

# ALLERGY WATCH®

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

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

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## Serum $\alpha$ -Protryptase Levels Help in Diagnosis of Systemic Mastocytosis

**T**HE diagnostic value of serum  $\alpha$ -protryptase levels in patients with suspected systemic mastocytosis was evaluated. The retrospective study included 22 patients with suspected mastocytosis and 30 with suspected anaphylaxis. All patients had high total serum tryptase levels of 20 ng/mL or greater and normal or slightly elevated serum  $\beta$ -tryptase levels--no higher than 5 ng/mL. Biopsy results were available in 15 of the patients with suspected mastocytosis: the biopsy was positive in 12 patients and negative in 3. Serum  $\alpha$ -protryptase level was calculated by subtracting the measured  $\beta$ -tryptase level from the total tryptase level.

Nine of the 15 patients with available biopsies had a serum  $\alpha$ -tryptase level of greater than 75 ng/mL. In each of these patients, the biopsy was positive for systemic mastocytosis. Measurement of serum  $\alpha$ -protryptase level appeared to be more sensitive than bone

marrow biopsy. In some cases, elevated  $\alpha$ -protryptase levels returned to normal over time. Some patients with an elevated  $\alpha$ -protryptase level had anaphylaxis as the initial manifestation of systemic mastocytosis or mast cell hyperplasia.

Serum  $\alpha$ -protryptase levels may be a useful screening test for systemic mastocytosis or systemic mast cell hyperplasia. Postmortem studies of patients with suspected anaphylaxis show high total tryptase/ $\beta$ -tryptase ratios, consistent with an elevated mast cell burden at the time of death. The findings suggest that many patients with severe anaphylaxis may have unrecognized systemic mastocytosis.

**COMMENT:** *Systemic mastocytosis can be difficult to diagnose. This retrospective study documents that a simple blood test to estimate  $\alpha$ -protryptase--by measuring the difference between total tryptase and  $\beta$ -tryptase--is useful in screening for mastocytosis. A clinical pearl from this work is that anaphylaxis can be a presenting manifesta-* ➤➤

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- 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 Occupational and Environmental Medicine
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine

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*tion of systemic mastocytosis. This test would therefore be useful in evaluating patients with idiopathic anaphylaxis.*

*M. S. B.*

*Kanthawatana S, Carias K, Arnaout R, et al: The potential clinical utility of serum  $\alpha$ -protryptase levels. J Allergy Clin Immunol 103:1092-1099, 1999. ♦♦*

## Interaction Between Clarithromycin and Methylprednisolone Demonstrated

**I**N patients with steroid-dependent asthma, macrolide antibiotics are commonly used as steroid-sparing agents, an effect which arises partly through their ability to delay glucocorticoid clearance. The newer macrolide antibiotic clarithromycin is being increasingly used as a steroid-sparing agent. This study examined the effect of clarithromycin on the pharmacokinetics of prednisolone and methylprednisolone.

The open-label study in patients with mild to moderate asthma found that clarithromycin reduced methylprednisolone clearance by 65%. In addition, mean plasma methylprednisolone concentrations increased significantly from before to after treatment with clarithromycin. In contrast, clarithromycin had no effect on prednisolone clearance or plasma levels.

Interaction between clarithromycin and methylprednisolone—which are commonly used together in the treatment of asthma—could lead to an increased risk of steroid-induced adverse effects. This risk can be avoided by using prednisone instead of methylprednisolone in patients receiving prolonged clarithromycin therapy.

**COMMENT:** *Macrolide antibiotics are commonly prescribed in asthma for secondary Mycoplasma and Chlamydia infections and because of their possible immunomodulatory and anti-inflammatory effects. Some macrolides, such as troleandomycin, can potentiate corticosteroid side effects. The authors studied a newer commonly used macrolide, clarithromycin, and found it delayed clearance of methylprednisolone, but not prednisone. Physicians should be aware of this important interaction and avoid using clarithromycin and methylprednisolone together.*

*M. S. B.*

*Fost DA, Leung DY, Martin RJ, et al: Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. J Allergy Clin Immunol 103:1031-1035, 1999. ♦♦*

## Adverse Effects of Inhaled Corticosteroids Reviewed

**T**HE use of inhaled corticosteroids has greatly reduced the adverse systemic effects of oral corticosteroid therapy in patients with asthma. The author reviewed published data on the systemic adverse effects of inhaled corticosteroids, including meta-analysis of relevant endpoints where possible.

The data indicated that marked adrenal suppression occurs at inhaled corticosteroid doses of greater than 1.5 g/d. With fluticasone propionate, adrenal suppression occurs at doses above 0.75 mg/d. Meta-analysis suggested that fluticasone has significantly greater potency for dose-related adrenal suppression compared with beclomethasone dipropionate, budesonide, or triamcinolone acetonide. In contrast, prednisolone and fluticasone propionate have equivalent effects on a 10:1 mg basis. Above the doses causing adrenal suppression, inhaled corticosteroids appear to cause reduced bone density. A 400 µg/d dosage of beclomethasone dipropionate appears to cause growth suppression, although final adult height is unaffected. Other possible adverse outcomes of long-term therapy with high-dose inhaled corticosteroids include posterior subcapsular cataracts, ocular hypertension, and glaucoma. The risk of skin bruising increases with the degree of adrenal suppression.

Published data confirm that inhaled corticosteroids have adverse systemic effects, though not as severe as oral corticosteroids at similar ➤➤

doses. Fluticasone propionate appears to cause adverse effects at a lower dosage than other inhaled corticosteroids. To minimize the long-term risk of systemic adverse effects in patients with asthma, the dosage of inhaled corticosteroids should be kept as low as possible while maintaining good asthma control and quality of life.

**COMMENT:** *A superb analysis of the literature illuminating the adverse effects of corticosteroid therapy. Meta-analysis reveals that fluticasone propionate exhibits greater dose-related adrenal suppression than other available inhaled steroids, especially at doses above 0.8 mg/d. Dr. Lipworth feels the differences cannot be accounted for by enhanced potency alone when comparing therapeutically equivalent doses, and probably represent the particular pharmacokinetic properties of fluticasone. The issue will assume greater importance as inhaled steroids are used earlier in the treatment of asthma, especially in the presence of emerging nonsteroidal therapies that may facilitate lower doses of inhaled steroids.*

E. J. B.

Lipworth BJ: *Systemic adverse effects of inhaled corticosteroid therapy: a systemic review and meta-analysis.* Arch Intern Med 159:941-955, 1999. ♦♦

## Chronic Salmeterol Therapy Does Not Cause Subsensitivity to Albuterol

**T**HERE is controversy over the development of subsensitivity in patients taking long-acting  $\beta_2$ -agonists for asthma. The effects of salmeterol maintenance therapy on the bronchodilator response to the short-acting  $\beta_2$ -agonist albuterol were assessed in two placebo-controlled, crossover trials. One study included 27 asthma patients previously untreated with corticosteroids, and the other 24 patients on a stable regimen of inhaled corticosteroids. After a 2-week  $\beta$ -agonist washout period, changes in FEV<sub>1</sub> in response to cumulative doubling doses of inhaled albuterol were measured. These responses were re-evaluated after 4 weeks of treatment with salmeterol, 42  $\mu$ g twice daily, or placebo.

In both studies, 21 patients completed both crossover periods. The albuterol dose response was not significantly different after salmeterol vs placebo. This was so regardless of whether or not the patients were receiving inhaled corticosteroids. At each evaluation, the increases in FEV<sub>1</sub> persisted for 6 hours after the final dose of albuterol.

In contrast to some previous reports, these studies find no evidence that salmeterol causes tolerance to the bronchodilator effect of albuterol. The results are similar in corticosteroid-naïve and corticosteroid-treated patients. The findings support the use of salmeterol with inhaled corticosteroids as an alternative to increasing the inhaled corticosteroid dosage.

**COMMENT:** *Tolerance to the bronchodilator effects of  $\beta$ -agonists used in asthma therapy has been the subject of debate. This paper describes the observations of two placebo-controlled crossover studies to assess the bron-*

*chodilator response to a short-acting  $\beta$ -agonist before and after chronic therapy with salmeterol. The results showed that irrespective of concurrent corticosteroid treatment, chronic therapy with salmeterol does not result in tolerance to the bronchodilator effects of albuterol.*

J. B.-M.

Nelson HS, Berkowitz RB, Tinkelman DA, et al: *Lack of subsensitivity to albuterol after treatment with salmeterol in patients with asthma.* Am J Respir Crit Care Med 159:1556-1561, 1999. ♦♦

## Low-Dose Inhaled Fluticasone Can Cause Adrenal Suppression

**A**T recommended doses, the inhaled glucocorticoid fluticasone propionate causes few systemic adverse effects. A case of hypothalamic-pituitary-adrenal axis suppression and exogenous glucocorticoid excess in a child receiving inhaled fluticasone is reported.

The 9-year-old girl was started on fluticasone propionate, 550  $\mu$ g/day, because of severe labile asthma, as diagnosed by history and methacholine challenge. Six months later, she developed symptoms of increased appetite and nausea with physical signs of Cushing's syndrome. The patient had an undetectable 8:00 a.m. cortisol level, accompanied by an adrenocorticotrophic hormone level of 21 pg/mL. Her adrenal function returned to normal after a long taper of fluticasone propionate. No acute or chronic asthma exacerbations occurred.

This case suggests that fluticasone propionate can cause adrenal suppression at doses lower than previously suspected. The findings may have implications for the use of inhaled glucocorticoids in patients with milder asthma. Patients should receive the lowest possible glucocorticoid dose that controls their symptoms, along with regular follow-up.

**COMMENT:** *In this important case report, the authors detail clinical and biochemical adrenal suppression in a 9-year-old child on high-dose inhaled fluticasone. The report highlights the importance of physicians vigilantly following patients on high-dose inhaled corticosteroids. This potential complication is yet another reason for physicians to consider "add-on" therapy to low-dose inhaled corticosteroids as opposed to routinely increasing the dose when there is an incomplete clinical response.*

A. M.

Taylor AV, Laoprasert N, Zimmerman D, Sachs MI: *Adrenal suppression secondary to inhaled fluticasone propionate.* Ann Allergy Asthma Immunol 83:68-70, 1999. ♦♦

## Tolerance to Bronchoprotective Effects Develops During R-Salbutamol Treatment

**P**ATIENTS taking racemic salbutamol experience partial loss of the drug's bronchoprotective effect. The R enantiomer of salbutamol is a bronchodilator, whereas the S enantiomer is not. These two enan- ➤➤

tiomers were compared with racemic salbutamol for their effects on the development of tolerance to the bronchoprotective effect against methacholine challenge.

The study included 13 patients with well-controlled, mild to moderate atopic asthma. In crossover fashion, they were studied during treatment with racemic salbutamol, R-salbutamol, S-salbutamol, and placebo. The amount of R-salbutamol given alone (1.25 mg) was the same as that present in the dose of racemic salbutamol (2.5 mg). Under each condition, the bronchoprotective effect of a single dose of racemic salbutamol against methacholine-induced bronchoconstriction was assessed. Tolerance developed to a similar extent with both R-salbutamol and racemic salbutamol. Tolerance to the bronchoprotective effect of salbutamol did not develop with S-salbutamol. There was no loss of bronchodilation, and no exacerbation of asthma at any time.

Development of tolerance to the bronchoprotective effect of racemic salbutamol occurs during treatment with the R-salbutamol enantiomer, but not the S enantiomer. At equal weight, R-enantiomer appears to be a more potent bronchodilator when given alone than as racemic salbutamol. This study found no evidence of worsened asthma control during S-salbutamol treatment.

**COMMENT:** Racemic albuterol is a mixture of R- and S-enantiomers. R-albuterol is responsible for the airway effects and extrapulmonary side effects. Tolerance to the bronchoprotective effects of racemic albuterol is well known. This study demonstrates that tolerance to the bronchoprotective effects of R-albuterol against methacholine challenge develops as readily as with racemic albuterol. Separation of the enantiomers does not prevent development of this tolerance.

R. J. M.

Cockcroft DW, Davis BE, Swystun VA, Marciniuk DD: Tolerance to the bronchoprotective effect of  $\beta_2$ -agonists: comparison of the enantiomers of salbutamol with racemic salbutamol and placebo. *J Allergy Clin Immunol* 103:1049-1053, 1999. ♦♦

## Salmeterol and Theophylline Compared for Nocturnal Asthma

**T**HIS randomized, double-blind, crossover trial compared salmeterol with extended-release theophylline for use in the treatment of nocturnal asthma. The subjects were 19 adult patients with nocturnal asthma. All had a baseline FEV<sub>1</sub> of 50% to 90% of predicted and required regular bronchodilator therapy. Three treatments were compared for efficacy, safety, and effects on sleep quality: inhaled salmeterol, 42  $\mu$ g/dose; extended-release oral theophylline, titrated to achieve a serum level of 10 to 20  $\mu$ g/mL; and placebo.

Salmeterol treatment was associated with a significant increase in the percentage of days and nights without the need for albuterol. Daytime albuterol use was also lower during salmeterol treatment. Both salmeterol and placebo improved global sleep-quality scores, whereas theophylline did not. On polysomnography, the three treatments had comparable effects on

sleep architecture.

Inhaled salmeterol offers important advantages over extended-release theophylline for patients with nocturnal asthma. In addition to reducing albuterol requirement, salmeterol improves morning peak expiratory flow, prevents nighttime deterioration in lung function, and improves subjective sleep quality. Neither treatment significantly improves polysomnographic parameters of sleep quality. For most patients with nocturnal asthma, salmeterol is superior to theophylline.

**COMMENT:** This is an industry-sponsored, head-to-head comparison of salmeterol and theophylline in nocturnal asthma. The clinical and pulmonary function results favor salmeterol, while neither medication affected sleep architecture. Placebo use was associated with an improvement in patient-perceived sleep quality, which casts doubt on the value of the results obtained for this parameter. Since a previous head-to-head comparison in nocturnal asthma reported few significant differences, additional study is needed to settle the issue.

S. A. T.

Wiegand L, Mende CN, Zaidel G, et al: Salmeterol vs theophylline: sleep and efficacy outcomes in patients with nocturnal asthma. *Chest* 115:1525-1532, 1999. ♦♦

## Recurrent Wheezing in Infants Is Linked to High Exhaled NO Levels

**P**REVIOUS studies have demonstrated elevated levels of exhaled nitric oxide (ENO) in adults and school-age children with asthma exacerbations. Exhaled NO is believed to provide a noninvasive marker of asthma activity. This study examined ENO levels in infants and young children during exacerbations of recurrent wheezing. Thirteen children with recurrent wheezing, mean age 20 months, were studied during acute exacerbations and after 5 days of treatment with oral prednisone (group 1). Also studied were 9 healthy controls, mean age 17 months (group 2); and 6 patients, mean age 11 months, with a first episode of viral wheezing (group 3). Measurements of ENO were made by chemiluminescence in air collected via face mask.

Mean ENO level in group 1 during the acute wheezing episode was 14.1 ppb, compared with 5.6 ppb in group 2 and 8.3 ppb in group 3. With steroid treatment, ENO decreased by a mean of 52%. To assess the impact of the pulmonary airway on measured ENO levels, measurements were made in 2 healthy infants before and tracheal intubation for elective surgery. The ENO level decreased from 6 ppb before to 5 ppb after intubation in one child and from 7 to 6 ppb in the other.

In infants with recurrent wheezing, levels of ENO are significantly increased during wheezing exacerbations. These elevations decrease in response to steroid therapy. The findings suggest that young children with recurrent wheezing may develop airway inflammation at a very early age. Further studies will help to determine whether ENO measurements can help to differentiate among the various patterns of wheezing in infancy. ➤➤

**COMMENT:** Though this article doesn't answer the question of whether young infants with wheezing will go on to develop recurrent episodes of asthma, it does indicate that such symptoms indicate the presence of airway inflammation that responds to corticosteroids. It also suggests that further studies should be done to determine whether the airways remodeling, or permanent lung damage, that occurs in older children and adults with uncontrolled asthma might begin at an earlier age than previously expected.

J. M. P.

Baraldi E, Dario C, Ongaro R, et al: Exhaled nitric oxide concentrations during treatment of wheezing exacerbation in infants and young children.

Am J Respir Crit Care Med 159:1284-1288, 1999. ♦♦

## Genetic Influences on Allergy and Asthma Reviewed

THE genetic component of allergic disorders has long been recognized, but remains incompletely understood. This article reviews current understanding of genetic factors involved in allergic disorders and asthma.

Although these diseases have an obvious genetic predisposition, none of the classic mendelian patterns of inheritance are apparent. Thus asthma and allergy are complex gene disorders, resulting from interactions among multiple genes. Some genes may serve protective functions, while others promote disease development, and all have variable expression. Furthermore, specific environmental triggers are required for disease expression.

Several approaches have been used to study the genetic bases of allergy and asthma. A genome-wide search can lead to the identification of the causative gene on a human chromosome, leading to the discovery of nearby genes that may be involved. Alternatively, genes known to be involved in a specific condition may be studied for disorders of gene structure or regulation. Previous studies using these approaches have identified several genes as potential contributors to allergy and asthma. These include the cytokine gene cluster on chromosome 5, affecting multiple interleukins (ILs); the  $\beta$  chain of the high-affinity IgE receptor on chromosome 11; the IL-4 receptor on chromosome 16; and genes on chromosome 12 affecting stem cell factor, interferon- $\gamma$ , insulin growth factor, and Stat 6. There is also evidence that genes affecting antigen presentation of T-cell responses may play significant roles. Furthermore, genes for the  $\beta$ -adrenergic receptor, 5-lipoxygenase, and leukotriene C4 synthase may include disease-contributing alleles.

Allergic disease and asthma appear to be genetically complex diseases, involving many different genes with various functions. Further genetic studies are needed to find ways of identifying children at high risk of asthma and to discern specific asthma phenotypes. Most important, studies of the genetic basis of allergy and asthma may help in understanding their pathophysiology, and thus in developing the next generation of asthma therapies.

**COMMENT:** In this outstanding review article, Dr. Borish details the current understanding of the genetics of allergy and asthma. He highlights candidate genes and their linkage and points to the multiple potential genotypes and the redundancy of gene products. The importance of the genetic control of pro-inflammatory mediators on asthmatic inflammation is reviewed. This article clearly and carefully provides an up-to-date, state-of-the-art review that should be of interest to all clinicians.

A. M.

Borish L: Genetics of allergy and asthma.

Ann Allergy Asthma Immunol 82:413-426, 1999. ♦♦

## Data Show Increasing Prevalence of Allergic Rhinitis and Asthma

THIS study reviews published data to discuss trends in the prevalence of allergic rhinitis and asthma, along with the relevant risk factors and prognosis. Studies from Britain suggest that the prevalence of allergic rhinitis at 16 years of age increased from 12% for children born in 1958 to 23% to those born in 1970. It is unclear whether similar increases have occurred in the United States. Local studies performed between 1962 and 1965 found prevalences of allergic rhinitis ranging from 15% to 28%, whereas a national survey performed from 1976 to 1980 reported a prevalence of 26%. A family history of allergic rhinitis is a major risk factor; dust mite allergy is another. Long-term remission rates for allergic rhinitis are only 10% to 20%.

Many studies have suggested that the prevalence of asthma is increasing around the world. Rates as low as 4% have been reported from India and Algeria, while British and Irish studies have reported prevalences of 30% and higher. A 1992 British survey reported a 23% cumulative prevalence of wheezing. In the United States, annual surveys suggest that asthma prevalence rose from 3.1% in 1980 to 5.4% in 1994. Much higher rates are reported for poor, inner-city children: including undiagnosed cases, more than one-fourth of inner-city children may have asthma. As for allergic rhinitis, family history and the presence of allergy are major risk factors for asthma. The prognosis of asthma has a major impact on its prevalence. Asthma persists into adulthood for at least one-fourth of young children with the disease.

Studies from around the world have documented an increasing prevalence of asthma and allergic rhinitis. The reasons for this increase, and for the differences between countries, remain unknown. However, the impact of these diseases can be reduced through avoidance of known allergens and provision of appropriate treatment.

**COMMENT:** In this outstanding review article, Michael Sly once again enhances our understanding of the prevalence of asthma and rhinitis. Worldwide prevalence data are reviewed in multiple studies, which indicate significant variability among many populations. Although no definitive explanations are ►►

detailed for the change and variability of rhinitis and asthma prevalence, several observations and hypotheses are detailed. Furthermore, the impact of differing prognoses of asthma around the world on disease prevalence is discussed.

A. M.

Sly RM: *Changing prevalence of allergic rhinitis and asthma.* Ann Allergy Asthma Immunol 82:233-252, 1999. ♦♦

## Budesonide Does Not Slow Decline in Lung Function for COPD Patients Who Smoke

**P**ATIENTS with chronic obstructive pulmonary disease (COPD) should quit smoking, but not all are successful in doing so. This double-blind, placebo-controlled study examined the effects of inhaled budesonide therapy for patients with mild COPD who continued to smoke. One thousand two hundred seventy-seven patients with mild COPD were randomized to receive inhaled budesonide, 400 µg twice daily, or placebo for 3 years. At baseline, mean FEV<sub>1</sub> was 77% of predicted. Three-fourths of the patients were men; most had been heavy smokers for many years and had mild but poorly reversible airflow limitation.

Among the 912 patients who completed the study, median decline in FEV<sub>1</sub> was 140 mL in the budesonide group (4.3% of predicted FEV<sub>1</sub>) vs 180 mL in the placebo group (5.2% of predicted FEV<sub>1</sub>). For the first 9 months of the study, FEV<sub>1</sub> actually improved in the budesonide group. Thereafter, however, the rate of decline was similar in the two groups. Skin bruising occurred in 10% of the budesonide group vs 4% of the placebo group.

For patients with mild COPD who continue to smoke, inhaled budesonide can improve lung function for a few months. In the long term, however, lung function continues to decline at the same rate as with placebo.

**COMMENT:** *In this European study, patients with mild COPD (average age 52, FEV<sub>1</sub> 77% of predicted with little reversibility after a bronchodilator) who continued to smoke about a pack a day were treated for three years with either placebo or inhaled budesonide, 400 µg bid. In the first 6 months of treatment, the FEV<sub>1</sub> of the budesonide group improved compared to the placebo group, but thereafter the rate of decline of FEV<sub>1</sub> over time was similar. The message: if you continue to smoke, an inhaled corticosteroid won't save you.*

R. J. M.

Pauwels RA, Löfdahl C-G, Latinen LA, et al: *Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking.* N Engl J Med 340:1948-1953, 1999. ♦♦

## In Persistent Asthma, Salmeterol Provides Better Control Than Zafirlukast

**T**HE leukotriene receptor antagonist zafirlukast is a new alternative for asthma treatment. Its role in comparison to other treatments, such as the long-acting

β<sub>2</sub>-agonist salmeterol, is unclear. This randomized trial compared inhaled salmeterol and oral zafirlukast in 189 patients with persistent asthma. About 80% of patients in both groups were following a stable regimen of inhaled corticosteroid therapy. The patients received either inhaled salmeterol xinofoate, 42 µg twice daily via metered-dose inhaler, or oral zafirlukast, 20 mg twice daily. Both treatments lasted for 4 weeks.

Both groups had significant improvements in disease control, as reflected by pulmonary function measures, asthma symptoms, and supplemental albuterol requirement. The improvements were significantly greater in the salmeterol group—salmeterol was associated with a 29.6 L/min gain in morning peak expiratory flow, compared with 13.0 L/min with zafirlukast. Adverse events were similar between groups.

In patients with persistent asthma—including those receiving concurrent inhaled corticosteroids—inhaled salmeterol and oral zafirlukast both provide improved asthma control. However, salmeterol offers better pulmonary function and symptom control. More research is needed to clarify the role of leukotriene modifiers in asthma, especially as compared with inhaled corticosteroids.

**COMMENT:** *As a relatively new class of antiasthma drugs, the leukotriene modifiers are still looking for their place among the various treatment options. This multicenter study compared the efficacy and safety of zafirlukast against salmeterol as controllers of persistent asthmatics, most of whom were already taking inhaled corticosteroids. While both treatments were effective in the treatment of asthma, salmeterol was superior in the parameters that were measured.*

R. J. M.

Busse W, Nelson H, Wolfe J, et al: *Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma.* J Allergy Clin Immunol 103:1075-1080, 1999. ♦♦

## Cross-Reactivity May Complicate Specific IgE Testing

**T**HE authors recently encountered an allergic patient whose symptoms were consistent with his skin test responses; however, testing of specific IgE (sIgE) showed many positive results that conflicted with the clinical findings. This prompted a study of the effects of cross-reacting carbohydrate determinants (CCDs)—epitopes shared by taxonomically distinct allergenic sources—on the results of in vitro allergy testing. Glycoproteins of known carbohydrate structure were used for specific IgE inhibition to study CCD involvement. Various direct and indirect inhibition assays were performed, and binding to the periodate-oxidized carbohydrate structure of glycoproteins and allergenic extracts was assessed. In a study of 428 consecutive allergy patients, the results of skin testing were compared with the specific IgE test results.

With one commercially available specific IgE test, CCDs were responsible for false-positive sIgE results. In addition, CCDs caused high reactivity in all solid-phase in vitro tests evaluated. There were no positive skin test results to any of the cross-reacting carbohydrate allergens tested. IgE binding to the vari-

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ous antigens was reduced to a variable extent by treatment with periodate, suggesting a differing role of CCDs in each antigen studied. In the patient study, 41% of pollen-allergic subjects showed sIgE for a glycoprotein, in the absence of a positive skin test result.

At least for patients with pollen allergy, the results of in vitro sIgE assays may be affected by CCDs. False-positive or clinically irrelevant results of commercial sIgE tests can be avoided by examining the assay's ability to detect sIgE for CCDs. The results of sIgE testing should always be compared with those of skin testing.

**COMMENT:** There has been increased use of in vitro techniques in allergy to document specific IgE sensitivities. This important study confirms that cross-reacting carbohydrate determinants (CCD) can cause false-positive results in in vitro specific IgE assays for pollens. Until in vitro tests are developed to account for the presence of IgE antibodies to CCD, the continued gold standard for assessing specific allergen sensitivity is a good history and appropriate allergy skin tests.

M. S. B.

*Mari A, Iacovacci P, Afferni C, et al: Specific IgE to cross-reactive carbohydrate determinants strongly affect the in vitro diagnosis of allergic diseases.*

J Allergy Clin Immunol 103:1005-1011, 1999.

group; and headache, reported by 6% of patients in the loratadine/bclomethasone group.

For patients with moderate to severe symptoms of seasonal allergic rhinitis, monotherapy with azelastine nasal spray appears to be as effective as a combination of oral loratadine and intranasal beclomethasone. In addition to its antihistamine effect, azelastine appears to reduce congestion, which is usually ascribed to the late-phase inflammatory response. The results support pharmacologic studies suggesting that azelastine has a clinically significant anti-inflammatory action.

**COMMENT:** Azelastine is a novel anti-allergy drug that has multiple mechanisms of action in addition to blocking the H1-receptor. This very large, blind, randomized study conducted at 71 sites showed that monotherapy with azelastine compared favorably in terms of symptom control with beclomethasone/loratadine combination therapy. It is possible that the anti-inflammatory effects of azelastine may be almost as significant as the cost savings to the patient who needs only one drug.

S. R. W.

Berger WE, Fineman SM, Lieberman P, et al: Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis.

Ann Allergy Asthma Immunol 82:535-541, 1999. ♦♦

## Azelastine Monotherapy Is Effective for Seasonal Allergic Rhinitis

**T**HE H1-receptor antagonist drug azelastine hydrochloride, which also has anti-inflammatory properties, is available as a nasal spray for the treatment of seasonal allergic rhinitis. Azelastine nasal spray alone was compared with the combination of oral loratadine and intranasal beclomethasone in patients with moderate to severe symptoms seasonal allergic rhinitis. The 1,070 patients participated in three randomized, double-blind trials. The separate trials were performed to assess the reproducibility of the study design; all were conducted during a single spring allergy season. To be eligible, the patients had to have inadequate response to an oral antihistamine or an intranasal corticosteroid alone. The azelastine group received 2 sprays per nostril bid, for a dosage of 1.1 mg/d. The combination therapy group received oral loratadine, 10 mg/d, and intranasal beclomethasone dipropionate monohydrate, 2 sprays per nostril bid, for a dosage of 336 µg/d. Efficacy measures included a physician's judgment of the need for additional anti-rhinitis drugs and a patient global evaluation. Adverse events were monitored as well.

The percentage of patients not requiring additional anti-rhinitis medications ranged from 32% to 45% with azelastine monotherapy vs 39% to 46% with the loratadine/becломethasone combination. Subjective evaluations suggested symptom improvement rates of 77% to 84% with azelastine vs 85% to 90% with combination therapy. Both treatments were well tolerated. The most frequent adverse effects were a transient aftertaste, reported by 8% of patients in the azelastine

## No Escaping Cat Sensitization—Even on an Island Without Cats

**P**REVIOUS studies have found cat allergen even in places where no cats are present. This study assessed sensitization to cat allergen in the isolated island of Tristan da Cunha, where cats were eliminated in 1974. Allergy skin testing was performed in 282 residents of the island. In addition, house dust mite and cat allergens were measured in dust samples from 20 homes on the island.

Twenty percent of residents of Tristan da Cunha had a positive skin test reaction to cat allergen. This included 13% of residents born after the elimination of cats from the island, and even one subject born in 1983 who had never been away from the island. Cat allergen was found at low levels in just 1 of 20 homes; in contrast, all homes had measurable levels of house dust mite allergen.

The results document the presence of sensitization of cats even on an island with no direct exposure to cats. This phenomenon is probably explained by the persistence of allergen long after the elimination of cats, or by the carriage of allergen on visitors' clothing. Cross-reactivity between the IgE epitopes of major cat and dog allergens may play a role in some cases.

**COMMENT:** Studies have demonstrated that passive carriage of cat allergen on clothing and personal articles can introduce significant levels of the allergen into schools and medical facilities where no cats are present. This article even more dramatically demonstrates ►►

*that passive carriage of cat allergen can cause exposure and sensitization to cats in environments that are far distant from cats.*

M. S. D.

Chan-Yeung M, McClean PA, Sandell PR, et al: Sensitization to cat without direct exposure to cats. *Clin Exp Allergy* 29:762-765, 1999.



## Pre-Employment Testing Does Not Predict Platinum Allergy

**T**HE associations between IgE, atopy, and sensitization to platinum salts remain unclear. This prospective study assessed the value of total IgE measurement and the response to Phadiatop testing in prediction and diagnosis of platinum salt sensitivity in refinery workers. The study included 78 healthy subjects recruited for work in a primary platinum refinery. All were free of evidence of atopy, including a negative response to skin prick testing with common allergens. Subsequently, 22 workers developed sensitization to platinum salts, as evidenced by a positive skin prick test, while 46 remained unsensitized.

Phadiatop status was positive in 18% of subjects who went on to develop sensitization to platinum salts and 17% of those who remained unsensitized. Sixteen subjects had total IgE levels of greater than 100 kU/L, a finding that was associated with positive Phadiatop status. After the start of employment, conversion to positive Phadiatop status occurred in 67% of sensitized workers vs 16% of unsensitized workers. Total IgE levels were also more likely to increase in sensitized subjects. On multivariate analysis, the increase in total IgE was independent of Phadiatop status.

Pre-employment Phadiatop testing of platinum refinery workers cannot predict the subsequent development of platinum salt sensitivity. After employment, however, conversion to positive Phadiatop status and increased total IgE are both associated with the development of sensitization. High exposure to platinum salts is related to increased total IgE, and some sensitized workers develop positive skin test responses to common allergens.

**COMMENT:** *An ongoing dilemma is how to predict which individuals are at greater risk for development of sensitization and occupational asthma in environments where there are potential sensitizers. This study demonstrates the limitations of in vitro approaches to predicting risk of sensitization to platinum.*

M. S. D.

Calverley AE, Rees D, Dowdeswell RJ: Allergy to complex salts of platinum in refinery workers: prospective evaluations of IgE and Phadiatop® status.

*Clin Exp Allergy* 29:703-711, 1999.



## Current Status of In Vitro Testing Reviewed

**T**HIS guest editorial summarizes the findings of a recent workshop on in vitro testing for allergen-

specific IgE in allergy diagnosis. Some allergy tests may seek to demonstrate the symptoms of allergy, as in direct challenges and avoidance trials. However, provocation tests have important limitations; for example, they may not address all the factors involved in the clinical response to allergen. Other types of tests seek to demonstrate sensitization, such as skin testing and in vitro measurement of allergen-specific IgE. In vitro IgE antibody testing can provide a basis for etiologic diagnosis of allergy. The antibodies used for in vitro testing must be absolutely IgE specific—they must be non-cross-reactive with IgG, and must give the same result on repeated testing over time. The allergen sources must be representative, and must not contain contaminating allergens from other sources. Many different factors may affect skin test responses, and the specific IgE antibody level may vary widely among subjects with similar skin test results.

In vitro testing is indicated in certain clinical situations, such as when skin testing cannot be performed because the patient is unable to stop taking anti-histamines or tricyclic antidepressants, during pregnancy, or for specific allergens such as venom or latex for which in vitro testing is easier or more efficient. In vitro testing provides information on the specific cause of allergic disease, with important implications for avoidance measures and immunotherapy. Information on total serum IgE vs absolute and relevant amounts of specific IgE antibodies may help in identifying relevant allergens or missed allergens. There is no "gold standard" for detection of allergen-specific IgE. The results of skin tests and in vitro tests may differ for various reasons; currently, skin testing is probably more sensitive than available in vitro tests. It is currently recommended that all patients receiving regular asthma therapy be tested for sensitization to relevant indoor allergens. Sensitization is also assessed as part of specialist evaluation of allergic rhinitis and atopic dermatitis. The use of in vitro tests vs skin tests for these purposes depends on clinical and cost issues.

Standardized in vitro tests offer a viable alternative to in vivo skin testing for allergy. Although in vitro testing is indicated in certain situations, in vivo skin testing is currently regarded as more sensitive. For now, in vitro testing should have a limited role in generalist practice. Allergy specialists should take the lead in using in vitro testing and in educating other clinicians regarding its most appropriate use.

**COMMENT:** *This paper reviews the results of a workshop held to address the value of in vitro testing in clinical allergy. The workshop was led by many outstanding leaders, researchers, and educators who have nicely summarized the "state of the art." They raise many useful and clinically relevant issues which affect all of our practices. They conclude that in vitro testing can indeed provide a valuable alternative to skin testing and that allergist/immunologists need to be proactive in educating their peers on the merits and limitations of these studies.*

A. M.

*Current issues relating to in vitro testing for allergen-specific IgE: a workshop report. Ann Allergy Asthma Immunol* 82:407-412, 1999 (editorial).



## Causes of Drug-Induced Aseptic Meningitis Reviewed

**D**RUG-induced aseptic meningitis (DIAM) has been linked to a wide variety of drugs, prescribed by physicians in many different specialties. This condition poses difficult diagnostic and treatment challenges, especially if the causative drug is an antibiotic. The authors reviewed the literature on DIAM, with a focus on specific causative drugs and the differentiation of DIAM from other causes of meningitis.

The presenting symptoms of DIAM include headache, fever, meningismus, and mental status changes--the same as in infectious meningitis. The presentation may vary somewhat for DIAM induced by different drugs, and the interval between taking the drug and the development of meningitis may range from minutes to months. The outcome of DIAM appears to be excellent as long as the causative agent is discontinued. Systemic lupus erythematosus is the most frequent predisposing condition to DIAM. Analysis of 29 patients with a total of 71 episodes found that the most frequently involved agents were antibiotics, nonsteroidal anti-inflammatory drugs, OKT3 monoclonal antibodies, and intravenous immunoglobulins. In addition to systemic lupus erythematosus, common underlying conditions included Sjögren syndrome, idiopathic thrombocytopenic purpura, and human immunodeficiency virus infection.

Infectious causes must be considered in the differential diagnosis of DIAM, particularly acute bacterial meningitis. Patients with DIAM generally recover after withdrawal of the offending agent, so chronic infectious meningitis does not usually confuse the diagnosis. If necessary, cultures and other cerebrospinal fluid studies can be performed. Viral aseptic meningitis is another diagnosis to consider, along with the many noninfectious causes of aseptic meningitis. The pathogenesis of DIAM is unclear, and may vary for different drugs. For most common causes, a hypersensitivity mechanism is likely. For OKT3, cytokine release probably plays a role.

Various drugs can cause DIAM; antibiotics are probably an under-recognized cause. The distinction from infectious meningitis can be difficult, especially on clinical grounds. Systemic lupus erythematosus is an important predisposing factor. Most cases of DIAM resolve within days after stopping treatment with the causative drug.

**COMMENT:** *It is important that clinicians be able to recognize all putatively immunologic adverse reactions to drugs. This article reviews clinical characteristics of drug-induced aseptic meningitis, a relatively recently described syndrome that can be a diagnostic and patient management challenge.*

*M. S. D.*

*Moris G, Garcia-Monco JC: The challenge of drug-induced aseptic meningitis.*

*Arch Intern Med* 159:1185-1194, 1999.

## Childhood Risk Factors Adult Bronchial Responsiveness Studied

**T**HE occurrence and outcomes of asthma depend largely on the degree of bronchial responsiveness (BR). Childhood variables associated with severity of BR in adulthood—including factors associated with improvement or worsening of BR over time—were studied. During the late 1960s, 119 children with allergic asthma were studied, including spirometry, response to histamine, skin tests, blood eosinophil count, and serum total IgE measurement. Age at this time ranged from 5 to 14 years. One hundred one subjects were studied again at age 22 to 32 years and at 32 to 42 years. In addition to childhood factors associated with adult BR, cross-sectional risk factors for BR in adulthood were assessed.

Children with greater FEV<sub>1</sub> values had less severe BR in adulthood. Adulthood BR was also less severe for subjects having greater increases in FEV<sub>1</sub> between visits, a longer interval between visits, and pets during childhood. Among nonsmoking subjects, BR at age 32 to 42 years was higher for those who had a higher IgE level at age 22 to 32 years. At the last visit, subjects with a low level of lung function and those with symptoms of asthma had more severe BR.

This study identifies longitudinal and cross-sectional risk factors for BR in adulthood. Subjects who have lower lung function in childhood and less improvement in FEV<sub>1</sub> over time have more severe BR in adulthood. The prevalence and severity of BR seem to decrease from childhood to early adulthood, but then to increase again during adulthood.

**COMMENT:** *Pediatricians frequently tell their patients that they will "outgrow" their asthma. The literature supports this assertion in that many individuals with asthma do have decreased BR as they go through adolescence, only to have it increase again in adulthood. Given the concern with airways remodeling and the change in pulmonary function with time in asthmatic people, it is important to identify predictors for BR in young children. This study identifies two predictors of worse asthma in adulthood: decreased lung function and less improvement in FEV<sub>1</sub> with time. Though the results are not surprising, they can be used to monitor a patient's progress over time. These results also provide a rationale for a study to determine whether aggressive treatment to achieve improved pulmonary function in young children improves adult pulmonary function.*

*J. M. P.*

*Grol MH, Postma DS, Vonk JM, et al: Risk factors from childhood to adulthood for bronchial responsiveness at age 32-42 yr.*

*Am J Respir Crit Care Med* 160:150-156, 1999.



## IVIG Can Reduce Oral Steroid Requirement in Severe Asthma

**M**ANY patients with severe asthma require oral steroids for disease control, which places them at high risk for severe steroid side effects. ►►

Intravenous immunoglobulin (IVIG) was studied as a possible steroid-sparing therapy in patients with severe asthma. The randomized, double-blind trial included 38 patients with severe, steroid-dependent asthma. One group received Iviegam Immune Globulin Intravenous (Human) 5%, while the control group received 5% albumin as a placebo. Outcomes included assessments of disease activity and immunology and allergy evaluations.

Twenty-eight patients completed the trial. Both the IVIG and placebo groups had a significant reduction in oral steroid requirement. Further analysis showed that IVIG had a significant steroid-sparing effect among patients receiving the highest oral steroid dose (ie, a prednisone requirement of more than 5.5 mg/d, or 2,000 mg/y), whereas placebo did not. Within this subgroup, median oral steroid dosage decreased from 16.4 to 3 mg/d. The reduction was achieved with no increase in other asthma medications, including  $\beta$ -agonists; changes in pulmonary function tests; or increases in hospitalization or days or days off work or school.

For patients with severe asthma requiring very high dosages of oral steroids, IVIG has a significant steroid-sparing effect. This finding must be confirmed in larger studies. This treatment may act by reducing vascular inflammation and cytokine production by immune effector cells. Many different possible mechanisms of action have been studied, including Fc receptor blockade, idiotype-anti-idiotypic antibody interaction, and enhancement of T-cell suppressor function.

**COMMENT:** *Intravenous immunoglobulin (IVIG) has shown promise in the treatment of asthma in previous open-label pilot studies. This is the first report of a placebo-controlled, blinded and randomized trial of IVIG in patients with oral steroid-dependent asthma. IVIG showed a significant steroid-sparing effect, which was most evident in the patients previously taking the highest oral steroid doses.*

R. J. M.

*Salmin LM, Barlan I, Wolf HM, et al: Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: a double-blind, placebo-controlled, randomized trial.*

J Allergy Clin Immunol 103:810-815, 1999.



## Antibiotics During Infancy Are an Asthma Risk Factor

IT has been suggested that infections during infancy may affect the risk of later asthma. Alternatively, this relationship might be explained by the use of antibiotics to treat such infections. This hypothesis was studied in a unique sample of 456 parents of 5- to 10-year-old children attending Rudolf Steiner schools. Parents following this philosophy would tend to permit the use of certain conventional medical approaches only as a last resort, and thus were considered likely to recall antibiotic use accurately. In response to a questionnaire, the parents provided information on the children's history of asthma and wheezing and their past use of antibiotics.

About 25% of the children had never received antibiotics, and nearly two-thirds had not received

antibiotics during the first year of life. Children who had received antibiotics were significantly more likely to have a history of asthma (odds ratio 2.74, 95% confidence interval 1.10 to 6.85) and a history of wheezing (odds ratio 1.86, 1.06 to 3.26). Antibiotic usage was not a significant risk factor for current wheezing, however. The risk of asthma was particularly strong for children who had received antibiotics in the first year of life: odds ratio 4.05, 95% confidence interval 1.55 to 10.59. Children who had received antibiotics were also more likely to develop hay fever, although this relationship was not significant. Antibiotic usage was not a risk factor for eczema.

Antibiotic usage during infancy appears to be strongly related to the development of asthma later in childhood. The reasons for this association are unclear; they may be related to a reduced intensity and duration of bacterial infections or to an effect on bowel flora.

**COMMENT:** *This study reports a striking association between early antibiotic use and asthma, especially in children who had received multiple antibiotic courses in the first year of life. The authors cleverly selected a population of children whose parents were less likely to allow antibiotic treatment and were more likely to recall prior antibiotic usage accurately. A cause-effect relationship is supported by the fact that the association holds even with antibiotics used for nonrespiratory infections.*

S. A. T.

*Wickens K, Pearce N, Crane J, Beasley R: Antibiotic use in early childhood and the development of asthma. Clin Exp Allergy 29:766-771, 1999.*



## Inhaled Aspirin Protects Against Early Allergic Response

THE aspirinlike drugs have powerful anti-inflammatory effects. Two such drugs with differing pharmacologic activities—sodium salicylate (SSA) and indomethacin—were compared with lysine acetylsalicylate (LASA) for their effect on asthmatic responses when given by inhalation. Patients with mild allergic asthma inhaled SSA, indomethacin, or LASA 30 min before challenge with a single dose of allergen producing a 25% reduction in FEV<sub>1</sub>. Both the early and late responses were partially prevented by SSA, which provided about 20% protection compared with placebo. By comparison, LASA provided about 40% protection, though the difference was not significant.

In further experiments, indomethacin did not alter the early response whereas LASA provided protection of 31%. Both drugs reduced the late response to a similar extent—44% and 39%, respectively. Indomethacin blocked the late allergen-induced increase in bronchial hyperresponsiveness even in subjects with an early response.

Inhaled salicylates appear to inhibit the early allergic response in subjects with mild asthma, whereas indomethacin does not. The differing effects of the drugs tested do not result from differences in their cyclooxygenase inhibitory activity. Aspirin, SSA, and ►►

indomethacin do have comparable protective effects against the late allergic response and against allergen-induced hyperreactivity. The findings could lead to a better understanding of the pathogenesis of bronchoconstriction in asthma and thus to new treatment strategies.

**COMMENT:** *The conventional wisdom is that aspirin triggers asthma despite being referred to an anti-inflammatory agent. A recent trend in asthma research has been to have patients inhale just about anything that might affect their airways in order to see what happens. In this article, late-phase responses to allergen challenge were attenuated with inhaled aspirin and indomethacin, while only aspirin blocked early responses. Cyclo-oxygenase inhibitory activity clearly is not the mechanism of such protection, suggesting that these agents have other, as yet unidentified, effects on inflammatory responses in asthma.*

J. M. P.

Sestini P, Refini R, Pieroni MG, et al: *Different effects of inhaled aspirinlike drugs on allergen-induced early and late asthmatic responses.* Am J Respir Crit Care Med 159:1228-1233, 1999. ♦♦

## Rhinovirus Itself Does Not Cause Asthma Exacerbations

Asthma exacerbations often occur in association with rhinovirus (RV) infections. This study compared the inflammatory changes caused by RV in the upper and lower airways of asthma patients vs healthy controls. Eleven adult patients with atopic asthma and 10 healthy, nonatopic controls, underwent nasal inoculation with a 2,000 tissue culture infective dose 50%/*mL* of RV-16. Symptoms and peak flow were assessed daily. Spirometry, methacholine challenge testing, nasal lavage, and sputum induction were performed at baseline and at intervals throughout the month after inoculation.

The acute cold was associated with a slight increase in asthma symptoms among the asthmatic group, while the controls had a reduction in methacholine PC<sub>20</sub>. Neither group showed any change in peak flow, bronchodilator use, or spirometry. The two groups also had similar cytokine responses.

This study finds no difference in the upper or lower airway response to RV-16 infection in asthma patients compared with healthy controls. The findings suggest that RV on its own is not sufficient to cause asthma exacerbations. More study is needed to define the viral and/or patient factors associated with asthma exacerbations during viral upper respiratory infections. ♦♦

**COMMENT:** *The conventional wisdom is that rhinovirus infections trigger exacerbations of asthma in patients with increased bronchial hyperresponsiveness. That is why this study, in which mild intermittent asthmatics and controls were experimentally infected with rhinovirus, is so interesting. There was essentially no difference in upper or lower respiratory symptoms between the two groups other than that which was pre-*

*sent prior to the infection. In fact, the normal subjects became similar to the group with asthma. The authors' conclusion that rhinovirus itself is not sufficient to trigger an asthma attack leads to the obvious question of just what does cause asthma exacerbation during an acute upper respiratory infection.*

J. M. P.

Fleming HE, Little FF, Schnurr D, et al: *Rhinovirus-16 colds in healthy and in asthmatic subjects: similar changes in upper and lower airways.* Am J Respir Crit Care Med 160:100-108, 1999. ♦♦

## Asthma Linked to Osteoporosis Risk in Perimenopausal Women

Corticosteroids used for asthma treatment may adversely affect bone mineral density (BMD), and thus increase the risk of osteoporosis. The effects of asthma on BMD among perimenopausal women were analyzed. The study included spinal and femoral BMD values measured in 3,222 women, aged 47 to 56 years, as part of a Finnish population-based study of osteoporosis. The values of 119 women with asthma were compared with those of 3,103 nonasthmatic subjects.

Of the asthmatic women, 65 had used oral corticosteroids, 26 had used inhaled corticosteroids, and 28 had used no corticosteroids. Eighty-three were not receiving hormone replacement therapy (HRT). Spinal and femoral BMD values were significantly reduced in asthmatic women not receiving HRT, compared with nonasthmatic patients. Women with asthma who had used inhaled corticosteroids only did not have significantly reduced BMD. However, the longer the duration of inhaled corticosteroid use, the lower the spinal BMD.

Asthma appears to be a risk factor for decreased BMD in perimenopausal women. Risk appears greatest in asthmatic women receiving oral corticosteroids, but inhaled corticosteroids may reduce spinal BMD. This bone loss may be preventable with HRT.

**COMMENT:** *This study compared BMD values of 119 asthmatic women with those of 3,103 nonasthmatics. Women with asthma were found to represent a risk group with regard to osteoporosis. In this setting, oral steroids represented the greatest risk. Inhaled steroids were felt to have a possible negative impact on spinal BMD. Hormone replacement therapy was protective against bone loss in these asthmatic women.*

J. B.-M.

Laatikainen AK, Kröger HPJ, Tukiainen HO, et al: *Bone mineral density in perimenopausal women with asthma: a population-based cross-sectional study.* Am J Respir Crit Care Med 159:1179-1185, 1999. ♦♦

## Study Shows Efficacy of SLIT in House Dust Mite-Related Asthma

This placebo-controlled trial examined the efficacy of sublingual-swallow immunotherapy ►►

(SLIT) in patients with moderate or moderately severe asthma caused by house dust mite. The patients were randomized to receive either SLIT with a standardized *Dermatophagoides pteronyssinus-Dermatophagoides farinae* 50/50 extract or placebo. The immunotherapy dose gradually increased to 300 IR every day for 4 weeks, then 3 times weekly for 24 months, for a cumulative dose of approximately 104,000 IR. The Der p1 and Der f 1 contents of 1 mL 100 IR allergenic extract were 8 and 14 µg, respectively. Response assessments including symptom and medication scores and respiratory function tests.

Both groups showed reduced use of inhaled corticosteroids and  $\beta_2$ -agonists. Respiratory function score and daytime asthma score improved significantly in the SLIT group. There were no significant differences in symptom scores. Methacholine PD<sub>20</sub> was 1.75 times higher than baseline after SLIT, compared to no change with placebo. Specific IgE and IgG levels also increased significantly with SLIT, and quality-of-life scores were better than with placebo. The two groups had comparable adverse event rates.

Sublingual-swallow immunotherapy appears efficacious in patients with moderate or moderately severe house dust mite-related asthma. The results sug-

gest that SLIT is a safe treatment that improves respiratory function, bronchial hyperreactivity, and quality of life. The mechanisms of SLIT need to be clarified.

**COMMENT:** *There is significant controversy as to the effectiveness of immunotherapy administered by the oral or sublingual route. Eighty-five patients with moderate or moderately severe asthma were studied with either placebo or sublingual immunotherapy with house dust mite extract. Doses administered were 200 times higher than standard subcutaneous doses for a comparable treatment period. Though treated patients showed significant improvements in respiratory function at the end of the study, bronchial hyperreactivity was only marginally improved, and there were no significant differences in symptom scores between the two groups. Unfortunately, this study will not settle the skepticism regarding the efficacy of this form of therapy.*

E. J. B.

Bousquet J, Scheinmann P, Guinnepain MT, et al: Sublingual-swallow immunotherapy (SLIT) in patients with asthma due to house-dust mites: a double-blind, placebo-controlled study. *Allergy* 54:249-260, 1999.



American College of  
Allergy, Asthma & Immunology  
85 West Algonquin Road, Suite 550  
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