42.0% female) and 2,078 aged 20 or older (66.7% female). Variations in ED practice and their consistency with guidelines were analyzed. Hospital adherence to guidelines was compared with site characteristics and patient admission and relapse rates.

Patients seen at different hospitals varied substantially in terms of asthma severity, comorbidity, access to care, and prehospital management. Peak expiratory flow was documented in only 27.2% of children aged 7 or younger, compared to 44.3% of adults. Use of systemic steroids in the ED or at discharge was documented in only about one-third of pediatric or adult charts, with significant variation among sites. Referral to asthma services was charted in less than 3% of patients in both age groups. In adults, admission rate was directly related to the time before receiving systemic steroid therapy. Adults receiving a new inhaled steroid prescription at discharge were less likely to make repeat ED visits.

The findings highlight persistent gaps and variation in ED management of asthma. Areas in need of improvement include underuse of objective measures of airflow obstruction and systemic steroids and low rates of referral for specialist care.

COMMENT: *The findings in this epidemiologic study are not surprising. Delayed steroid administration was associated with increased admissions, and there was considerable variation in assessments, treatment, and referrals in the province of Ontario. This study identifies areas that are incongruous with current management guidelines. Importantly, this data is a product of single-payer database. The Canadian model of collecting and interpreting this data may have relevance to future U.S. healthcare.*
S.F.W.

Lougheed MD, Garvey N, Chapman KR, et al: Variations and gaps in management of acute asthma in Ontario emergency departments.
Chest. 2009; 135:724-736. ♦♦

Anti-IL-5 Update

PREVENTION of asthma exacerbations is a major goal of asthma treatment. Eosinophilic airway inflammation may be an important contributor to exacerbations, supporting a possible role of anti-eosinophil therapy. The anti-interleukin-5 (IL-5) antibody mepolizumab was evaluated for use in patients with refractory eosinophilic asthma.

The randomized controlled trial included 61 patients with refractory eosinophilic asthma and recurrent severe exacerbations. One group received mepolizumab, 750 mg IV once monthly, or monthly placebo infusions for 1 year. The frequency of severe exacerbations over the 50-week treatment period was compared between groups, along with secondary outcomes.

Mean number of exacerbations per patient was 2.0 in the mepolizumab group versus 3.4 in the placebo group, relative risk 0.57. Mepolizumab was also associated with significant improvement in quality of life--mean difference 0.35 points on the Asthma Quality of Life Questionnaire. Blood and sputum eosinophil counts also decreased significantly in the mepolizumab group. Asthma symptoms, postbronchodilator FEV_1, and airway hyperresponsiveness did not differ between groups. Mepolizumab had an acceptable safety profile; hospitalizations for severe acute asthma were the only serious adverse events.

Anti-IL-5 therapy with mepolizumab reduces the rate of severe exacerbations in patients with refractory eosinophilic asthma. Disease-related quality of life is also improved, compared to placebo. The response supports the hypothesis that eosinophils contribute to the pathogenesis of exacerbations in this group of patients.

Haldar P, Brightling CE, Hargadon RGN: Mepolizumab and exacerbations of refractory eosinophilic asthma.
N Engl J Med. 2009;360:973-984. ♦♦

ALTHOUGH anti-IL-5 therapy reduces blood and airway eosinophil levels, it has not improved outcomes for patients with asthma in previous clinical trials. This study evaluated the effects of anti-IL-5 therapy with mepolizumab in a rare subgroup: patients with sputum eosinophilia and persistent airway symptoms despite continued prednisone therapy.

The randomized, controlled trial included 20 patients with prednisone-dependent asthma associated with sputum eosinophilia. One group received five monthly mepolizumab infusions; controls received placebo infusions. Responses to planned reductions ➤➤

in prednisone dosage were compared between groups. Sputum and blood eosinophil counts, asthma symptoms, and airflow limitation were evaluated as well.

In 11 patients assigned to placebo, there were 12 asthma exacerbations, 9 associated with sputum eosinophilia. In contrast, just 1 exacerbation occurred in 9 patients receiving mepolizumab; none were associated with sputum eosinophilia. Prednisone dosage was reduced by a mean of 83.8% of the maximum possible dose in the mepolizumab group, compared to 47.7% in the placebo group. Mepolizumab reduced sputum and blood eosinophils. These changes persisted for 8 weeks after the last mepolizumab treatment, as did improvements in asthma control and FEV_1.

In patients with a rare subtype of persistent asthma associated with sputum eosinophilia despite oral prednisone, mepolizumab has a significant prednisone-sparing effect. In addition to its clinical implications, the study highlights the need to select patients with airway eosinophilia when evaluating anti-eosinophil therapies.

COMMENT: *These two studies investigated mepolizumab (anti-IL-5) in severe, steroid resistant adult asthmatics. They found that mepolizumab reduced exacerbations and prednisone requirements, but did not seem to affect daily symptoms or spirometric performance. Previous studies in patients with milder asthma failed to show an effect of mepolizumab. This seems to indicate once again that asthma is a heterogeneous disease with different phenotypes, some of which depend on the eosinophil more than others. This treatment is not for everyone, but may have selective benefit in the adult-onset, non-allergic, eosinophilic asthmatic.*
R.J.M.
Nair P, Pizzichini MMM, Kjarsgaard M, et al: Mepolizumab for prednisone-dependent asthma with sputum eosinophilia.
N Engl J Med. 2009;360:985-963. ♦♦

How Many Reactions to Immunotherapy Are Biphasic?

PATIENTS with anaphylactic reactions to allergen immunotherapy are generally discharged home after treatment with epinephrine and a period of observation. However, the potential for biphasic reactions in this situation is unknown--only 4 cases of biphasic reactions after allergen immunotherapy have been reported. This study assessed the incidence and clinical characteristics of biphasic reactions after allergen immunotherapy.

The prospective study included 66 systemic reactions occurring after allergen immunotherapy in 55 patients. All reactions were treated with epinephrine. The occurrence and characteristics of biphasic reactions were assessed using a 31-symptom scoring system, completed at baseline and after 24 hours.

There were 14 biphasic reactions, for a rate of 23%. Biphasic reactions were more likely to occur in women, older patients, and those who received more than one dose of epinephrine. Other characteristics did not differ for patients with single-phase versus biphasic reactions: type of immunotherapy, diagnosis of asthma, initial symptom scores, time to symptoms, initial epinephrine treatment, or improvement after treatment. There was no specific symptom that predicted biphasic reactions.

There were no biphasic reactions in children. The biphasic reactions were less severe than the initial reactions, did not require further treatment with epinephrine, and did not warrant an emergency department visit.

Nearly one-fourth of systemic reactions to allergen immunotherapy requiring epinephrine are biphasic reactions. Such patients should be warned about the possibility of biphasic reactions. Such reactions are relatively mild, tend to be self-limited, and do not require further epinephrine treatment.

COMMENT: *Anaphylaxis can be biphasic, with symptoms recurring up to eight hours after the initial event and treatment with epinephrine. However, anaphylaxis after allergen immunotherapy hasn't been specifically analyzed. In this study, biphasic reactions occurred in 23% of subjects experiencing primary systemic reactions to immunotherapy. They were more common in older women, but were not predicted by time to first epinephrine, symptom pattern, or current asthma. Only 57% of patients with biphasic reactions had extracutaneous symptoms in the later phase. It is reassuring that the later phase was much milder and did not require additional epinephrine.*
R.J.M.
Scranton SE, Gonzalez EG, Walbel KH: Incidence and characteristics of biphasic reactions after allergen immunotherapy.
J Allergy Clin Immunol. 2009;123:493-498. ♦♦

Herbal Formula Prevents Allergic Reactions to Peanut in Mice

PEANUT allergy is a common and serious problem, with no preventive therapy or cure. In previous studies, the authors have reported that an herbal combination called Food Allergy Herbal Formula-2 (FAHF-2) prevented anaphylactic reactions in peanut-allergic mice, with protection lasting up to 4 weeks after treatment. This study examined the long-term protective effects of FAHF-2 and explored the underlying mechanisms.

After 7 weeks of treatment with FAHF-2, peanut-allergic mice underwent a series of seven oral peanut challenges. Challenges were given 4 to 10 weeks apart over 36 weeks; symptoms of anaphylaxis, body temperatures, and plasma histamine levels were measured after each challenge. In a subset of animals, the effects of CD4+ or CD8+ T-cell-depleting antibodies or interferon (IFN)-γ-neutralizing antibodies were assessed.

The protective effects of FAHF-2 persisted for at least 36 weeks after treatment. None of the treated mice had any reaction to peanut challenge at 40 weeks, whereas sham-treated mice had near-fatal anaphylactic ➤➤

reactions. The protective effect of FAHF-2 was associated with up to a one-half reduction in peanut-specific IgE and up to a 60% increase in IgG_{2a}, both of which persisted over time.

Production of Th2 cytokines by FAHF-2-treated mice showed a three-fourths reduction. At the last challenge, there was up to an 85% increase in CD8+ T-cell IFN-γ. Treatment with CD8+ T-cell-depleting or IFN-γ-neutralizing antibodies greatly reduced the protective effect of FAHF-2.

The herbal combination evaluated in this study provides lasting protection against peanut-induced anaphylaxis in mice. The mechanism of this effect appears to involve a shift in allergen-specific immune responses, especially increased production of CD8+ T-cell IFN-γ. Clinical trials of FAHF-2 are underway in the United States.

COMMENT: *At this time, there is no treatment that can protect patients who are allergic to peanuts. Avoidance is their only option. Hugh Sampson's group has identified a unique mixture of herbs, called FAHF-2, that prevents anaphylaxis in peanut-allergic mice and is now in human clinical trials. This study shows that the preventive effect in mice lasts at least 36 weeks after completion of 7 weeks of treatment with FAHF-2. It further shows that the effect is mediated by T-cell IFN-γ. The excitement builds.*
R.J.M.

Srinivasta KD, Qu C, Zhang T, et al: Food Allergy Herbal Formula-2 silences peanut-induced anaphylaxis for a prolonged period via IFN-γ-producing $CD8^+$ T cells.
J Allergy Clin Immunol. 2009;123:443-451. ♦♦

High Rates of Oseltamivir-Resistant Influenza in U.S.

THE 2007-08 influenza season saw the first reports of oseltamivir-resistant influenza A(H1N1) viruses in the United States and elsewhere. The prevalence of these resistant viruses is likely to be higher in 2008-09. Surveillance data on oseltamivir-resistance influenza A(H1N1) in 2007-08 and the early part of the 2008-09 influenza season were analyzed.

The analysis included influenza A(H1N1) viruses submitted to the U.S. Centers for Disease Control and Prevention throughout the 2007-08 season, as well as from September 2008 to February 2009. Neuraminidase inhibition assay and pyrosequencing analysis were performed to assess oseltamivir resistance. For patients reported in 2007-08, the characteristics of infection with oseltamivir-resistant and oseltamivir-susceptible viruses were compared.

In 2007-08, 19% of circulating influenza A(H1N1) viruses were oseltamivir resistant. Testing was performed in a total of 1,155 viruses from 45 states; oseltamivir resistance was found in 12.3% of viruses from 23 states. On analysis of 99 oseltamivir-resistant patients, the median age was 19 years, the hospitalization rate was 5%, and the mortality rate was 4%. Oseltamivir-resistant and -susceptible cases were similar in terms of patient characteristics, underlying illnesses, and symptoms. In early data from the 2008-09 season, oseltamivir resistance was found in 98.5% of samples tested.

The findings show the high rate of circulating oseltamivir-resistant influenza A(H1N1) virus during the 2007-08 influenza season. These infections are similar to those caused by oseltamivir-susceptible virus, and appear unrelated to oseltamivir use. The prevalence of oseltamivir resistance appears higher in the 2008-09 influenza season.

COMMENT: *Influenza vaccine should be routine part of our practice as we see high-risk subjects and we are immunologists. If you needed more incentive, this paper provides disturbing news of biologic resistance to our best antiviral for at risk subjects. Give the vaccine!*
D.K.L.

Dharan NJ, Gubareva LV, Meyer J et al: Infections with oseltamivir-resistant influenza A (H1N1) virus in the United States.
JAMA. 2009;301:1034-1041. ♦♦

Update on Reactions to Chemotherapy Drugs

ALLERGISTS are frequently called upon to aid in managing hypersensitivity reactions to chemotherapy drugs. These situations can lead to difficult clinical dilemmas, in which the risks of potentially life-threatening reactions must be weighed against discontinuation of potentially life-saving therapies. Published literature relevant to the diagnosis and management of hypersensitivity reactions to chemotherapy drugs was reviewed.

Some chemotherapy agents are commonly associated with hypersensitivity reactions. Carboplatin and other platinum-containing drugs may cause IgE-mediated hypersensitivity reactions. Skin testing is indicated in some cases; the incidence of cross-hypersensitivity between cisplatin and carboplatin remains to be determined. Reactions to the taxane drugs paclitaxel and docetaxel are generally not IgE-mediated, and may be preventable with corticosteroid and antihistamine pretreatment.

Hypersensitivity reactions to asparaginase are frequent, and are probably IgE-mediated or related to complement activation. Although asparaginase skin testing has been recommended, this has yet to be validated. Reactions to procarbazine may be IgE-mediated, but some patients have type III reactions with pulmonary toxicity. Hypersensitivity reactions to the epipodophyllotoxins etoposide and teniposide may include both immunologic and nonimmunologic mechanisms. These reactions can usually be prevented by slow infusion, with corticosteroids and antihistamines if necessary.

Hypersensitivity reactions are possible to most common cancer chemotherapy drugs. As the use of these agents continues to increase, education regarding their diagnosis and management will be critical, with➤➤

important implications for decision to rechallenge or discontinue treatment.

COMMENT: *Hospital consults for this allergist/immunologist, particularly for adult patients, are increasingly limited to drug allergy. This is a superb review of adverse drug reactions due to oncologic therapeutics. Table 1 should be in your ectopic brain if you see such patients.*
D.K.L.
Lee C, Gianos M, Klaustemeyer WB: Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents.
Ann Allergy Asthma Immunol 2009;102:179-187. ♦♦

Low Rate of Systemic Reactions to Cluster Immunotherapy

SUBCUTANEOUS allergen immunotherapy is generally given in an induction phase followed by a maintenance phase. Recent studies have suggested that following rapid or clustered regimens during the induction phase, if tolerated, may help in reaching the maintenance phase more rapidly. The tolerability of various clustered regimens was evaluated in a retrospective study.

The analysis included data on 1,147 patients undergoing subcutaneous immunotherapy with standardized allergen extracts at three Spanish allergy units. The patients received a total of nine different dosing schedules during the induction phase, with a total of 6,982 doses of immunotherapy. The maintenance dose was reached in two to five sessions, with a total of four to ten doses. The rate of systemic reactions was assessed, along with associated factors.

There were 42 systemic reactions, occurring in 0.6% of doses and 3.4% of patients. Based on European Academy of Allergy and Clinical Immunology criteria, 16.7% of reactions were grade 0, 61.9% grade 1, 19.0% grade 2, and 2.4% grade 3. There were no grade 4 (anaphylactic shock) reactions. The risk of systemic reactions was increased when the initial dose was higher than 0.3 index of reactivity (IR). Just two reactions occurred after the initial dose of the clustered protocol; in both cases, the initial dose was 0.4 IR. There were no reactions to doses lower than 0.35 IR.

This study suggests a low rate of systemic reactions in a large group of patients receiving various clustered immunotherapy induction regimens with IR-standardized allergen extracts. The experience supports the use of clustered regimens as an alternative to classic immunotherapy. The initial dose should be no higher than 0.35 IR.

COMMENT: *The evidence-based medical literature and clinical experience validate the value of specific allergen immunotherapy. Cluster immunotherapy may overcome the barriers of the inconvenience of frequent visits and the cost of copays during build-up. This European retrospective study is reassuring, but keep in mind that a limited number of allergens and adsorbed vaccines were used. The risks are likely different with a broader number of allergens or with aqueous extracts typically used in the United States. See also the accompanying editorial by Cox (Ann Allergy Asthma Immunol. 2009;102:177-178). Cluster, sublingual, modified, rush. . . . "Change is the process by which the future invades our lives" (Alvin Toffler).*
D.K.L.
Serrano P, Justicia J-L, Sánchez C, M et al: Systemic tolerability of specific subcutaneous immunotherapy with index-of-reactivity-standardized allergen extracts administered using clustered regimens: a retrospective, observational, multicenter study.
Ann Allergy Asthma Immunol 2009;102;2427-252. ♦♦

Loratadine-Montelukast for Seasonal Allergic Rhinitis

FOR patients with allergic rhinitis (AR), nasal congestion is a troublesome and difficult-to-treat symptom. Reliable new oral treatments are needed. A combination of loratadine and montelukast was evaluated for use in the treatment of nasal congestion and other AR symptoms.

The experimental study included 379 patients with AR who met minimum symptom criteria on exposure to ragweed pollen in an environmental exposure unit. After a series of priming visits, the patients were randomly assigned to treatment with loratadine-montelukast, 10 mg/10 mg; phenylephrine, 10 mg; or placebo. Before and during 8 hours of pollen exposure, nasal congestion and other symptoms were rated. Peak nasal inspiratory flow was measured as well.

At 6 hours, loratadine-montelukast produced a greater decrease in nasal congestion score compared to placebo, which was not significantly different from phenylephrine. Improvements in total symptoms, nasal and non-nasal symptoms, and peak nasal inspiratory flow were also greater with the combination treatment, compared with the other two groups. Adverse event rates were 3.9% with loratadine-montelukast, 7.9% with phenylephrine, and 7.1% with placebo.

In patients with allergic rhinitis, the loratadine-montelukast combination improves nasal congestion and other symptoms in patients with AR exposed to ragweed pollen. Efficacy is significantly higher than with phenylephrine, which is no different from placebo. Loratadine-montelukast is an attractive therapeutic option, targeting two inflammatory pathways in a single medication.

COMMENT: *In subjects with persistent symptoms, inhibiting more than one mediator with the use of an antihistamine and leukotriene antagonist appeals to my common sense and my medical sense, although it costs more cents (dollars). This study documents the value of such an approach, although other studies have not confirmed clinical efficacy. I currently try a combination approach with chronic nasal congestion and/or eustachian tube dysfunction.*
D.K.L.

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Day JH, Briscoe MP, Rata JD, et al: Efficacy of loratadine-montelukast on nasal congestion in patients with seasonal allergic rhinitis in an environmental exposure unit.
Ann Allergy Asthma Immunol. 2009;102:323-335. ♦♦

What's the Best Denominator for Measuring Quality of Asthma Care?

WORK is ongoing to increase the specificity of the Healthcare Effectiveness Data and Information Set (HEDIS) denominator for persistent asthma. A previous report by a Joint Task Force of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology concluded that a measure associated with reduced exacerbations would be a better indicator of quality of care. A number of additional denominators were tested for optimal discrimination in predicting episodes of acute asthma.

Three different denominators were evaluated in each of three administrative claims databases. Some important differences were noted between patients continuously enrolled for 2 years versus 1 year; a 1-year denominator appeared more representative and more comparable between plans. The three databases were similar in terms of patient age and sex distribution and relative denominator population sizes. They were also similar in terms of relative proportions with at least a 0.5 ratio of controllers to total medications, which was previously shown to be consistently associated with improved outcomes across age groups. This ratio measure showed the highest discrimination with a "DX4" denominator population, consisting of at least one asthma encounter and at least four medication dispensing events. This was so in terms of emergency hospital care in both the measurement year and the following year, as well as asthma exacerbations in the following year.

Based on this analysis, the DX4 denominator is recommended at the best denominator for use with the ≥ 0.5 ratio measure for assessment of asthma quality of care using administrative data. The DX4 denominator is the most specific of the 1-year denominators tested for both emergency hospital care and asthma exacerbations.

COMMENT: *The looming storm front of pay-for-performance coupled with documenting maintenance of certification and competency (should I retire?) makes this clinical metric a useful index for you to look at your practice. I am confident physicians who read* AllergyWatch *will hit this target. The problem is that we control recommendations and prescriptions but do not control filling prescriptions or adherence. What may differentiate us is the types of patients we see, and that is not a valid or fair metric.*
D.K.L.
Schatz M, Broder M, Chang E, O;Connor R, Luskin A, Solari PG. Asthma quality-of-care measures using administrative data: identifying the optimal denominator.
Ann Allergy Asthma Immunol 2009;102:90-102. ♦♦

Apolipoprotein AI Linked to Wheezing in Children

PREVIOUS studies have suggested a possible link between serum cholesterol and asthma. The relationship between serum apolipoprotein concentrations and symptoms of atopy and asthma were evaluated in children.

The investigators measured plasma apolipoprotein AI (apoAI) and apolipoprotein B (apoB) in a population-based sample of 462 children, aged 10 years. Associations with atopy and asthma symptoms--assessed by parental questionnaire--were evaluated by multivariate logistic regression.

Children with elevated apoAI levels of 1.74 g/L or higher had an increased prevalence of wheezing, odds ratio 3.65. There was also a trend toward an increased risk of asthma. Linear analyses suggested positive associations of apoAI with wheezing and nonatopic wheezing, again with a trend for asthma. Plasma ApoB levels were unrelated to allergic symptoms or asthma.

High apoAI levels may be associated with asthma and allergy symptoms in school-age children. The mechanisms of these associations are unclear, but immune processes are likely involved. The findings are limited by the small sample size.

COMMENT: *Dietary factors such as increased fatty acids are thought to contribute to an increase in asthma. Several studies have suggested that serum cholesterol levels are associated with asthma and allergy both in children and adults, and that plasma cholesterol levels can enhance the expression of proinflammatory genes and cytokines.This interesting study evaluated the associations between serum apolipoprotein concentrations and symptoms of asthma and atopy in children. High plasma concentrations of apoAI, but not apoB, were associated with high prevalence of wheeze and a trend was seen with asthma. The authors supported their hypothesis that high apoAI is associated with the manifestation of asthma and atopy. They stated the underlying pathologic mechanism still remains to be fully elucidated, but suggest that immune mechanisms may play a central role. Larger studies are warranted to confirm these observations.*
M.F.
Nagel G, Weiland SK, Rapp K, et al: Association of apolipoproteins with symptoms of asthma and atopy among school children.
Int Arch Allergy Immunol. 2009;149:259-266. ♦♦

Benefits of IVIg in IgG Subclass and/or Antibody Deficiency

QUESTIONS remain about the efficacy of Ig-replacement therapy for patients with IgG subclass and/or antibody deficiency. In the absence of published data, there are few guidelines regarding the use of intravenous gammaglobulin (IVIg).

The investigators report an open-label trial of IVIg therapy in 10 adult patients with IgG subclass ➤➤

and/or antibody deficiency, all with a history of recurrent respiratory infections. Monthly IVIg continued for 12 months, after which the patients were observed for 3 months. A wide range of clinical and immunologic outcomes were assessed, including quality of life (QOL), incidence of infections, need for antibiotics, frequenc of hospitalizations due to infections, tetanus and pneumococcal levels, toll-like receptors (TLR) polymorphisms, mannan-binding lectin (MBL) levels, and genotypes.

Treatment with IVIg was associated with significantly improvement in QOL, with fewer infections and less need for antibiotics. Serum levels of IgG subclass and antibody were significantly improved. There was no consistent evidence of correction of the immune defects during IVIg therapy, however.

This study documents the benefits of monthly IVIg for adult patients with IgG subclass and/or antibody deficiency. The findings have implications for patient evaluation and management.

COMMENT: *Recurrent respiratory tract infections are common in Ig deficiency both in adults and children who have primary Ig, selective IgA deficiency, or adult-onset common variable immunodeficiency. These investigators studied patients with recurrent respiratory infections and IgG subclass and/or antibody deficiency receiving monthly IVIg for 12 months, followed by observation for 3 months without IVIg infusions. Monthly IVIg significantly improved QOL, decreased the number of infections and the need for antibiotics, and improved IgG subclass and antibody serum levels. There was no consistent finding of innate immunity; however, sicker patients were homozygous for MBL genotypes with low serum MBL levels but had no obvious and consistent quantitative defect in MBL and TLR. The authors felt genotyping patients for TLR and MBL could be beneficial in predicting the course of patients with IgG subclass and/or antibody deficiency. Functional assays for TLR and MBL need to be performed in the future, when these tests become routinely available.*
M.F.

Nabih I, Abdou NI, Greenwell CA, et al: Efficacy of intravenous gammaglobulin
for immunoglobulin G subclass and/or antibody deficiency in adults.
Int Arch Allergy Immunol 2009;149:267-274. ♦♦

Antibiotic Use in Infancy Linked to Increased Asthma Risk

STUDIES suggest that the overall prevalence of asthma doubled from 1980 to the end of the 1990s. The use of antibiotics to treat infections in young children increased significantly in the late 1980s to early 1990s, leading some to suggest a possible causal association. Exposure to antibiotics during the first year of life was evaluated as a risk factor for the later development of childhood asthma.

The population-based study used linked administrative health data on 251,817 children born in British Columbia from 1997 through 2003. Prescription drug data were used to assess the children's exposure to antibiotics during the first year of life. The later development of asthma was assessed using records of hospitalizations, medical claims, and prescriptions for asthma medications. Associations between antibiotic exposure and asthma were assessed using Cox proportional hazards models, with adjustment for potential confounders.

Forty-three percent of children received one or more antibiotic prescriptions during their first year of life. During a mean follow-up of 5.5 years, asthma occurred in 7% of children, for an overall incidence of 2.3 per 100 person-years. At age 2 to 3, the incidence was 2.7 per 100 person-years.

On adjusted analysis, there was a significant and positive association between antibiotic exposure in the first year of life and asthma: hazard ratio 1.12. Several factors were associated with increased asthma risk, including male sex, urban residence, lower socioeconomic status, lower birth weight, lower gestational age, initial cesarean delivery, assisted delivery, visits to specialists, more frequent physician visits, increased rates of bronchitis or upper or lower respiratory tract infections, and decreased rate of otitis media.

Asthma risk increased with number of antibiotic courses during the first year of life: adjusted hazard ratio 1.30 for children receiving four or more courses. The strongest association by type of antibiotic was noted for macrolide exposure, hazard ratio 1.11.

The results show a small but significant increase in the risk of asthma for children exposed to antibiotics during the first year of life. Risk appears to increase with number of courses of antibiotics during infancy. Since randomized trials of this association are infeasible, further pharmacoepidemiologic studies and prospective observational studies will be needed.

COMMENT: *The data regarding early antibiotic use and subsequent asthma risk have been conflicting. This is the largest such prospective study done to date, to assess whether an association exists. From a methodology standpoint, the authors are very careful here to exclude patients treated for lower respiratory infections and patients with an early asthma/wheezing diagnosis. In the final analysis, antibiotic use is likely only part of the story, as the relative increase in asthma risk is small and required multiple courses.*
K.R.M.

Marra F, Marra CA, Richardson K, et al: Antibiotic use in children is associated with increased risk of asthma.
Pediatrics. 2009;123:1003-1010. ♦♦

REVIEWS OF NOTE

COMMENT: *A must-read for those considering a nitric oxide analyzer purchase. I still use nitric oxide measurements in clinical practice but there problems. This paper, written by experienced investigators, provides a balanced summary of the literature.*
D.K.L.
Oppenheimer J, Sorkness CA: Does exhaled nitric oxide measurement have a role in asthma care?
Ann Allergy Asthma Immunol. 2009;102:253-255. ♦♦

COMMENT: *If you are looking for a complete and concise review of the drug therapy of asthma, you can do no better than this. It's unlikely allergists will find anything new here, but it's a helpful exercise to read this, and you might send it to referring doctors with your consultations.*
R.J.M.
Fanta CH: Asthma.
N Engl J Med. 2009;360:1002-1014. ♦♦

COMMENT: *Adipose tissue is an active inflammatory organ. This study reports negative findings that asthma challenge has no effect on adiponectin, an anti-inflammatory adipokine, is contrary to mouse model of asthma. However, adiponectin levels were lower at baseline in asthmatics compared to controls. Future investigations will center on effects of adipokine on asthma.*
S.F.W.
Sood A, Qualls C, Seagrave JC, et al: Effect of specific allergen inhalation on serum adiponectin in human asthma.
Chest. 2009;135:287-294. ♦♦

COMMENT: For those of us who treat infants and young children with asthma, this meta-analysis provides reassuring evidence for the efficacy of inhaled corticosteroids in these patient populations.
K.R.M.
Castro-Rodriguez JA, Rodrigo G: Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis.
Pediatrics. 2009;123:e519-e525. ♦♦

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