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 9, Number 1 January-February 2007

From the Editor

WELCOME to a new year and a new volume of *AllergyWatch*. As the new Editor, I would like to welcome our new Associate Editor, Steve Tilles, as well as three new Assistant Editors, Marianne Frieri, Kathleen May, and Steven Weinstein. We would like to acknowledge the outstanding contributions of outgoing assistant editors John Anderson and Tammy Heinly. I would also like to publicly acknowledge and thank Bud Bardana for his wisdom, guidance and friendship as the Founding Editor of *AllergyWatch*. We are proud of our previous efforts, but look forward to continuing to provide what we hope is a valuable educational tool to our readership. If you have suggestions for improving future editions, please feel free to contact me at any time.

Best Regards, and Happy New Year!

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The American College of Allergy, Asthma & Immunology expresses its appreciation to AstraZeneca for its unrestricted 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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Never Too Young to Consider Aeroallergen Sensitization

EARLY identification of children who are sensitized to aeroallergens--before age 2--may aid in clinical follow-up for the emergence of allergic respiratory disease. Parental history of allergic disease is a known risk factor for childhood asthma, but few studies have looked at patterns of skin prick test (SPT) results among children of atopic parents. A birth cohort study was done to assess the prevalence of sensitization to aeroallergens among infants of sensitized parents.

The analysis included 680 infants from the Cincinnati Childhood Allergy and Air Pollution study. All infants had a parent with confirmed allergic sensitization, based on the presence of allergic symptoms and a positive SPT result to at least one of a panel of 15 aeroallergens. At age 1, the infants underwent SPT using the same aeroallergen panel.

Overall, 28.4% of the infants were already sensitized to at least one allergen, including food allergens, at age 1. The rate of sensitization to aeroallergens was 18.0%. Infants were most frequently sensitized to pollens, 9.7%; followed by molds, 7.5%; house dust mite or cockroach, 4.3%; and dog or cat, 3.4%. When retested at age 2 years, 65.7% of sensitized infants were still SPT-positive. Four questions on an allergic symptom questionnaire--regarding itchy or stuffy nose, sneezing or shortness of breath near animals, itchy or watery eyes, or itchy or stuffy nose or sneezing near grass, trees, or flowers--were highly sensitive in identifying atopic parents.

Infants of atopic parents have a high rate sensitization to aeroallergens by age 1. The 18% rate of aeroallergen sensitization, as demonstrated by SPT, includes nearly a 10% rate of sensitization to pollen. Further study is needed to determine whether a more aggressive approach to identification and treatment of allergies in infants and young children could help to reduce the rates and severity of allergic disease.

COMMENT: *That an infant of atopic parents is at increased risk for aeroallergen sensitization is not surprising. What is more compelling is something our specialty already realizes: percutaneous skin tests can be positive (and clinically relevant) in infants and toddlers. This study also indicates that initial pollen sensitization may occur earlier than commonly thought. An important caveat here: sensitization does not imply clinical relevance. This study did not correlate the findings with personal history of atopy or clinical exposure in these children. As these children age, their annual clinical follow-up will be quite informative.*
K. R. M.

LeMasters GK, Wilson K, Levin L, et al: High prevalence of aeroallergen sensitization among infants of atopic parents.
J Pediatr. 2006;149:505-511. ♦♦

Does Evidence Support Controller Therapy for Mild Persistent Asthma?

THE 1997 National Asthma Education and Prevention Program Guidelines recommend daily controller therapy for patients with mild persistent asthma, well as for those with moderate or severe asthma. However, the recommendation for regular inhaled corticosteroid therapy in mild persistent asthma is not evidence-based and is not followed by many patients. A review of recent studies relevant to the management of mild persistent asthma is presented.

Several studies since 2000 have evaluated the outcomes of inhaled corticosteroid therapy for mild-to-moderate asthma. Some have shown improvement in outcomes such as severe exacerbations and symptom days--however, they have provided little evidence that regular controller therapy affects the long-term outcomes of asthma at the milder end of the severity ➤➤

range. In the Improving Asthma Control Trial (IMPACT)--with inclusion criteria closely matching the guideline definition of mild persistent asthma--1 year of intermittent, symptom-based therapy did not lead to a faster rate of decline in lung function, or to a higher frequency of exacerbations. There was also no significant decrement in quality of life with intermittent therapy, perhaps because symptoms are mild, occasional, and easily relieved.

The analysis highlights the need to clarify the most important outcomes in mild persistent asthma, as well as the definition of asthma control. Although the decision to give inhaled corticosteroids may be based on the presence of airway inflammation, this does not necessarily translate into better clinical outcomes. Another limitation of the research is that, because of fluctuations in severity, relatively few patients meet strict criteria for mild persistent asthma.

Recent studies do not support the recommendation for daily controller therapy in patients with mild persistent asthma. There is some evidence that intermittent, symptom-based therapy--as self-selected by many patients--may be an effective alternative. Further studies are needed to assess the clinical and economic outcomes of this approach, as well as to define the interrelationships among asthma symptoms, markers of inflammation, and long-term asthma outcomes.

COMMENT: *In the 10 years since publication of the last NAEPP asthma guidelines, the loudest debate has centered on the classification and treatment of mild persistent asthma. The promise of anti-inflammatory controller therapy to improve long-term clinical outcomes has not been realized. This author's perspective highlights discrepancies among the various measures of outcomes and in the definition of control. He argues that intermittent symptom-based therapy is what many patients choose anyway, and that we have no convincing data to alter that approach.*
R. J. M.
Lazarus SC: Mild persistent asthma: is any treatment needed?
J Allergy Clin Immunol. 2006;118:805-808. ♦♦

'Tis the Season!

CHILDREN who attend daycare are known to have more acute respiratory infections (ARIs) than those cared for at home. Little is known about factors that might modify this relationship, such as age and time since enrollment in childcare. Danish registry data were used to analyze the relationship between daycare attendance and ARIs in children, including the role of child- and family-related factors.

Population data on children born in Denmark from 1989 to 2004 were linked to data on childcare attendance and hospitalization. The final analysis included data on 138,821 hospitalizations for ARI in children from birth to 5 years old--follow-up totaled nearly 4 million person-years. The effect of daycare attendance on risk of hospital admission for ARI was evaluated in terms of incidence rate ratios, estimated by Poisson regression.

Childcare attendance had the greatest impact on ARI risk for the youngest children. For infants under age 1, the incidence of hospitalization for ARI during the first 6 months in daycare was 69% higher than for children cared for at home. This excess risk decreased to 47% for 1-year-old children, 41% for 2-year-olds, and 8% for children aged 3 or older. The childcare-related increase in ARI risk lessened after the first 6 months, and was no longer significant at 1 year or after. Data on second enrollments in childcare yielded a similar pattern of risk.

The number of other children living at home also had a significant impact on ARI risk. For children aged 0 to 2 who lived in households with no other children under age 5, the excess risk of ARI hospitalization during the first 6 months in childcare was 100%. This risk decreased to 25% when there was one other young child at home and 9% when there were two or more other children.

Other factors contribute to the excess risk of ARI associated with childcare in infants and young children. The risk of ARI is highest within the first 6 months after starting daycare--particularly for children under 2 when there are no other children living at home. To limit the impact on ARI risk, it might be best to delay childcare enrollment until age 1.

COMMENT: *We are often asked by parents about childcare attendance and risk of serious infection. This large Danish study stratifies risk of hospitalization from respiratory infections using age, childcare status, and presence of other children in the home. Not surprisingly, the youngest and least exposed (to other young children at home) are at higher risk with daycare attendance. The authors' suggestion that children with no outside exposure be cared for at home may be ideal, but is impractical for our society. (Denmark has extended parental leave, to a total of 52 weeks!)*
K. R. M.
Kamper-Jørgensen M, Wohlfart J, Simonsen J, et al: Population-based study of the impact of childcare attendance on hospitalizations for acute respiratory infections.
Pediatrics. 2006;118:1439-1446. ♦♦

AS rates of atopic disease increase, so do rates of hospitalization for respiratory syncytial virus (RSV) infection in infants and young children. Studies have linked RSV bronchiolitis in infancy to an increased risk of asthma later in childhood. Other reports suggest that a family history of atopy increases the risk of RSV lower respiratory infection. This study sought to determine whether atopy is a risk factor for RSV hospitalization in infants and young children.

The analysis included data from the Danish National Birth Cohort, in which subjects were prospectively followed up from birth until 18 months of age. Risk factors for RSV hospitalization were assessed by comparing 2,564 children hospitalized for RSV infection to 12,816 matched controls without RSV disease. Atopic dermatitis, infrequent or recurrent wheezing, and parental ➤➤

asthma were analyzed as risk factors for RSV hospitalization.

Parental history of atopic diseases was associated with increased rates of RSV hospitalization: adjusted relative risks were 1.11 for maternal atopic dermatitis, 1.72 for maternal asthma, and 1.23 for paternal asthma. For infants less than 6 months old, the presence of atopic dermatitis in the child was also a significant risk factor for RSV hospitalization: relative risk 1.33. Risk of RSV hospitalization was also increased for children with a history of wheezing: relative risk 2.98 for infrequent wheezing and 5.90 for recurrent wheezing. Analysis excluding infants with medical risk factors yielded similar results for wheezing.

Genetic predisposition to asthma and a history of wheezing are strong risk factors for RSV hospitalization during the first 18 months. For infants, the risks of airway hypersensitivity and severe respiratory infections are influenced by a combination of host and environmental factors, in utero and during the first few months of life. Studies adjusting for atopic predisposition and history of wheezing would be needed to determine whether RSV infection affects the risk of later wheezing.

COMMENT: *The debate continues: does being hospitalized for RSV predispose to asthma, or vice versa? This is another study to add to the arsenal suggesting the latter--it found that wheezing, diagnosed asthma, and parental history of asthma were predictors of later RSV hospitalization. In this evaluation, atopic dermatitis was also investigated, and was found to be a determinant in the youngest infants.*
K. R. M.

Stensballe LG, Kristensen K, Simoes EAF, et al: Atopic disposition, wheezing, and subsequent respiratory syncytial virus hospitalization in Danish children younger than 18 months: a nested case-control study. **Pediatrics**. 2006;118:1360-1368. ♦♦

Ragweed Immunotherapy in Six Injections?

ALTHOUGH standard allergen immunotherapy is effective, alternative approaches to immunotherapy are needed to overcome problems with adverse reactions and noncompliance. One possible new approach is to conjugate immunostimulatory DNA sequences (ISS) to specific allergens. A vaccine consisting of the ragweed pollen antigen Amb a 1 conjugated to a phosphorothioate oligodeoxyribonucleotide ISS that binds to toll-like receptor 9 was evaluated in a phase 2 clinical trial.

The study included 25 adult patients with a history of seasonal allergic rhinitis with sensitization to ragweed. Patients were randomly assigned to receive the Amb a 1-immunostimulatory oligodeoxyribonucleotide conjugate (AIC) vaccine or placebo, given in six weekly injections before the fall ragweed season. Outcomes of interest included nasal provocation studies, allergic symptom scores, and specific IgE levels over two ragweed seasons.

There were no systemic reactions to the AIC vaccine and no clinically relevant laboratory abnormalities. Vascular permeability responses to nasal ragweed challenge were not significantly affected. However, AIC-treated patients had significant reductions in symptom scores during the first ragweed season, including peak-season rhinitis and daily nasal symptom scores, as well as midseason quality of life scores. Active vaccination was followed by a transient rise in Amb a 1-specific IgG antibody, but with abrogation of the expected seasonal increase in Amb a 1-specific IgE antibody. Reductions in interleukin-4-positive basophil counts were correlated with reductions in rhinitis symptom scores.

Reductions in allergy symptoms persisted through the second ragweed season. The seasonal increase in allergen-specific IgE was again suppressed, compared with the placebo group.

This preliminary clinical trial supports the effectiveness of the AIC vaccine as immunotherapy for ragweed allergy. Allergic symptoms are significantly reduced during the ragweed season after the six-injection vaccination regimen, as well as during the subsequent ragweed seasons. With further study, including research to clarify the mechanism of clinical benefit, the AIC vaccine could provide a new alternative for allergen immunotherapy.

COMMENT: *Immunotherapy, after about 100 years of clinical use, is getting quite interesting and competitive, with the recent interest in sublingual treatment and now a novel injection treatment with an adjuvant-antigen combination. An ISS was combined with ragweed antigen and given in a regimen of only six injections, resulting in significant clinical improvement (compared to placebo, but not an active control) for two seasons. This provocative study raises many questions that should be addressed in future studies (efficacy compared with active conventional immunotherapy, other possible ISS sequences, multiple antigen combinations, etc.). These are very preliminary data on very few patients, but we should hope this treatment has a fast track to success.*
R. J. M.

Creticos PS, Schroeder JT, Hamilton RG, et al: Immunotherapy with ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. **N Engl J Med**. 2006;355:1445-1455. ♦♦

PEF% and FEV_1% Are Not Interchangeable

MEASUREMENT of peak expiratory flow (PEF) is a widely used alternative to spirometry for assessing the severity of airflow limitation. Like FEV_1, PEF may be expressed as a percentage of the predicted value. However, it is unclear whether PEF% and FEV_1% are truly equivalent for use in assessing obstructive airway disease. The correlation between PEF% and FEV_1% was analyzed in a large sample of patients.

The analysis included PEF% and FEV_1% values from 6,167 adult patients showing an obstructive defect on spirometry. The tests were performed at a large tertiary referral center in India over a 6-year period. The level of correlation between PEF% and FEV_1% was ➤➤

assessed, including analysis of variables related to discrepancies between the two measurements.

There was significant variability between the PEF% and FEV_1% measurements. In one model, PEF% tended to overestimate FEV_1% when obstruction was less severe, and to underestimate it when obstruction was more severe. Across the entire study population, PEF% underestimated FEV_1% by a mean of just 0.7%--however, the limits of agreement exceeded 25% in both directions. The difference between measurements exceeded 5% in nearly three-fourths of patients, and 10% in more than half. The chances of discordance greater than 5% were higher in women than in men, odds ratio 1.26; and at higher FEV_1% values, odds ratio 1.09 per 10% increase.

This large analysis questions the equivalence of PEF% and FEV_1% for assessment of airway obstruction. Significant discrepancies are common, particularly in women and in patients with less severe obstruction. Using PEF% as a substitute for FEV_1% may lead to misclassification of airflow limitation in a large number of patients.

COMMENT: *This very large series of objective lung function measurements adds to the literature documenting variability and lack of uniform concordance between PEF and FEV_1. This highlights that (a) the use of only one measure to determine asthma control and (b) guideline classification based on equivalence of PEF and FEV_1 may be in error.*
S. F. W.

Aggarwal AN, Gupta D, Jindal SK: Relationship between FEV_1 and peak expiratory flow in patients with airways obstruction is poor.
Chest. 2006;130:1454-1461. ♦♦

Inhaled Steroids Have Early Benefits in Acute Asthma

IN patients with acute asthma exacerbations, clinical improvement after systemic corticosteroid treatment is delayed, reflecting the time needed for genomic effects of the medication to occur. Inhaled corticosteroids (ICS) have generally been considered ineffective for acute asthma exacerbations--however, several reports suggest that ICS have nongenomic effects that become apparent within minutes after administration. The author reviews available data on the early clinical effects of ICS for acute asthma.

A literature review identified 17 randomized controlled trials evaluating the early clinical effects of ICS for acute asthma management in the emergency department (ED). The studies included 663 pediatric and 470 adult patients. Study outcomes were analyzed, focusing on hospital admission and ED discharge rates within the first 1 to 4 hours after ICS administration.

Trials using multiple doses of ICS showed greater reductions in admission rate within 2 to 4 hours, odds ratio (OR) 0.30. This difference was particularly apparent when ICS were compared with placebo. Compared with either placebo or systemic corticosteroids, patients receiving ICS had faster clinical improvement, resulting in a better chance of early discharge from the ED: OR 4.70. Improvements in lung function and clinical asthma scores became significant within 1 hour after ICS administration. The latter benefits were noted only when multiple doses of ICS were given along with β-agonists.

Data from randomized trials support the early benefits of ICS for emergency treatment of acute asthma exacerbations. When ICS are given in multiple doses at intervals of 30 minutes or less over 90 to 120 minutes, clinical benefits may be realized within 1 to 2 hours. The early benefits seem to result from nongenomic effects on sympathetic control of vascular tone, reducing airway obstruction and leading to rapid improvements in clinical and spirometric outcomes.

COMMENT: *Use of inhaled corticosteroids in acute asthma is controversial. Dr. Rodrigo discriminates between genomic and nongenomic effects. This analysis suggests that early, multiple high doses of inhaled corticosteroids may exhibit nongenomic vasoconstrictor effects on mucosal blood flow and clinically decrease hospitalizations. However, the studies reviewed vary in the use of concomitant medications such as anticholinergic and beta agonists, placebo, aerosol or nebulized drug delivery, and systemic corticosteroids. Nevertheless, the data point to a new approach to our acutely ill asthmatics.*
S. W. F.

Rodrigo GJ: Rapid effects of inhaled corticosteroids in acute asthma.
Chest. 2006;130:1301-1311. ♦♦

Hospital Deaths Account for One-Third of Asthma Mortality

SEVERE asthma exacerbations are a common reason for hospitalization. There are no national estimates of the outcomes of these hospitalizations, and no data on whether the outcomes are influenced by race. A large inpatient database was used to estimate mortality among patients hospitalized for asthma exacerbations, including a comparison of outcomes for black vs white patients.

Information on patients hospitalized for asthma exacerbations in 2000 was obtained from the Agency for Healthcare Research and Quality's Nationwide Inpatient Sample. The analysis included data on 65,381 asthma admissions in patients aged 5 years or older. Hospital mortality was the main outcome of interest; length of hospital stay and total hospital charges were analyzed as well.

Overall in-hospital mortality among patients admitted for asthma was 0.5%. The mean length of stay was 2.7 days, with charges of $9,078. Hospital deaths were estimated to account for one-third of asthma deaths in the United States during 2000.

More than three-fourths of the deaths occurred in patients aged 35 years or older. Mortality was not significantly different by geographic region or hospital characteristics. Mortality was higher for white patients than for black patients, 0.6% vs 0.3%, respectively. However, race was not a significant factor on multi-➤➤

variate analysis.

Hospital deaths account for a substantial proportion of all U.S. deaths from asthma. Deaths among hospitalized patients cannot explain the excess mortality among black patients with asthma. The findings will be useful in comparing asthma outcomes across hospitals, and as a baseline for improvements in inpatient management. Changes in prehospital management of asthma exacerbations are likely to have the greatest impact in reducing asthma mortality and correcting racial disparities in risk of asthma death.

COMMENT: *In patients who die from asthma, death occurs before arrival at the hospital in two-thirds of cases. These data continue to support the need for explicit home-based asthma action plans to abort life-threatening or fatal events.*
B. E. C.
Krishnan V, Diette GB, Rand CS, et al: Mortality in patients hospitalized for asthma exacerbations in the United States.
Am J Respir Crit Care Med. 2006;174:633-638. ♦♦

Symbicort Reduces Inflammation in Mild Intermittent Asthma

CURRENT guidelines for the management of mild intermittent asthma call for as-needed rapid-acting β_2-agonist treatment only, with no regular controller medication. However, some of these patients have signs of airway inflammation, suggesting a possible benefit of anti-inflammatory therapy. The benefits of adding an inhaled corticosteroid to as-needed β_2-agonist therapy for mild intermittent asthma were evaluated.

The randomized controlled trial included 92 nonsmoking adults with mild intermittent asthma who were currently using only as-needed β_2-agonist therapy. The patients were 64 women and 28 men, mean age 37 years and mean FEV_1 101% of predicted. All had a fractional exhaled nitric oxide (FeNO) concentration of 20 ppb or higher. Patients were assigned to one of two as-needed treatments: formoterol 4.5 µg (Oxis) or budesonide/formoterol 160/4.5 µg (Symbicort). Both medications were administered via Turbuhaler; treatment continued for 24 weeks.

Patients receiving as-needed budesonide/formoterol had a greater reduction in FeNO, the main efficacy outcome. From a baseline mean of about 60 ppb, FeNO decreased by 18.2 ppb in the budesonide/formoterol group compared to 2.8 ppb with formoterol only. With the combination treatment, most of the reduction in FeNO occurred in the first 4 weeks. In the budesonide/formoterol group, mean FEV_1 increased by 1.8% of predicted normal, compared with a decrease of 0.9% predicted normal in the formoterol group. Patients using the combination therapy also had fewer days in which they required four or more inhalations: 21 vs 74 days, respectively.

The combination of budesonide and formoterol, used on an as-needed basis, is an effective treatment option for patients with mild intermittent asthma and evidence of airway inflammation. This treatment may address both obstruction and the underlying inflammation. The long-term outcomes of this approach are unclear.

COMMENT: *With the approval of Symbicort, this study gives more support to the use of formoterol and budesonide, as both a regularly scheduled and as-needed strategy. This indication is approved in Europe and enjoys wide acceptance.*
B. E. C.
Haahtela T, Tamminen K, Malmberg LP, et al: Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: a SOMA study.
Eur Respir J. 2006;28:748-755. ♦♦

Antifungal Nasal Lavages Don't Help in CRS

CHRONIC rhinosinusitis (CRS) is a common problem of uncertain pathogenesis. Some reports have suggested that an exaggerated immune response to fungi may play a role in this condition, and thus that treatment with intranasal amphotericin B might be beneficial. A randomized, placebo-controlled trial evaluated the effectiveness of amphotericin B nasal lavage for CRS.

The multicenter trial included a random sample of 116 patients with CRS, with or without nasal polyps. One group was assigned to use amphotericin B nasal lavages: 25 mL of a 100 µg/L solution, instilled in each nostril twice daily for 3 months. Controls received placebo nasal lavages. The main outcomes of interest were change in total visual analog scale (VAS) score and nasal endoscopy score at the end of treatment.

The two groups had similar baseline characteristics. At the end of treatment, there was no significant difference between groups in VAS score, total or individual; or in nasal endoscopy score. Secondary outcomes were also similar between groups, including nasal inspiratory flow, polyp score, and quality of life measures. Subgroup analyses also showed no significant difference in outcomes, including for patients with documented allergy to fungi.

For patients with CRS, 13 weeks of treatment with amphotericin B nasal lavages yields no clinical improvement, compared with placebo lavage. The findings question the pathophysiologic significance of upper airway fungi in CRS.

COMMENT: *It has been suggested that the treatment of CRS should include topical antifungals, particularly amphotericin B. In this carefully designed and controlled multicenter European study, the researchers found that there was no benefit to the use of amphotericin B for CRS. No one disputes that fungi are found in patients with CRS, but the usefulness of antifungal therapy has been questioned. These authors suggest that the fungi are merely "innocent bystanders" and not pathogens.*
S. M. F.
Ebbens FA, Scadding GK, Badia L: Amphotericin B nasal lavages: not a solution for patients with chronic rhinosinusitis.
J Allergy Clin Immunol. 2006;118:1149-1156. ♦♦

Home *Alternaria* Levels Linked to Asthma Symptoms

EXPOSURE to *Alternaria alternata* is a recognized risk factor for asthma. However, there are few data on indoor exposure to this fungus. Data from a national housing study were used to analyze the relationship between indoor *A. alternata* exposure and asthma.

The analysis included cross-sectional data on a nationally representative sample of 831 housing units across the United States, including information on 2,456 inhabitants. Levels of *A. alternata* antigen were measured in dust samples collected from various rooms in each home. Asthma-related symptoms and other health measures were assessed using an interviewer-administered questionnaire.

Overall, 12.9% of the subjects had ever received a physician's diagnosis of asthma, while 6.9% reported asthma symptoms during the past year. Detectable levels of *A. alternata* were measured in almost every location sampled--levels were highest in living rooms and lowest in bedrooms.

As the level of *A. alternata* antigen in the home increased, so did the prevalence of current asthma symptoms. The adjusted odds ratio for asthma symptoms in the past year was 1.84 for subjects living in homes in the highest tertile of *A. alternata* level, compared with the lowest tertile. For homes in the middle tertile, the odds ratio was 1.52. Use of asthma medications was also related to *A. alternata* level. There was no apparent relationship with hay fever or other allergy diagnoses.

Exposure to *A. alternata* in U.S. homes is significantly associated with current asthma symptoms. The results suggest that regular home cleaning to prevent mold and other moisture-related problems may have health benefits for patients with asthma.

COMMENT: *The National Survey of Lead and Allergens in Housing measured various allergens collected from a sampling of 831 homes. Using nonparametric regression analysis, these authors demonstrated that higher levels of* Alternaria *mold were associated with increased risk of having doctor-diagnosed asthma. The report was not able to assess seasonal changes in mold levels. Interestingly, there was no association with hay fever. The bottom line is that household mold continues to be associated with respiratory conditions. We should continue to help our patients with sound advice to reduce mold levels in their homes.*
S. M. F.

Salo PM, Arbes SJ, Sever M, et al: Exposure to Alternaria alternata *in US homes is associated with asthma symptoms.*
J Allergy Clin Immunol. 2006;892-898. ♦♦

Arg16Gly Genotype Doesn't Affect Response to Salmeterol/Fluticasone

SOME reports have suggested genetic variation in responses to asthma drugs--specifically, that patients homozygous for arginine at codon 16 of the β-receptor may have worsening asthma in response to albuterol. The possible effects of this Arg/Arg genotype on responses to long-acting β_2-agonists are unknown. The effects of variation in the β_2-adrenergic receptor gene (*ADRB2*) on clinical responses to salmeterol and fluticasone propionate were analyzed.

The analysis included data from two large randomized trials, both of which included *ADRB2* genotyping. A total of 183 patients with persistent asthma were randomly assigned to twice-daily single-inhaler therapy with salmeterol 50 µg plus fluticasone propionate 100 µg; or once-daily montelukast. Treatment continued for 12 weeks, followed by a 2- to 4-day run-out period. Differences in response to salmeterol/fluticasone were analyzed in terms of Arg16Gly genotype, including clinical stability during withdrawal of therapy.

Twenty-nine patients had the Arg/Arg genotype, while 89 had Arg/Gly and 65 had Gly/Gly. In all three genotype groups, treatment with salmeterol was associated with significant and lasting improvement in measures of asthma control. Mean improvements in morning peak expiratory flow were 89.0 L/min in Arg/Arg patients, 93.7 L/min in the Gly/Gly group, and 92.5 in the Arg/Gly group. Pairwise changes were similar across the three genotypes, and there was no apparent modifying effect of haplotype pairs. There were also no genotype differences in loss of asthma control after withdrawal of treatment.

For patients with persistent asthma, genetic variation in *ADRB2* does not significantly affect the clinical response to treatment with the long-acting β-agonist salmeterol plus the inhaled corticosteroid fluticasone. Across Arg16Gly genotypes--including the Arg/Arg group--this combination treatment produces significant and sustained improvements in asthma control.

COMMENTS: *Patients who are homozygous for Arg/Arg on codon 16 have been reported to have a reduction in lung function with chronic use of β-agonists. This is in contrast to the more common Arg/Gly or Gly/Gly haplotypes. Using genetic data from two previously reported pharmaceutical trials, these authors report that 12 weeks of treatment with salmeterol and fluticasone had no significant detrimental effect on asthmatics, regardless of their β-adrenergic receptor genetic coding. Weaknesses include the sample size, study design, severity of asthma in the population and the relatively short duration of treatment. Although the data are reassuring, the question of the safety of chronic use of β-agonists in asthmatics with the Arg/Arg genotype remains unanswered.*
S. M. F.

Bleeker ER, Yancey SW, Baltinger LA, et al: Salmeterol response is not affected by β_2-adrenergic receptor genotype in subjects with persistent asthma.
J Allergy Clin Immunol. 2006;118:809-816. ♦♦

Genetics Explain Most Atopic Disease Correlations in Twins

STUDIES in identical twins support the hypothesis that genetic factors contribute to atopic disease. However, environmental causes clearly play a role as well. Most twin studies of atopic disease have focused on self-reported measures of atopic disease and have not included multivariate analysis. This study analyzed multiple clinical and objective atopic disease traits to assess genetic and environmental contributors to atopic disease among twins.

From more than 21,000 subjects enrolled in the Danish Twin Registry, the investigators identified 575 twins, aged 20 to 49 years, in which at least one member of the pair had self-reported asthma. Data on wheezing and rhinitis, were obtained through interviews; airway responsiveness and skin test reactivity were assessed at clinical examination. Multivariate analysis, including estimates of correlations in liability and variance components analysis, was performed to examine the extent of genetic and environmental sharing between these atopic disease traits.

There were significant phenotypic correlations between all four traits, ranging from 0.50 to 0.86. Genetic correlations were strongest for wheezing-rhinitis and rhinitis-skin test reactivity, weaker for wheezing-airway responsiveness and rhinitis-skin test reactivity. Environment correlation was strong for rhinitis-skin test reactivity and wheezing-skin test reactivity, weaker for wheezing-rhinitis. The correlations remained significant after correction for ascertainment and adjustment for age and sex, inhaled corticosteroid therapy, and smoking. In general, about three-fourths of the phenotypic correlation between traits was ascribed to shared genetic factors and one-fourth to environmental factors.

The findings of this twin study support a common genetic basis for various atopic disease traits. Upper and lower respiratory allergy symptoms may be differing phenotypic manifestations of a shared set of genes. The results lend new insight into the clinical variation of atopic disease, and may help guide the search for pleiotropic genes affecting the risk of such diseases.

COMMENT: *In recent years, twin studies have taken a back seat to the direct molecular study of DNA in order to answer gene vs environment questions in asthma. This has resulted in the discovery of numerous candidate asthma genes, but has really not improved on taking an old-fashioned clinical and family history when it comes to predicting an individualís risk of developing asthma. Using a clever statistical approach, the authors of this adult twin study were able to show a high correlation between wheezing, rhinitis, airway hyperresponsiveness, and positive skin tests. These correlations appear to be due more to genetic than environmental factors. As pointed out in the accompanying editorial (*Clin Exp Allergy. *2006;36:1353-1354), this study demonstrates how twin studies can be used to make a significant contribution to future research into* the genetics of asthma.
S. A. T.

Thomsen SF, Ulrik CS, Kyvik KO, et al: Multivariate genetic analysis of atopy phenotypes in a selected sample of twins. **Clin Exp Allergy**. 2006;1382-1389. ♦♦

Preoperative Allergy Evaluation Reduces Vancomycin Use

WHEN skin testing is unavailable, patients with a history of penicillin allergy commonly receive prophylactic vancomycin before surgery. The emergence of vancomycin-resistant enterococci raises concerns about this practice. The results of a clinical pathway to reduce the use of preoperative vancomycin in patients with a history of penicillin allergy are reported.

The clinical pathway for patients with self-reported allergy to penicillin was established in the preoperative evaluation clinic of the authors' medical center. Of 11,819 patients seen at the clinic over a 14.5-month period, 1,204 underwent evaluation for penicillin or cephalosporin allergy. The current analysis included 1,111 consenting patients with available data.

Penicillin skin testing was performed in 93% of patients--the rate of positive skin tests was 4%. After allergy evaluation, β-lactam use was recommended for 85% of patients with a self-reported history of allergy to these antibiotics. In the remaining 15%, β-lactam avoidance was recommended. Of 955 patients who went on to receive prophylactic antibiotics, 75% received cefazolin while 16% received vancomycin. This was significantly lower than the 30% rate of preoperative vancomycin treatment in a historical control group.

Of 675 patients who had a negative penicillin skin test but received prophylactic cephalosporin treatment, 5 had probable adverse drug reactions--a rate of 0.7%. None of the reactions was serious.

A clinical pathway for patients with self-reported penicillin allergy can significantly reduce the use of prophylactic vancomycin in surgical patients. Penicillin skin tests are negative in more than 90% of patients; those who go on to receive preoperative cephalosporins are at low risk of adverse reactions. The unavailability of major and minor determinants currently limits the use of preoperative allergy evaluation.

COMMENT: *This article demonstrates the value of allergy/immunology expertise in preoperative evaluations. Drug allergy is an area in which we can increase our visibility among other specialists and among hospital-based physicians. The major drawback is that an allergist in practice does not have access to the major determinant and minor determinant mixtures, reducing our effectiveness in antibiotic testing. Nonetheless, quoting this article is an excellent way to accentuate the value of allergy/immunology expertise.*
D. K. L.
Park M, Markus P, Matesic D, Li JTC: Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy.
Ann Allergy Asthma Immunol. 2006;97:681-687. ♦♦

Leukotriene Modifiers Make Oral Aspirin Challenges Safer

ASPIRIN-exacerbated respiratory disease (AERD) is an underappreciated problem that can be treated by aspirin desensitization, including daily aspirin treatment. However, serious asthmatic reactions are possible even with low doses of aspirin. Recent studies have suggested that pretreatment with leukotriene modifier drugs may help to prevent reactions in patients taking oral aspirin challenges. This retrospective study evaluated the effects of leukotriene modifiers and other controller medications on the safety of oral aspirin challenges in patients with AERD.

The investigators reviewed the records of 676 patients with AERD who underwent oral aspirin challenges followed by aspirin desensitization between 1981 and 2004. Controller medications taken during aspirin challenges included inhaled corticosteroids in 513 patients, systemic corticosteroids in 274, leukotriene modifier drugs (most commonly montelukast) in 260, and long-acting bronchodilators in 123. Seventy-two patients took no controller medications. The effects of type of controller medication on severity of asthmatic reactions were analyzed.

The percentage of patients experiencing more than a 20% reduction in FEV_1 during oral aspirin challenge was 17.7% among those taking leukotriene modifiers, compared with 38.6% in those not taking these controller medications. Leukotriene modifier drugs reduced the degree of asthmatic reactions whether or not the patients were taking systemic corticosteroids. When leukotriene modifiers were added to systemic corticosteroids, there was a significant shift toward milder asthmatic reactions. Sample sizes were too small to assess the effects of leukotriene modifiers alone.

Leukotriene modifier drugs have a bronchoprotective effect in patients with AERD undergoing oral aspirin challenge. Although other controller medications can help to stabilize the airways, only leukotriene modifiers lead to a significant reduction in the severity of asthmatic reactions. Such protective pretreatment makes outpatient oral aspirin challenges a viable option for properly selected patients.

COMMENT: *The subset of subjects with airway disease and aspirin sensitivity tends to be a treatment challenge. This group of senior investigators has added immeasurably to our understanding of aspirin-induced respiratory disease and the potential value of aspirin desensitization. Pretreatment with leukotriene inhibitors provides a safety advantage if aspirin challenge is to be considered, but 17% of individuals pretreated with both a LTD4 receptor antagonist and zileuton experienced a 20% decrease in FEV_1 during challenge. We currently offer our patients outpatient aspirin desensitization in a clinic that is not within a hospital. However, this decision requires thorough knowledge of the risks and benefits and the capabilities of assessing and treating severe asthma. Look before you leap into aspirin desensitization.*
D. K. L.

White A, Ludington E, Mehra P, et al: Effect of leukotriene modifier drugs on the safety of oral aspirin challenges.
Ann Allergy Asthma Immunol. 2006;97:688-693. ♦♦

Formaldehyde Exposure Increases Bronchial Responses to Mite Allergen

IT has been demonstrated that co-exposure to outdoor air pollutants such as ozone can enhance the effect of allergen exposure. Indoor exposures may include an array of chemical irritants and biologic pollutants such as microorganisms, nitrogen oxides, and volatile organic compounds. Formaldehyde exposure may occur from materials or furnishings, as well as in laboratory workers or forensic physicians and employees. It has been suggested that formaldehyde may increase the risk of childhood asthma.

This double-blind French study assessed the effect of standardized exposure to low levels of formaldehyde on airway response to *Dermatophagoides pteronyssinus* in 19 patients with mild asthma, aged 19 to 35 years. Immediately after standardized exposure to formaldehyde or air in a chamber, each patient underwent bronchial challenge with mite allergen. At 24 hours before and after mite challenge, induced sputum was collected 24 hours for measurement of eosinophil cationic protein (ECP). Domestic exposure to Der p 1 in mattress and floor dust was evaluated by a standard enzyme-linked immunosorbent assay.

After formaldehyde exposure, patients developed an immediate bronchial response at a significantly lower dose of mite allergen than after air exposure. The late-phase FEV_1 response was also significantly higher after formaldehyde exposure. There was a trend toward higher sputum ECP at 24 hours after formaldehyde exposure, as well as a greater increase in blood eosinophils at 3 and 6 hours after allergen challenge.

In asthmatic patients sensitized to dust mite, low-level formaldehyde exposure increases bronchial responsiveness to mite allergen challenge. A ubiquitous indoor air pollutant, formaldehyde may be among the factors affecting asthma severity.

COMMENT: *This novel study demonstrated that exposure to low levels of formaldehyde enhanced bronchial responsiveness to mite allergen in mite-sensitized asthmatics. This observation is of importance, especially in early-life exposure, which can progress into adolescence and adulthood and possibly contribute to remodeling in a small subset of patients. Of interest, studies have also shown that formaldehyde exposure enhances eosinophilic airway inflammation by increasing interluekin-5 and RANTES.*
M. F.
Casset A, Marchand C, Purohit A, et al: Inhaled formaldehyde exposure: effect on bronchial response to mite allergen in sensitized asthma patients.
Allergy. 2006 61:1344-1350. ♦♦

T-Cell Activation and Blocking Antibodies in Specific Allergen Immunotherapy

UNDERSTANDING of the immunologic mechanisms of specific allergen immunotherapy (SIT) has advanced dramatically since the institution of this immunomodulatory treatment for allergic disease. The authors of this review from the Netherlands and Denmark elegantly summarize the current knowledge and clinical relevance of blocking IgG antibodies induced by SIT and anti-IgE monoclonal antibodies that interfere with IgE-mediated allergen presentation.

The authors discuss the relevance of allergen presentation in Th2 activation and the role of CD23, which can be internalized and transports IgE into the antigen-processing pathway, followed by MHC class II presentation. They define the role of FcεRI, expressed by Langerhans cells and present on monocytes and dendritic cells, along with the role of anti-IgE therapy. Thus the clinical effect of anti-IgE therapy results not only from decreasing peripheral blood IgE levels, but also indirectly from down-regulation of FcεR1 surface expression.

The authors review the immunologic effects of SIT involving the shift from Th2 to Th1, a reduction in T-cell activation as a result of inhibitory cytokines (interleukin-10 and transforming growth factor-β) by regulatory T cells, and inhibition of basophil and mast cell degranulation by blocking antibodies. Finally, the therapeutic use of blocking antibodies for seasonal allergy treatment is discussed.

COMMENT: *This excellent review should be read to understand the progress, efficacy and complexity of SIT, our major immunomodulatory treatment. New and novel diagnostic methods may be developed in the future, leading to better monitoring of the clinical status of our allergic patients.*
M. F.
van Neerven RJJ, Knol EF, Ejrnaes A, Würtzen PA: IgE-mediated allergen presentation and blocking antibodies: regulation of T cell activation in allergy.
Int Arch Allergy Immunol. 2006;141:119-129. ♦♦

CLINICAL TIDBITS

No Link Between Very Low IgE and CRS

A FEW reports have described increased rates of chronic rhinosinusitis (CRS) and chronic lung disease in patients with very low IgE levels--below the detection limit of commercial assays. The link between IgE deficiency and CRS was investigated in a sample of 626 pregnant women. On a standard assay, 34% of women had total serum IgE levels below the level of detection: 2.0 IU/mL. On re-evaluation using a more sensitive assay with a detection limit of 0.02 IU/mL, detectable levels of IgE were found in 20 of 21 samples--geometric mean level 1.2 IU/mL. None of the women with very low levels of IgE had sinusitis, compared to 19% of those with levels of 2.0 IU/mL or higher. Reported hay fever symptoms were more common in the low-IgE group, but diagnosed hay fever was less common. Very low IgE levels are common in pregnant women, but do not seem to be associated with CRS.

COMMENT: *The importance of this paper is the additional reassurance that low IgE levels are not associated with an increase in upper respiratory disease, as has been shown in other publications. The use of omalizumab does not lower IgE levels to the degree identified in this study, but it is reassuring to me that decreased IgE was not associated with pathology. It would be helpful if these investigators would follow this cohort of women to verify that there is no increased risk of malignancy.*
D. K. L.
Levin TA, Ownby DR, Smith PH, et al: Relationship between extremely low total serum IgE levels and rhinosinusitis.
Ann Allergy Asthma Immunol. 2006;97:650-652. ♦♦

Does Pretreatment Prevent Repeat Reactions to RCM?

FOR patients with a history of reactions to iodinated radiocontrast media (RCM), current guidelines call for drug pretreatment to prevent repeated reactions. A systemic review identified nine randomized, placebo-controlled trials of pretreatment for patients with previous reactions to RCM. The studies included a total of 10,011 adult patients. Various pretreatment strategies reduced the risk of serious reactions--however, reactions were rare with or without pretreatment. For example, data on 3,093 patients from trials evaluating oral methylprednisolone showed a 0.2% rate of serious reactions with pretreatment vs 0.9% with placebo--odds ratio 0.28. Although the review supports continued pretreatment, the authors note the deficiencies of research in this area, including a lack of studies focusing on patients with a history of allergic reactions.

COMMENT: *Current practice recommends that patients with a history of reaction following RCM administration be pretreated before their next procedure. This meta-analysis of nine trials reviews the efficacy of pretreatment to prevent systemic reactions following the use of RCM. Although the final conclusion favored pretreatment, there was a paucity of good data, and the authors point out that the usefulness of pretreatment may be doubtful in certain patients. The bottom line is that, although we may not have strong data, we should continue to pretreat those patients at potential risk.*
S. M. F.
Tramér MR, von Elm E, Loubeyre P, Hauser C: Pharmacological prevention of serious anaphylactic reactions to iodinated contrast media: systematic review.
BMJ. 2006;333:675. ♦♦

Small Airway Changes Persist After Allergen Challenge

LITTLE is known about the contribution of the small airways--ie, diameter less than 2 µm--to late asthmatic reactions to allergen. Ten patients with cat-induced asthma underwent pulmonary function studies and high-resolution CT (HRCT) scans before and after naturalistic exposure to cat allergen in a "cat room." There was no significant reduction in FEV_1 at 6 or 23 hours after allergen exposure. Forced expiratory flow at 25% to 75% of forced vital capacity was reduced at 6 hours, but normalized by 23 hours. However, the HRCT scans and closing volume studies showed increased air trapping at both times. On image analysis, the small airways showed significant hyperresponsiveness to methacholine challenge at 23 hours. In cat-allergic asthma patients, exposure to cat allergen causes long-lasting obstruction and hyperresponsiveness of the small airways, which are not detected by conventional physiologic studies.

COMMENT: *Using HRCT, these researchers found that the smaller, distal airways in the lungs of allergic asthmatics had significant obstruction at both 6 and 23 hours after cat allergen challenge. Most interestingly, these smaller airway changes could not be detected by conventional pulmonary function studies. The fact that prolonged inflammatory changes persist in the airways after allergen challenge is of potential clinical significance.*
S. M. F.
Zeidler MR, Goldin JG, Kleerup EC, et al: Small airways response to naturalistic cat allergen exposure in subjects with asthma.
J Allergy Clin Immunol. 2006;118:1075-1081. ♦♦

Patients with Shrimp Allergy Can Take Glucosamine

THE nutritional supplement glucosamine, widely used by patients with arthritis, is sometimes made from the shells of crustaceans. Fifteen patients with documented shrimp allergy underwent double-blind, placebo-controlled food challenges using shrimp-derived or synthetic glucosamine. The glucosamine dose of 1,500 mg was similar to that recommended for therapeutic use. All patients tolerated both forms of glucosamine--there were no immediate hypersensitivity responses and no changes in peak flow or blood pressure. Up to 24 hours after challenge, no delayed reactions occurred. At least for the commercial preparation tested in this study, glucosamine supplements derived from shellfish appear do not appear to cause reactions in shrimp-allergic subjects.

COMMENT: *Glucosamine is commonly manufactured using the shells of crustaceans. Its widespread use as a dietary supplement has led to concern regarding the possibility of anaphylactic reactions in patients with shellfish allergy. In this study, patients with IgE-mediated shrimp allergy were able to tolerate therapeutic doses of shrimp-derived glucosamine without developing symptoms. These data are reassuring, although it is still unclear whether all commercially available glucosamine products are devoid of shellfish allergen contamination.*
S. A. T.
Villacis J, Rice TR, Bucci LR: Do shrimp-allergic individuals tolerate shrimp-derived glucosamine?
Clin Exp Allergy. 2006;36:1457-1461. ♦♦

How Does CVID Present in Children?

SYMPTOMS of common variable immunodeficiency (CVID) most often develop in the second and third decades of life, but can also appear in childhood. Records of 12 patients diagnosed with CVID before age 18. The patients were seen at one immunology clinic between 1992 and 2005. Average age at presentation was 8; two-thirds of the patients were boys. The patients had low IgG levels and poor functional antibody responses. Sinusitis, otitis media, and pneumonia were the most frequent presenting infections. Three patients had bronchiectasis, while two had failure to thrive. Most had asthma, but this diagnosis was usually made later. The wide range of accompanying diseases included autoimmune disorders, growth hormone deficiency, hypothyroidism, end-stage renal disease, and sarcoma. The findings highlight the variable presentation and diagnostic difficulties of pediatric CVID.

COMMENT: *While clinicians frequently consider CVID as an adult disease, it clearly can present in childhood. Most children present, like adults, with recurrent sinopulmonary infection. However, CVID should be considered in children who present with autoimmune disease, malignancy, or failure to thrive and a history of recurrent infection.*
A. M.
Ogershok PR, Hogan MB, Welch JE, et.al.: Spectrum of illness in pediatric common variable immunodeficiency.
Ann Allergy Asthma Immunol. 2006;98:653-656. ♦♦

REVIEWS OF NOTE

COMMENT: *An epidemiologic study of a syndrome is very difficult when the syndrome is often difficult to diagnose and transient. The problems of such a review are discussed in this paper. Useful information is provided despite the limitations. Allergists/immunologists should communicate these observations to the public and to other physicians and health care providers. Additional research is needed, although the possibilities of controlled trials are limited.*
D. K. L.
Lieberman P, Camargo CA Jr, Bohlke K, et al: Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group.
Ann Allergy Asthma Immunol. 2006;97:596-602. ♦♦

COMMENT: *This is a concise (7-page) review of what is known, and not known, about the reported increase in worldwide prevalence of asthma. Although allergists will find little that is new in this article, it does emphasize the often-conflicting data on prevalence, causation, and prevention of this condition, which has so many issues with definitions, phenotype variability, and confounding environmental variables. We have a lot to learn about asthma.*
R. J. M.
Eder W, Ege MJ, von Mutius E: The asthma epidemic.
N Engl J Med. 2006; 355:2226-2235. ♦♦

COMMENT: This is an excellent summary of the positive and negative effects of the R and S isomer of albuterol, presented in a "Pro/Con" format.
B. E. C.
Ameredes BT, Calhoun WJ: (R)-Albuterol for asthma: pro [a.k.a (S)-albuterol for asthma: con].
Am J Respir Crit Care Med. 2006;174:965-974. ♦♦

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