AllergyWatch®

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

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¡Viva la Diferencia!

ASTHMA prevalence, morbidity, and mortality vary significantly among U.S. ethnic groups. Puerto Ricans have a fourfold higher asthma burden than Mexicans. One possible explanation for this disparity is genetic variation in the β_2-adrenergic receptor (β_2-AR). Mexican and Puerto Rican asthma patients were compared for β_2-AR genotype and responsiveness to albuterol.

The analysis included 667 probands with asthma--393 Puerto Rican and 274 Mexican--and their parents. All subjects underwent genotyping studies for eight single nucleotide polymorphisms of β_2-AR. Interactions among β_2-AR genotype, disease severity, and responsiveness to albuterol were assessed.

In Puerto Rican subjects, both family-based and cross-sectional analyses found a significant association between increased responsiveness to albuterol and the arginine 16 allele of β_2-AR. There was a significant interaction between the arginine 16 glycine (Arg16Gly) polymorphism and bronchodilator response. For Puerto Rican asthmatics with a baseline FEV_1 of less than 80% predicted, an Arg16 genotype was very strongly related to increased responsiveness to albuterol. For Mexican subjects with asthma, Arg16Gly was unrelated to albuterol responsiveness.

The Arg16 allele of the β_2-AR appears to predispose to more severe asthma in Puerto Ricans, but not in Mexicans. This represents an ethnic-specific pharmacogenetic difference, affecting asthma severity and responsiveness to the most widely used medication for asthma. The results lend new insights into the significant disparities in asthma burden among two Latino ethnic groups.

COMMENT: *It is clear that different people respond differently to the same medication. Many reasons have been advanced for this disparity, most recently genetic based. If specific populations could be identified who would be differentially responsive to pharmacotherapy, this would potentially allow more focused therapeutic decisions. This paper studied two distinct ethnic Hispanic populations with differing asthma* ➤➤

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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

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prevalence, morbidity, and mortality rates and looked at genetic differences at the single nucleotide polymorphism level of the β_2-adrenergic receptor. Results showed an association with asthma severity and responsiveness to bronchodilators in the Puerto Rican (more severe) but not Mexican asthma population. Such data further support the need for new pharmacotherapy research to include racial/ethnic and genetic differences in study design.
G. D. M.
Choudrhy S, Ung N, Avila PC, et al: Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with Asthma.
Am J Respir Crit Care Med. 2005;171:563-570. ♦♦

Acetaminophen: Not So Benign After All

SEVERAL different maternal exposures carry an increased risk of asthma and atopy in offspring. In a previous study, the authors reported an increased rate of early wheezing in children born to women who frequently took acetaminophen late in pregnancy. The effects of prenatal acetaminophen exposure on asthma, wheezing, and other atopic outcomes at age 6 to 7 were assessed.

The analysis included data on mothers and children enrolled in the prospective, population-based Avon Longitudinal Study of Parents and Children. The mothers provided information on their use of acetaminophen at aspirin during late pregnancy--from 20 to 32 weeks. Associations with atopy and allergic disease outcomes at age 6 to 7 were assessed by logistic and linear regression analysis.

Asthma was significantly more likely for children whose mothers took acetaminophen during late pregnancy. Odds ratios were 1.22 for "sometimes" use of acetaminophen and 1.62 for "most days/daily" use, compared with no use. Significant associations with wheezing and total IgE were noted as well. If the association were a causal one, 7% of childhood asthma would be attributable to maternal use of acetaminophen during late pregnancy.

Taking acetaminophen during late pregnancy may increase the risk of childhood asthma and wheezing. Prenatal acetaminophen exposure may influence pulmonary and immune system development, with clinical manifestations occurring later in childhood as "new wheezing." Even a small association could have a large impact, as many mothers use acetaminophen at least occasionally during the last weeks of pregnancy.

COMMENT: *Acetaminophen use late in pregnancy has been previously shown to be associated with wheezing of the offspring early in life. This prospective population-based study found that wheezing was more prevalent in 7-year-olds whose mothers took acetaminophen late in their pregnancies. The total IgE level was also higher in this group. Perhaps we should be counseling mothers to avoid acetaminophen during pregnancy.*
S. A. T.
Shaheen SO, Newson RB, Henderson AJ, et al: Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood.
Clin Exp Allergy. 2005;35:18-25. ♦♦

Beta-Blockers: Worth Considering with Venom IT

BETA-blockers (BBs) have been linked to severe or difficult-to-treat anaphylaxis, and so are regarded as contraindicated in patients who ➤➤

have a history of anaphylaxis or are receiving specific allergen immunotherapy. The authors recently reported a patient who died of ventricular fibrillation during *Vespula* venom immunotherapy (VIT) after her BB therapy was withdrawn. The safety and outcomes of continuing BB treatment during *Hymenoptera* VIT were analyzed.

Of 1,389 patients for whom *Hymenoptera* VIT was recommended, 11.2% either had cardiovascular disease or were taking BBs. Mean age in this subgroup was 53 years, compared to 35 years in the overall experience. In most patients who were taking BBs before VIT, the medication was replaced by another drug. However, the risks of stopping BB treatment were considered too high in 4 patients, while another 9 were restarted on BBs after reaching their maintenance dose. Another 12 patients started BB therapy during VIT.

Among the 25 patients taking BBs during VIT, the rate of allergic side effects during VIT was just 3%. This was nonsignificantly lower than the 16.7% rate among patients with cardiovascular disease who were not taking BBs. For patients re-exposed to *Hymenoptera* stings after VIT, systemic allergic symptoms developed in 14.3% of those who received BBs during treatment and 13.8% of those who did not.

A significant percentage of patients receiving *Hymenoptera* VIT have cardiovascular disease and/or are receiving BBs. This retrospective study suggests that, at least in some patients, BB therapy can be safely continued during VIT. The authors believe that the contraindication for BB treatment during VIT should be considered relative rather than absolute.

COMMENT: *These Swiss researchers analyzed their venom-allergic patients to determine the risk of concomitant use of beta-blockade with VIT. Of the 1,398 patients in their institution who received VIT, 11.2% had cardiovascular disease. A total of 25 patients ended up receiving BB and VIT simultaneously. Interestingly, the percentage of patients having systemic allergic reactions to both VIT and repeat stings was similar in patients either with or without BB. The Practice Parameters state that BB therapy should be considered a relative contraindication for immunotherapy. These data suggest that BB should not be withheld in our venom-allergic patients with cardiovascular disease.*
S. M. F.

Müller UR, Haeberli G: Use of beta-blockers during immunotherapy for Hymenoptera *venom allergy.*
J Allergy Clin Immunol. 2005;15:606-610. ♦♦

Asthma Therapy Should Be Individualized

RESPONSES to asthma control medications--including inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRAs)--vary significantly between patients. Data from the Childhood Asthma Research and Education Network were used to assess variability in response to ICS and LTRAs.

The analysis included 126 children, aged 6 to 17 years, with mild to moderate persistent asthma. Patients were randomized to receive one of two crossover sequences of asthma control medications, with each sequence including 8 weeks on fluticasone propionate, 100 µg twice daily, and 8 weeks of montelukast, 5 to 10 mg/d. The study definition of response was at least a 7.5% improvement in FEV_1. Predictors of response to each medication were analyzed.

Mean percentage of improvement in FEV_1 was 6.8% with fluticasone and 1.9% with montelukast. Fifty-five percent of patients did not meet the study definition of response to either medication. Twenty-three percent responded to fluticasone alone, 5% to montelukast alone, and 17% to both. Factors associated with a better response to fluticasone included higher values for exhaled nitric oxide, total eosinophil count, eosinophil cationic protein, and IgE. Factors associated with response to montelukast alone included younger age and shorter duration of asthma.

In children with persistent asthma, responses to ICS and LTRAs vary substantially. Treatment should consist of ICS for children with low pulmonary function measures or high markers of allergic inflammation. Others should be started on either ICS or LTRA, followed by assessment of response.

COMMENT: *The NHLBI Childhood Asthma Research and Education (CARE) Network report data from their research on children with chronic mild-moderate persistent asthma. Of the 126 children aged 6 to 17 years who completed this prospective, double-blind, crossover study, 45% had improvement in FEV_1 at least 7.5% with either inhaled fluticasone or oral montelukast or both. The most interesting analysis is the variability in pulmonary responses to the two treatment regimens. The authors suggest that patients with lower pulmonary function and methacholine PC20 values and higher exhaled nitric oxide and other markers of inflammation respond better to fluticasone. The group responding to montelukast alone was younger, had a shorter duration of asthma, and had lower pulmonary function and higher urinary leukotriene levels than those not responding to either controller. The main limitation of the study was that only one pulmonary function measurement was used at the 8-week point in each treatment period. The bottom line is that asthma therapy should be individualized. Although population-based studies are essential, we really have to focus on the outcomes of each patient.*
S. M. F.

Sfezler SJ, Phillips BR, Martinez FD, et al: Characterization of within-subject responses to fluticasone and montelukast in childhood asthma.
J Allergy Clin Immunol. 2005;15:233-242. ♦♦

Look Before You Leap!

ATOPIC dermatitis is a common and costly disorder in children. In recent years, the topical immunosuppressants pimecrolimus and tacrolimus have ➤➤

been suggested as alternatives to corticosteroids. Research data on topical pimecrolimus and tacrolimus for the treatment of atopic dermatitis were reviewed and analyzed.

The researchers identified 25 randomized, controlled trials of pimecrolimus or tacrolimus including data on efficacy or tolerability. Of the total 6,897 patients enrolled in the trials, 61% received one of the two immunosuppressants. Both pimecrolimus and tacrolimus were significantly more effective than vehicle placebos. At 3 weeks tacrolimus 0.1% was as effective as potent topical corticosteroids, while at 12 weeks it was more effective than a combination regimen of hydrocortisone butyrate 0.1% plus hydrocortisone acetate 1%.

Tacrolimus 0.1% or 0.03% was more effective than hydrocortisone acetate 1%, but tacrolimus 0.03% was less effective than hydrocortisone butyrate 0.1%. Tacrolimus 0.1% was consistently more effective than tacrolimus 0.03%, although it took 12 weeks for the difference to become apparent. Pimecrolimus was much less effective than betamethasone valerate 0.1%. Both topical immunosuppressants were associated with an increased rate of skin burning, compared to corticosteroids.

Topical tacrolimus and pimecrolimus are effective treatments for atopic dermatitis in children. However, their long-term advantages over topical corticosteroids remain open to question. Topical tacrolimus may be useful for resistant cases, particularly on sites where corticosteroid side effects develop rapidly.

COMMENT: *This meta-analysis reviews the data from 25 randomized controlled trials in patients with atopic dermatitis receiving either pimecrolimus or tacrolimus. The authors report effectiveness for both agents compared to placebo. However, in studies comparing topical corticosteroids to these agents, tacrolimus was only as potent as a mild corticosteroid while pimecrolimus was not as effective as potent corticosteroids. There were no direct comparative studies of pimecrolimus and tacrolimus. In light of the FDA Alert issued in March 2005, we should be cautious about using these agents--particularly in young children--until there are more data available to confirm their safety.*
S. M. F.

Ashcroft DM, Dimmock P, Garside R, et al: Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomized controlled trials.
BMJ. 2005;330:516-525. ♦♦

Let There Be Light

PHOTOTHERAPY techniques have well-documented immunosuppressive effects--they are widely used in the treatment of inflammatory skin conditions. A new intranasal phototherapy device was evaluated for the treatment of allergic rhinitis.

The randomized, controlled trial included 49 patients with allergic rhinitis, studied during ragweed season. One group was assigned to active phototherapy using a new intranasal device that delivers a combination of 70% visible, 25% UV-A, and 5% UV-B light. Controls used a device that delivered low-intensity visible light only. Patients used their assigned device three times weekly for 3 weeks.

Active intranasal phototherapy brought significant reductions in symptoms of sneezing, rhinorrhea, and nasal itching and in total nasal score. Controls had no improvement in any clinical outcome. Nasal lavage analyses showed reductions in eosinophil cationic protein and interleukin-5 after active treatment, while in vitro studies showed dose-dependent apoptosis of T cells and eosinophils.

Intranasal phototherapy may provide a useful new option for the treatment of allergic rhinitis and other immune-mediated mucosal diseases. Clinical symptoms and inflammatory markers are significantly reduced. The synergistic effect of the different wavelengths used in the new device achieves success with a lower dose of UV-B.

COMMENT: *The Rhinolight apparatus has been developed by a group of Hungarian researchers. According to their website (www.rhinolight.hu), it is indicated for patients who do not respond to or cannot take conventional antiallergic treatment. The Rhinolight uses a combination of low-dose UV-A, UV-B, and visible light frequencies and is used intranasally for 1.5 to 2.5 minutes in each nostril, three times per week. This device was studied in a double-blind protocol compared to visible light alone over a 3-week period in patients with allergic rhinitis during ragweed season. The results were impressive, with patients who received active UV-A and UV-B light reporting improved symptoms and intranasal inflammatory mediators. In vitro studies showed an impressive effect on T-cell and eosinophil apoptosis and on mediator release from basophils. This device might shed new light on our approach to the treatment of allergic rhinitis.*
S. M. F.

Kopeck AI, Coma Z, Bode L, et al: Rhinophototherapy: a new therapeutic tool for the management of allergic rhinitis.
J Allergy Clin Immunol. 2005;115:541-547. ♦♦

The Trodden Path Is Safest

EARLY inhaled corticosteroid (ICS) treatment helps prevent progression to more severe asthma. Large trials including the range of patients seen in routine practice are needed to add to the evidence in support of long-term ICS therapy for asthma. The safety and tolerability outcomes of a large, prospective "real-world" study of early ICS treatment for asthma are reported.

The Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study included 7,221 patients, aged 5 to 66 years, with mild persistent asthma present for less than 2 years. They were randomized to receive 3 years of treatment with placebo or budesonide--200 µg/d for children under 11 years old and 400 ➤➤

µg/d for older children and adults. Both groups continued their usual asthma therapy.

Numbers of adverse events were roughly equal in the budesonide and placebo groups--most frequently common respiratory infections. Serious adverse events were more common in the placebo group, the most frequent being worsening asthma. Local adverse effects, such as oral candidiasis or moniliasis, were more common with budesonide.

Early treatment with inhaled budesonide is well tolerated by patients with mild persistent asthma. Only local adverse events are more common with budesonide than with placebo. Asthma itself is far more dangerous than any adverse effects of ICS therapy in this patient population.

COMMENT: *The START trial will continue to provide useful information for patients and providers. In this multinational study of over 20,000 patients inhaled budesonide appeared safe and well tolerated. These are extremely powerful data when you're trying to convince a patient that ICS are indeed safer than asthma!*
A. M.
Sheffer AL, Silverman M, Woolcock AJ, et al: Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study.
Ann Allergy Asthma Immunol. 2005;95:48-54. ♦♦

Racial Heterogeneity in Response to Glucocorticoids

AFRICAN-Americans have increased morbidity and mortality from asthma, even after adjustment for socioeconomic and other factors. Glucocorticoids are the most effective form of asthma controller treatment, yet many patients do not have a good clinical response. The effects of race on responsiveness to glucocorticoids were evaluated.

The study included two groups of asthma patients--106 black and 289 white--as well as nonasthmatic controls of both races. Steroid response was evaluated using a glucocorticoid lymphocyte stimulation assay. The black and white asthma patients were comparable in terms of FEV_1% predicted and inhaled and oral glucocorticoid doses.

However, the black asthma patients had significantly lower glucocorticoid responses than their white counterparts. Median dexamethasone $\log_{10}$ IC_{50} value was 1.00 nmol for African-American asthmatics, compared with 0.78 nmol for whites. Glucocorticoid responses were also significantly lower for nonasthmatic blacks, with median $\log_{10}$ IC_{50} values of 1.26 vs 0.95 nmol, respectively. In addition to race, age and basal T-lymphocyte activity showed a positive correlation with $\log_{10}$ IC_{50} values.

African-Americans appear to have lower responsiveness to glucocorticoids, compared to whites. This racial difference is present for asthmatic patients as well as nonasthmatic controls. Decreased glucocorticoid responsiveness may contribute to the increased asthma morbidity observed in African-Americans.

COMMENT: *Marked differences persist in asthma morbidity and mortality between African-American and Caucasian patients, despite adjustment for age, sex, and socioeconomic status. In this study, both African-American asthmatics and non-asthmatic control subjects were noted to require higher doses of glucocorticoids to suppress T-lymphocyte activation. This decreased glucocorticoid responsiveness could account for the increased asthma morbidity. A 25% to 30% incidence of nonresponse to corticosteroids has been noted in asthmatics, pediatric and adult. Could the heterogeneity of the American population account for this on a racial basis alone?*
T. L. H.
Federico MJ, Covar RA, Brown EE, et al: Racial differences in T-lymphocyte response to glucocorticoids.
Chest. 2005;127:571-578. ♦♦

More on Omalizumab

THE anti-IgE monoclonal antibody omalizumab is a promising treatment to reduce exacerbations in patients with severe persistent asthma. This study pooled data from previous trials of omalizumab for severe persistent asthma.

The meta-analysis included seven trials including data on the effects of omalizumab on asthma exacerbations in severe persistent asthma. The studies included a total of 4,308 patients, 2,511 of whom received omalizumab. The main outcome of interest was the standardized exacerbation rate per year.

Pooled data suggested a 38% reduction in the asthma exacerbation rate for patients receiving omalizumab. Emergency department visits decreased by 47%. The benefits of omalizumab were similar by age, sex, baseline serum IgE, or dosing schedule. Patients with more severe asthma seemed to derive the greatest benefit.

Adding omalizumab to current therapy significantly reduces the exacerbation rate in patients with severe persistent asthma. Anti-IgE therapy may help to address an important medical need for asthma patients whose disease is inadequately controlled.

COMMENT: *These authors pooled data from seven studies to determine the effect of omalizumab on asthma exacerbations in patients with severe persistent asthma. They determined that, as an add-on to current asthma therapy, omalizumab significantly improved disease control with respect to exacerbations and the rate of asthma-related emergency consultations.*
E. J. B.
Bousquet J, Cabrera P, Berkman N, et al: The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma.
Allergy. 2005;60:302-308. ♦♦

IgA and IgG4 Modulate Atopic Phenotype

VARIOUS immune parameters have been linked to allergic disease, including IgA deficiency and low levels of IgG subclasses. In a previous study, the authors found an increased rate of allergic disease in the first 2 years of life for children with low IgA. For the current study, the children in that community-based cohort were followed up to age 4.

The study was based on a randomly selected cohort of Icelandic children followed up from birth through age 42 to 48 months. Serum immunoglobulins and salivary IgA were measured and compared with allergic disease outcomes.

From age 2 to 4, significant increases occurred in serum IgA, IgE, IgG1, IgG2, and IgG4. Children with positive skin prick tests had lower levels of serum IgA and IgG4 at age 4, compared to those with negative results. For children who developed allergic rhinitis between age 2 and 4, salivary IgA and IgG3 were significantly reduced at age 4. Low salivary IgA at age 4 was also related to atopic eczema. Salivary IgA levels were lower for children who developed eczema between age 2 and 4 than for those whose eczema cleared up after age 2.

Levels of immunoglobulins during early childhood are significantly associated with the risk of atopy and allergic disease by age 4. In predisposed children, an IgA level in the low-normal range may increase the risk of sensitization; the same may be true of IgG subclasses. Events during early maturation of the immune system appear to have an important impact on the emergence of allergic disease.

COMMENT: *The finding that low IgA and IgG4 levels were associated with an increased likelihood of positive skins tests suggests that the presence of these immunoglobulin isotypes may modulate the allergic phenotype. This is similar to the "blocking antibody" hypothesis that has been argued as the mechanism of action for conventional allergen immunotherapy. Alternatively, lower levels of IgA and IgG4 may merely be markers of atopy.*
S. A. T.
Lúdvíksson BR, Arason GJ, Thorarensen O, et al: Allergic diseases and asthma in relation to serum immunoglobulins and salivary immunoglobulin A in pre-school children: a follow-up community-based study.
Clin Exp Allergy. 2005;35:64-69. ♦♦

Exhaled NO Predicts Asthma Relapse

THE fact that asthma goes into remission in many children can make it difficult to decide when to reduce or stop treatment with inhaled corticosteroids (ICS). Current practice is based on clinical factors--there are few objective guidelines. The fractional nitric oxide concentration in exhaled air, a marker of eosinophilic airway inflammation, was evaluated as a predictor of asthma relapse after discontinuation of ICS.

The prospective study included 40 children with asthma, mean age 12 years, receiving ICS at a median dose equivalent to 400 µg of budesonide. Because they had been symptom free for at least 6 months, all patients were being considered for discontinuation of ICS. Exhaled NO measurements were obtained before ICS treatment was stopped and 2, 4, 12, and 24 weeks afterward.

Asthma relapse occurred in 9 patients. Their exhaled NO levels were significantly higher than in patients who did not relapse: geometric mean values for nitric oxide in exhaled air were 35.3 vs 15.7 ppb at 2 weeks and 40.8 vs 15.9 ppb at 4 weeks. A 4-week exhaled NO value of 49 ppb was the best predictor of asthma relapse: sensitivity was 71% and specificity 93%.

Exhaled NO measurement can predict the risk of relapse after discontinuation of ICS in children with asthma. Larger studies will be needed to confirm the value of this measurement and to clarify the optimal cut-off points.

COMMENT: *Since asthma remission is common in children, it may be difficult to determine the point at which inhaled corticosteroids should be reduced or discontinued. This small study of both allergic and nonallergic asthmatic children suggests that exhaled NO at 2 and 4 weeks after steroid cessation may be helpful in identifying children who will relapse. Though intriguing, larger studies will be required to confirm this observation.*
E. J. B.
Pijnenburg MW, Hofhuis W, Hop WC, De Jongste JC: Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission.
Thorax. 2005;60:215-218. ♦♦

Montelukast Is Anti-Inflammatory

IN young children with asthma, lack of response to inhaled anti-inflammatory medications may be at least partly explained by limited drug deposition in the lung. Oral montelukast might be a useful alternative. The effect of oral montelukast on exhaled nitric oxide, a marker of asthmatic inflammation, was investigated.

The study included 30 children, aged 2 to 5 years, with newly diagnosed allergy. All patients had a parental history of asthma and positive results on allergy testing. Exhaled NO and airway resistance were measured at baseline, after a 1-week run-in period, and after 4 weeks of treatment with montelukast, 4 mg/d.

Mean exhaled NO decreased significantly after montelukast treatment: from 33.1 to 11.6 ppb. Airway resistance also decreased, from 1.28 to 1.15 kPa/L/s. Bronchodilator responsiveness remained unchanged, with mean values of about 13%.

Oral montelukast treatment significantly reduces exhaled NO in preschoolers with allergic asthma. Positive effects on pulmonary function are noted as well. Montelukast may be a good alternative treatment for preschoolers with asthma, particularly those who have difficulty with inhaled medications. ➤➤

COMMENT: *There has been considerable debate over the years as to whether the leukotriene modifiers are bronchodilator or anti-inflammatory medications. Exhaled NO level is a marker of asthmatic inflammation that is emerging as a useful too in the clinical management of individual patients. In this study, montelukast reduced exhaled NO levels in young children after 4 weeks of treatment, adding to the evidence that montelukast has anti-inflammatory activity.*
S. A. T.
Straub DA, Minocchieri S, Moeller A, et al: The effect of montelukast on exhaled nitric oxide and lung function in asthmatic children 2 to 5 years old.
Chest. 2005;127:509-514 ♦♦

New Stuff on Fire Ant Stings

HYPERSENSITIVITY to imported fire ants (IFAs), *Solenopsis* spp., is a growing clinical problem in the southern United States. Current treatment recommendations are similar to those for flying Hymenoptera, but there is a lack of research data on the management of IFA stings in children. The outcomes of large local and cutaneous reactions to IFA stings in children without immunotherapy are reviewed.

The study was based on a review of records from a Texas military medical center from 1984 to 2004. During this time, 57 children aged 16 years or younger had generalized cutaneous or large local reactions to IFA stings and did not receive immunotherapy. Thirty-one patients were followed up for the occurrence of and reactions to subsequent stings.

Of 20 patients reporting subsequent stings, none developed a more severe reaction than at their initial evaluation. Most had only small to large local reactions at the sting site. Of the 11 patients who had not been stung again, 5 were no longer living in an area where IFAs were present.

The results suggest a benign outcome for children with cutaneous-only reactions to IFA stings, without immunotherapy. There is no evidence of more severe reactions to subsequent stings. Based on this small experience, immunotherapy does not appear necessary for children aged 16 or younger with large local and generalize cutaneous reactions to IFA stings.

COMMENT: *Management of IFA hypersensitivity is complicated by the lack of data with respect to clinical questions that have been investigated with other Hymenoptera. This is reflected in the variance in decisions concerning the treatment of children with cutaneous anaphylaxis or generalized urticaria following IFA stings. Almost 30% of allergists/immunologists recommend immunotherapy for such reactions in children, whereas immunotherapy is generally not recommended with similar reactions to other Hymenoptera stings. This small study confirms a similar benign prognosis in children with cutaneous reactions to IFA stings, suggesting that immunotherapy is not necessary.*
D. K. L.
Nguyen SA, Napoli DC: Natural history of large local and generalized reactions to imported fire ant stings in children.
Ann Allergy Asthma Immunol. 2005;94:387-390.

Workers Show High Rate of Platinum Salt Sensitization

MINING of platinum group elements (PGEs)--palladium, rhodium, and iridium, in addition to platinum--has increased significantly in recent years. Exposure to PGEs may cause hypersensitivity reactions, particularly respiratory symptoms and urticaria. Rates and symptoms of hypersensitivity to platinum salts were evaluated in occupationally exposed workers.

Examinations including skin prick testing were performed in 153 workers at a catalyst manufacturing and recycling plant. Twenty-two workers had positive skin prick reactions to platinum salts, a rate of 14%. Eight of these workers reacted to all six platinum salts tested.

Asthma and urticaria were the main symptoms related to platinum salt allergy. High occupational exposure to platinum was associated with an increased risk of allergy, odds ratio 2.4. Atopy was also significant, odds ratio 2.2. Although not a strong risk factor, smoking appeared to have a modifying effect.

Allergy to platinum salts is common among workers exposed to PGEs in the catalyst injury. Both pulmonary and cutaneous symptoms may occur. Highly exposed workers are at higher risk of sensitization.

COMMENT: *Metals have been reported to induce toxicity or hypersensitivity reactions with respiratory symptoms, contact urticaria, and contact dermatitis. The authors confirm this by studying 153 subjects working in a catalyst manufacturing and recycling factory. They found a 14% incidence of sensitization to platinum salts. Cigarette smoking was found to be a definite risk factor, and skin testing was a highly valuable surveillance tool in the industry.*
E. J. B.
Cristaudo A, Sera F, Severino V, et al: Occupational hypersensitivity to metal salts, including platinum, in the secondary industry.
Allergy. 2005;60:159-164. ♦♦

Rhinitis and Sleep Apnea Are Linked

THE presence of allergic rhinitis has been linked to an increased frequency of obstructive sleep apnea (OSA). Questions remain about the effects of treatment to reduce nasal obstruction on the occurrence of mouth breathing during sleep and on the severity of OSA. The benefits of treating nasal obstruction in patients with OSA were evaluated.

The randomized trial included 10 patients with OSA, clinically significant nasal obstruction, and a normal retroglossal airway. In crossover fashion, patients ➤➤

underwent overnight polysomnography after treatment with a topical nasal decongestant and after sham treatment with an external dilator strip. Outcomes of interest included nasal resistance, mouth breathing, and severity of OSA.

Nasal resistance decreased dramatically after decongestant treatment, remaining at or below a level of 3 cm H_2O/L/s. Active treatment was also associated with an average reduction of 12 on the apnea-hypopnea index, although the index fell to less than 15 in only 1 patient. The duration of obstructive events was unaffected by treatment. The oral fraction of ventilation during was 8% on the active treatment night, compared with 39% on the sham treatment night. Sleep architecture improved significantly as well.

For patients with OSA and severe nasal congestion, treatment with a topical nasal decongestant reduces mouth breathing while improving sleep architecture. Although nasal resistance is greatly reduced, there is only modest reduction in the severity of OSA. Even in the presence of severe obstruction, most breathing during sleep is nasal.

COMMENT: *With increasing appreciation of the relationships between rhinitis and OSA, it follows that allergists may have a prominent role in caring for these patients through specific management of their rhinitis. This small study looked at the effects of managing nasal congestion on mouth breathing and OSA severity scores. Not unexpectedly, treating nasal congestion dramatically reduced the oral fraction of ventilation during sleep, which improved symptoms but did not affect the baseline sleep apnea. Aggressive management of rhinitis is likely useful in the management of OSA severity.*
G. D. M.

McLean HA, Urton AM, Driver HS, et al: Effect of treating severe nasal obstruction on the severity of obstructive sleep apnea.
Eur Respir J. 2005;25:521-527. ♦♦

Are the Airways Really United?

THERE is a well-documented link between allergic rhinitis and asthma. It remains unclear whether allergic rhinitis and asthma are two separate diseases or the upper and lower airway manifestations of a single disease. This study compared the severity of atopic and nonatopic asthma in patients with and without nasal symptoms.

The analysis included records of asthma patients referred to a university clinic over a 10-year period: 178 with atopic and 218 with nonatopic asthma. Rates and clinical correlates of nasal symptoms were assessed in each group.

Of the patients with atopic asthma, 139 had nasal symptoms (78%). In this group, nasal symptoms were associated with a higher mean FEV_1, higher FVC, and higher FEV_1/FVC ratio. Atopic asthma patients with nasal symptoms also used less oral steroids and had fewer hospitalizations.

Nasal symptoms were present in 150 of the patients with nonatopic asthma (69%). Inhaled steroid use was greater among the patients with nasal symptoms, and nasal polyps were more likely to be present. On comparison of the two asthma groups, patients with atopic asthma were younger, had a longer history of asthma and a higher FEV_1/FVC ratio, and used less oral steroids.

Among patients atopic asthma, the presence of nasal symptoms is associated with less severe asthma symptoms. In contrast, in nonatopic asthma, nasal symptoms are associated with more severe asthma. In this referral population, asthma is more severe in the nonatopic group.

COMMENT: *There is little question that there are clear physiologic relationships between the upper and lower airways. While this study fails to associate atopic upper airway severity and asthma, it confirms the interesting association of nonatopic upper airway disease and asthma. There are many confounding variables in this study, but the airways remain "united."*
A. M.

Kanani AS, Broder I, Greene J, Tarlo SM: Correlation between nasal symptoms and asthma severity in patients with atopic and nonatopic asthma.
Ann Allergy Asthma Immunol. 2005;94:341-347. ♦♦

More on Probiotics

SOME evidence suggests that changes in the gut microflora may influence the development of infantile atopic eczema/dermatitis syndrome (AEDS). Initial studies show that probiotic bacteria may help to reduce symptoms of AEDS and cow's milk allergy. This double-blind, placebo-controlled trial evaluated the benefits of probiotic therapy for infants with AEDS.

The study included 230 infants with AEDS and other symptoms of suspected cow's milk allergy. All infants received an elimination diet and skin treatments. In addition, they were randomized to receive probiotic treatment--consisting of *Lactobacillus* GG alone or a mix of four probiotic bacteria--or placebo. Treatment continued for 4 weeks.

Disease severity decreased in the overall sample, with a mean 65% reduction in the Severity Scoring of Atopic Dermatitis (SCORAD) index. There were no significant differences between the three treatment groups--immediately or at the end of treatment, nor in infants with diagnosed cow's milk allergy. However, among babies with IgE-associated AEDS, those receiving *Lactobacillus* GG had significantly greater improvement: mean decrease in SCORAD index was 26.1, compared with 19.8 in the placebo group.

Single-probiotic treatment with *Lactobacillus* GG yields significant reductions in AEDS among IgE-sensitized infants. Probiotic therapy does not appear effective in unselected infants with AEDS; a mix of probiotics shows no benefit in any group.

COMMENT: *These authors confirm prior reports that influencing the gut microflora by administra-* ➤➤

tion of probiotic bacteria is effective in treating AEDS. However, they demonstrated it was effective only in infants with IgE-mediated disease and that mixtures of different probiotic strains suppressed the effect observed with Lactobacillus *GG alone. Allergists need to keep in mind potential adverse effects. (See* AllergyWatch *March/April 2005, pg 7.) Further studies are needed to explore mechanisms operative with different probiotic bacteria.*
E. J. B.
Viljanen M, Savilahati E, Haahtela T, et al: Probiotics in the treatment of atopic eczema/dermatitis syndrome (AEDS) in infants: a double-blind placebo-controlled trial.
Allergy. 2005;60:494-500. ♦♦

Hot Tub, Anyone?

"HOT TUB LUNG" is a hypersensitivity pneumonitis resulting from exposure to *Mycobacterium avium* complex infection from hot tubs. A patient with acute respiratory failure related to hot tub lung is reported.

A 67-year-old man was admitted to the ICU for treatment of acute respiratory failure, which developed after a 3-month history of chest congestion and cough. Radiographs showed progressive opacification of the lungs; mechanical ventilation was required. Over the subsequent week, the patient's condition improved, allowing him to be sent home. A few days later, shortness of breath and cough recurred after the patient had been sitting in a hot tub.

A high-resolution CT scan showed centrilobular ground-glass opacities, some with a rosette pattern, and sparing of some secondary pulmonary lobules. The differential diagnosis included various atypical pneumonias; mycobacterial culture identified *M. avium-intracellulare* complex. The patient reported that he had routinely used bromine to treat the hot tub water. He stopped using the tub, and the lung abnormalities resolved.

Contamination of hot tubs with *M. avium* complex can lead to hypersensitivity pneumonitis, which caused acute respiratory failure in this previously healthy patient. The rapid resolution of respiratory distress and its recurrence after repeated hot tub use are key clinical findings.

COMMENT: *Hypersensitivity pneumonitis can be caused by a variety of organic agents. One of the more recent additions to the list is* M. avium *complex. This organism is aerosolized by hot tubs, in which bromine additives probably enhance its antigenicity. I think I'll warm up by the fireplace from now on.*
R. J. M.
Systrom DM, Wittram C: Case 9-2005: a 67-year-old man with acute respiratory failure.
N Engl J Med. 2005;352:1238-1246. ♦♦

The Murky World of Mold

MANY questions remain about the respiratory health effects of home dampness and indoor mold. An experience with evaluation and follow-up of patients evaluated for mold-related health problems is presented.

Over a 1-year period, 135 patients presented for evaluation of health complaints related to indoor mold exposure. Most patients were referred on recommendation of an industrial hygienist and had an attorney at the time of evaluation. Skin sensitization to mold was strongly correlated with sensitization to aeroallergens. Atopic patients were more likely to have skin sensitization to molds identified in their home or workplace, while nonatopic patients were more likely to have upper and lower respiratory symptoms. Scores on a 9-point mold exposure scale were high but unrelated to the clinical findings.

Over 2 years' follow-up, most patients moved or remediated their mold problem, with a 99% rate of symptom reduction or elimination. Just 1 patient had health problems that were clearly related to mold exposure. Although mold seemed to aggravate rhinitis or asthma symptoms in many cases, it was difficult to show a cause-and-effect relationship. Most cases continued in litigation.

The findings of patients presenting for evaluation of symptoms attributed to mold exposure vary widely. Even with extensive investigation including skin testing and mold sampling, it is difficult to confirm that mold is the cause of the patient's symptoms.

COMMENT: *In this important paper, the authors review their experience with evaluation of patients with suspected mold hypersensitivity. The heterogeneity of exposure and response is highlighted. The significant limitations of our currently available tools for evaluation are reviewed. A thoughtful accompanying editorial further highlights the need for more study in the "gloomy, murky world of mold." Perhaps someday we can extricate ourselves from the "mold madness."*
A. M.
Bobbitt RC Jr, Crandall MS, Venkataraman A, Bernstein JA: Characterization of a population presenting with suspected mold-related health effects.
Ann Allergy Asthma Immunol. 2005;94:39-44. ♦♦

The Complexity of Asthma Treatment

LONG-term controller medications play a key role in the management of persistent asthma. However, nonadherence with these medications is common and is thought to lead to increased use of as-needed medications. Electronic monitoring devices were used to evaluate use of both classes of medications by children with persistent asthma.

The 1-month follow-up study included 75 children, aged 8 to 16 years, with persistent asthma. The MDILog monitor was used to track daily adherence with ➤➤

controller and as-needed antiasthma drugs. On average, just 46% of prescribed daily medications were actually taken. Use of as-needed medications varied widely.

Unexpectedly, there was no inverse relationship between controller and as-needed medication use. Use of controller medications was negatively related to emergency department visits and school absences, while use of as-needed medications was unrelated to any asthma morbidity indicator.

These objective monitoring data confirm problems with medication adherence among children with persistent asthma. The results suggest that medication use is "ideal" on only one-third of days, while no medications at all are used on another one-third. Long-term controller medication use is a better indicator of asthma morbidity than as-needed medication use.

COMMENT: *Using reliable, objective monitoring devices, accurate measurement of long-term controller and reliever medications was possible in children with persistent asthma. It is no surprise that only 46% of the prescribed controller medication doses were actually taken! However, contrary to expectations, low controller use did not correlate with high use of reliever medications In addition, although lower levels of controller medication did correlate with increased emergency department visits, high use of reliever medication did not. The authors found different patterns of asthma medication use, which may be helpful in unraveling the complex problem of effective asthma management in children.*

J. A. A.

Walders N, Kopel SJ, Koinis-Mitchell D, McQuaid EL: Patterns of quick-relief and long-term controller medication use in pediatric asthma.

Pediatrics. 2005;146:177-182. ♦♦

A Useful Pulmonary Index Score

ASSESSMENT of asthma severity in children can be challenging. The Modified Pulmonary Index Score (MPIS) was evaluated for its ability to predict clinical outcomes in children hospitalized with asthma.

The MPIS was performed by assigning a score of 0 to 3 for each of six categories: oxygen saturation, accessory muscle use, inhalation-exhalation ratio, wheezing, heart rate, and respiratory rate. This instrument was used to assess 30 consecutive children admitted with status asthmaticus. Its reproducibility, validity, and predictive value were assessed.

Interrater reliability was high, including minimal differences between ratings made by physicians, nurses, and respiratory therapists. Higher MPIS scores were positively associated with several important outcomes, including days of continuous albuterol administration and supplemental oxygen, length of stay, and ICU admission. Mean admission MPIS score was 10. A score of 12 or higher was a useful indicator of more severe exacerbation.

The MPIS appears to provide a useful tool for assessing asthma severity in children. It is reproducible across different groups of caregivers and is a good predictor of clinical outcomes. The MPIS may be valuable in standardizing treatment, enhancing communication among professionals, and evaluating the results of treatment for childhood asthma.

COMMENT: *Assessment of acute asthma is a challenge in all age groups, particularly in patients the physician has not cared for on a long-term basis. Severity ranking is particularly difficult in very young children, as they are usually not able to perform objective tests of lung function. This paper describes a relatively simple scoring system that is useful for physicians, nurses, and respiratory therapists. A similar score might help determine which children should be referred for hospitalization when being treated in the office for an acute exacerbation, a more common scenario.*

D. K. L.

Carroll CL, Sekaran AK, Lerer TJ, Schramm CM: A modified pulmonary index score with predictive value for pediatric asthma exacerbations.

Ann Allergy Asthma Immunol. 20005;94:355-359. ♦♦

Ciclesonide and the HPA Axis

CICLESONIDE is a newly developed inhaled corticosteroid--actually a prodrug that is converted to its active form in the lung. In an extrafine hydrofluoroalkane formulation, it offers high dose delivery and pulmonary bioavailability. The airway and systemic effects of ciclesonide were compared with those of fluticasone proprionate.

The randomized, crossover trial included 14 patients with moderate persistent asthma, mean FEV_1 67% predicted. Patients were studied during 4 weeks on ciclesonide, 200 µg four puffs twice daily; and 4 weeks on fluticasone, 250 µg four puffs daily. Assessments included plasma and urinary cortisol measurements, exhaled nitric oxide measurement, and methacholine bronchial challenge testing.

Fluticasone treatment caused significant suppression of both serum and urinary cortisol levels. Cortisol suppression was significantly greater after fluticasone than after ciclesonide, with a geometric mean fold difference of 1.5 Both treatments brought significant improvement in exhaled nitric oxide and bronchial responsiveness to methacholine. Secondary outcomes--including spirometry, symptoms, and quality of life--were unchanged.

At the high doses used in this study, ciclesonide does not produce the hypothalamic-pituitary-adrenal axis suppression observed with fluticasone proprionate. Ciclesonide improves relevant airway measures as well as fluticasone, without cortisol suppression. At higher doses, ciclesonide may offer a more favorable therapeutic ratio than fluticasone.

COMMENT: *This well-designed study clearly demonstrated the safety of the ciclesonide molecule in terms of its effect on the hypothalamic-pituitary axis. For those patients who need higher doses of inhaled corticos-* ➤➤

teroids, ciclesonide may offer a safer therapeutic profile. However, it is important to recognize the limited number of patients in clinical practice who actually require extreme doses of inhaled corticosteroids to achieve asthma control. In addition, in clinical practice and in accordance with national guidelines for treatment of asthma, the concomitant use of long-acting β_2-agonists and leukotriene modifiers limit the susceptible patient population even further.
T. L. H.
Lee DKC, Fardon TC, Bates CE, et al: Airway and systemic effects of hydrofluoroalkane formulations of high-dose ciclesonide and fluticasone in moderate persistent asthma.
Chest. 2005;127:851-860.

Exercise-Induced Dyspnea, But Not Asthma

IN children, the occurrence of exercise-induced dyspnea often leads to a diagnosis of exercise-induced asthma. However, other causes of exercise-induced dyspnea are possible, including vocal cord dysfunction. An experience with exercise-induced dyspnea in children who were tested and/or treated for asthma is reviewed.

The 7-year experience included 142 children and adolescents evaluated for exercise-induced dyspnea. Mean duration of the problem was 30 months; 69% of patients had been diagnosed with asthma by the referring physician. Exercise testing reproduced the symptoms of exercise-induced dyspnea in 117 patients. However, just 11 of these patients were diagnosed with exercise-induced asthma, defined as symptom reproduction with a 15% reduction in FEV_1.

Of 74 patients with normal physiologic exercise limitation, just 26 were classified as having poor cardiovascular conditioning. Other diagnoses associated with exercise-induced dyspnea were restrictive abnormalities in 15 patients, vocal cord dysfunction in 13, laryngomalacia in 2, and primary hyperventilation and supraventricular tachycardia in 1 patient each.

Most children referred for evaluation of exercise-induced dyspnea do not have exercise-induced asthma. The diagnosis of asthma should be questioned in patients with no other clinical signs or symptoms and no response to β_2-agonist pretreatment. Exercise testing plays a key role in making the correct diagnosis.

COMMENT: *I am seeing more patients with atypical symptoms and suspected emotional causes of symptoms that have been attributed to asthma. This probably reflects the increased efficacy of medications available to treat asthma. If an individual does not improve with effective therapy, the diagnosis is suspect. This study demonstrates the value of objective assessment of exercise-induced symptoms--less than 10% of subjects have exercise-induced asthma if bronchodilator therapy does not prevent or relieve symptoms. Exercise challenge is not always possible in our clinics but is clearly desirable.*
D. K. L.
Abu-Hasan M, Tannous B, Weinberger M: Exercise-induced dyspnea in children and adolescents: if not asthma then what?
Ann Allergy Asthma Immunol. 2005;94:366-371. ♦♦

ALLERGY AND IMMUNOLOGY REVIEWS OF NOTE

COMMENT: *This is an up-to-date review of what is known about how respiratory viruses trigger asthma exacerbations, including their synergy with allergic exposures and air pollutants.*
S. A. T.
Contoli M, Caramori G, Mallia P, et al: Mechanisms of respiratory virus-induced asthma exacerbations.
Clin Exp Allergy. 2005; 35:137-145.

COMMENT: *The innate immune system and the hygiene hypothesis are both hot topics in offering explanations for the growing problem of allergic disease and asthma. This is an excellent, readable review article of both the epidemiology and molecular mechanisms linking endotoxin and atopic disease. The confusing genetic relationships are briefly highlighted, leaving the reader in a quandary--but that is the state of the art at this time. I think this is must reading for the clinical allergist/immunologist, even if the final answers are not in.*
D. K. L.
Williams LK, Ownby DR, Maliarik MJ, Johnson CC: The role of endotoxin and its receptors in allergic disease.
Ann Allergy Asthma Immunol. 2005;94:323-332. ♦♦

COMMENT: *This review helps clarify the history, physiology, diagnosis and risk factors for patients with allergic reactions to insect stings. The duration of venom immunotherapy (VIT) is still not certain. However, patients who have had systemic reactions during VIT, those with honeybee allergy, those with the most severe reactions by history, and those who had less than 5 years of VIT are at greater risk of relapse. Unfortunately this review does not discuss fire ant allergy, which is a problem for Southerners.*
S. M. F.
Golden DBK: Insect sting allergy and venom immunotherapy: a model and a mystery.
J Allergy Clin Immunol. 2005;115:439-447. ♦♦

COMMENT: *Celiac disease is a common immune-mediated disorder triggered by ingestion of wheat gluten and related cereal proteins. It may be thought of as an "allergic" disorder and not infrequently referred to an allergist. This excellent review will* ➤➤

serve to update the reader on specific serologic tests that facilitate rapid and cost-effective screening for celiac disease.
E. J. B.
Alaedini A, Green PHR: Narrative review: celiac disease: understanding a complex autoimmune disorder.
Ann Intern Med. 2005;142:289-298. ♦♦

COMMENT: *In this excellent review the author proposes a role for airway dendritic cells--not only in sensitization to inhaled allergens, but also in maintenance of eosinophilic airway inflammation. Many of the concepts discussed are also applicable to allergic rhinitis and atopic dermatitis.*
E. J. B.
Lambrecht BN: Dendritic cells and the regulation of the allergic immune response.
Allergy. 2005;60:271-282. ♦♦

COMMENT: *This comprehensive review outlines the most recent literature on trends in asthma prevalence and considers the possible causes for these trends. The strengths and weaknesses of the literature reviewed are also cogently discussed.*
E. J. B.
von Hertzen L, Haahtela T: Signs of reversing trends in the prevalence of asthma.
Allergy. 2005;60:283-292. ♦♦

COMMENT: *There are many reasons why people cough, and we allergists are uniquely positioned to evaluate them. In the last 23 years, the annual number of reported cases of pertussis has increased 6-fold, mostly in the adolescent and adult age range. This article reviews the relevant issues of diagnosis, treatment, and prophylaxis. The authors suggest booster vaccinations for adolescents.*
R. J. M.
Hewlett EL, Edwards KM: Pertussis--not just for kids.
N Engl J Med. 2005;352:1215-1222. ♦♦

COMMENT: *Since the articulation of the hygiene hypothesis for the development of atopy, a spotlight has been on endotoxin as a central player in this drama. Much remains to be discovered about the roles of this ubiquitous environmental immune stimulant. The authors review the biology and genomics of the variable human responses to this fascinating agent.*
R. J. M.
Singh J, Schwartz DA: Endotoxin and the lung: insight into the host-environment interaction.
J Allergy Clin Immunol. 2005;115:330-333. ♦♦

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