ALLERGYWATCH®

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

Volume 1, Number 4 July-August 1999

Irreversible Asthma: A Major Problem in Adult Patients

WHEREAS many epidemiologic studies of asthma have concentrated on children and young adults, relatively little is known about irreversible airway obstruction in adult patients. The author reviews the natural history of asthma in adults, focusing on its irreversibility.

In contrast to the assumption that just one pathologic entity can cause airway obstruction in an individual patient, asthma, chronic bronchitis, and emphysema are regarded as differing manifestations of a single disease involving both endogenous and exogenous factors. Epidemiologic criteria used to identify cases of asthma vary--the diagnosis cannot be firmly established even by bronchial hyperresponsiveness to methacholine or histamine. Adult asthma may result from occupational exposures, respiratory viral infections, or perhaps air pollution. Though the prevalence of asthma varies, it may affect 5% to 10% of adults. It is a progressive disease, leading to irreversible airway obstruction in 80% of elderly patients. Other lung diseases are often present as well. Remissions may occur in up to 20% of older patients with asthma, a much lower rate than in children. Asthma symptoms are twice as severe, and the deterioration of lung function is faster, in patients who smoke.

Irreversible airway obstruction results from at least four different abnormalities: airway remodeling, caused by lymphocytic-eosinophilic inflammation; bronchiectasis; postinfectious pulmonary fibrosis; and emphysema and chronic bronchitis, caused by smoking. Among patients who have intrinsic asthma without allergy, the rate of decline in lung function is faster in the initial period after asthma onset and in older patients.

Key areas for future research include treatments to prevent small-airway remodeling, the causes and frequency of bronchiectasis and postinfectious fibrosis, and diagnostic criteria for each of these complications. Meanwhile, the mainstays of clinical management ➤➤

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Supported by an educational grant from Pfizer U.S. Pharmaceuticals and UCB Pharma.

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 Occupational and Enviromental 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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include quitting smoking, controlling sensitivity to occupational and environmental allergens, prescribing aerosolized glucocorticoids for all but the mildest cases, immunizing against influenza and pneumococcal infection, and identifying and treating respiratory infections.

COMMENT: *In this review, Dr. Reed cogently puts into perspective the long-term dangers of asthma. Irreversibility of airway obstruction in older, nonallergic patients is explored; it is probably multifactorial. Deaths from acute asthma are not as common as deaths from complications of long-term irreversible asthma. Dr. Reed suggests several strategies for clinical management.*
R. J. M.

Reed CE: The natural history of asthma in adults: the problem of irreversibility. **J Allergy Clin Immunol** 103:539-547, 1999. ♦♦

Immunotherapy Initially Increases Allergen-Specific IL-4 and IgE

ALLERGEN-specific immunotherapy produces clinical improvement once the patient is receiving the highest tolerated subcutaneous dose of allergen--ie, the maintenance dose. This improvement is associated with decreased production of interleukin-4 (IL-4) and increased production of interferon-γ (IFN-γ) and IL-2. Changes in CD4+ T cell cytokine secretion during conventional immunotherapy were studied in 6 patients with house dust mite or rye grass allergy. Peripheral blood CD4+ cells were stimulated with antigen to assess their production of IL-4 and IFN-γ. Changes in cytokine production were correlated with clinical response.

In 4 of the 6 patients, the ratio of allergen-specific IL-4/IFN-γ production increased dramatically with increasing allergen dose. Once the maintenance dose was reached, this ratio decreased significantly only in patients with a clinical response to immunotherapy. Responders also showed reduced late-phase skin reactions and allergen-specific IgE levels during immunotherapy.

In patients receiving conventional allergen immunotherapy, the initial response may be an increase in allergen-specific IL-4 and IgE production, thus exacerbating allergic disease. Later, production of these cytokines decreases and the patient's clinical condition improves. Though confirmatory studies are needed, failed immunotherapy may be associated with persistent increases in the IL-4/IFN-γ ratio and in allergen-specific IgE.

COMMENT: *Successful allergen immunotherapy (AIT) appears to work, at least in part, by converting T_{H2}-type allergen responses to T_{H1}-type responses. This study determined the T_{H1} / T_{H2} profile of isolated antigen-stimulated T helper cells (as measured by IFN-γ/IL-4) over the course of AIT. During the dose buildup, the ratio actually "worsened," but reversed at high maintenance doses. One patient who clinically failed to benefit from AIT treatment had a persistent T_{H2}-dominated profile. This study helps explain the delay in AIT benefit, the need for "high" doses, and a possible reason for treatment failure.*
R. J. M.

Benjaponpitak S, Oro A, Maguire P, et al: The kinetics of change in cytokine production by CD4+ T cells during conventional allergen immunotherapy. **J Allergy Clin Immunol** 103:468-475, 1999. ♦♦

Altered Immune System Maturation May Lead to Childhood Asthma

THIS review suggests that the development of childhood asthma is related to changes in immune system maturation, in control of airway ➤➤

tone, and in regulation of lung and airway growth. During the first few years of life, most children who will go on to develop asthma have recurrent lower respiratory tract illnesses (LRIs) with airway obstruction. The symptoms of these LRIs, often caused by respiratory syncytial virus (RSV), usually go into remission. However,when wheezing LRIs during the first 3 years of life are associated with acute increases in total serum IgE, the children are likely to still have wheezing at age 6. Eosinophilic immune responses are also heightened in this group. There are few data on the airway immune response to RSV infection in infants with and without wheezing later in life.

There is evidence that LRIs caused by RSV are associated with a predominant T_{H2}-like response. However, animal studies have found that measures to suppress the T_{H2} response are insufficient to eliminate RSV-mediated respiratory disease. The rate of sensitization to aeroallergens is much higher among young children with RSV-associated LRIs who develop persistent wheezing than in "transient wheezers." Factors affecting the maturation of antigen-presenting cells (APCs) during early childhood may play a key role in the development of a mature, T_{H1}-like response, and thus in preventing allergic sensitization. The author's research group is studying genetic factors regulating the production of CD14, which appears to be involved in the maturation of the APC system.

Thus the development of childhood asthma may involve the maturation of the immune system response during the first few years of life. Further study to identify the genetic and environmental factors affecting immune system maturation may lead to useful primary and secondary prevention strategies against asthma.

COMMENT: *Most asthmatic children first wheeze in association with lower respiratory tract infections. The ones who then go on to have persistent asthma seem to be those whose immune systems are programmed to develop T_{H2}- like responses to infections. In this review, Dr.Martinez summarizes nicely what is known about the immunology of developing asthma. Warning: may not be suitable for bedtime reading.*
R. J. M.
Martinez FD: Maturation of immune responses at the beginning of asthma.
J Allergy Clin Immunol 103:355-361, 1999. ♦♦

Dog Washing Reduces Allergen Levels--But Not For Long

MEASURES to reduce allergen exposure are needed for asthma patients who are allergic to dogs but refuse to part with their pets. The effects of dog washing on allergen levels were investigated. Twenty-five dogs were washed at a dog-grooming parlor using shampoo and a hand-held shower. Can f 1 levels in dog hair and in the homes in which the dogs lived were measured before and after washings.

Allergen levels in dog hair were significantly reduced for the first 2 days after the dog was washed. However, by the third day, allergen levels had returned to normal. Airborne Can f 1 levels were modestly but significantly reduced after dog washing.

The results suggest that dog washing can reduce allergen levels on the animal. However, twice-weekly washing appears necessary to sustain the reduction. Airborne allergen levels in the home are also reduced after dog washing. However, the reductions achieved in this study are unlikely to have a significant impact on asthma control in patients allergic to dogs.

COMMENT: *This study answers the question commonly asked by patients with dog allergy, "Will washing my dog decrease my allergy symptoms?" Since there was no major change in airborne allergen and within 7 days allergen levels on the dog were back to baseline, the answer is clearly, "No."*
M. S. B.
Hodson T, Custovic A, Simpson A, et al: Washing to dog reduces dog allergen levels, but the dog needs to be washed twice a week.
J Allergy Clin Immunol 103:581-585, 1999. ♦♦

Pertussis Vaccination Does Not Increase Wheezing Risk

THE hypothesis that pertussis vaccination is a risk factor for wheezing in young children was evaluated in a prospective cohort study of 9,444 children followed up from birth to 42 months of age. Full information regarding wheezing symptoms, pertussis vaccination, and various environmental and biologic factors was obtained from a structured questionnaire administered to parents at 6, 18, 30, and 42 months after the birth of their child.

There was no difference in the risk of wheezing symptoms between children who did and did not receive pertussis vaccine, regardless of parental asthma or allergy status. By 18 months of age, the rate of wheezing was higher in nonvaccinated children. On logistic regression analysis, vaccinated children were not at increased risk of wheezing at any age of onset or in any pattern. Pertussis antigens are known to stimulate IgE antibody responses, but the clinical significance of this findings is unclear.

This study finds no difference in wheezing outcomes between children who have and have not received the pertussis vaccine. Pertussis vaccination is not a risk factor for asthma or atopy.

COMMENT: *Previous studies have suggested a link between pertussis vaccination and development of atopy and asthma in children. This prospective study from the United Kingdom failed to discover an association between wheezing in children and administration of the pertussis vaccine, even in the presence of a family history of asthma or allergies. This information is reassuring to all pediatric health care providers.*
M. S. B.

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Henderson J, North K, Griffiths M, et al: Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. **BMJ** 318:1173-1176, 1999. ♦♦

Measles Infection or Vaccination Reduces Hay Fever Risk for Children From Large Families

THE effects of measles infection, measles vaccination, and birth order on hay fever risk were studied in a British birth cohort of 6,000 children. About half of the children received the measles vaccine within 2 years after it was licensed. Information on childhood diseases was collected by parental interview when the children were 5, 10, and 16 years old. The 26-year interview also assessed the occurrence of hay fever within the past year.

Univariate analysis showed a significantly reduced risk of hay fever among children infected with measles, odds ratio 0.86 (95% confidence interval 0.76 to 0.96). In contrast, hay fever risk was significantly increased among children who received the measles vaccine, odds ratio 1.16 (1.03 to 1.31). However, birth order was a powerful confounding factor--it significantly affected not only hay fever risk but the likelihood of measles vaccination. The interaction between measles vaccination/infection and birth order was so strong that hay fever risk was significantly reduced for children with many older siblings who had either been vaccinated against or infected with measles.

For children with multiple order siblings, measles infection and measles vaccination are both independently associated with a reduced risk of hay fever. Children from small families who receive the measles vaccine are at increased risk of hay fever, whereas children from large families who are exposed to measles virus are at low risk. The previously reported link between birth order and allergic disease may involve differences in exposure or response to the measles virus.

COMMENT: *In this epidemiologic study, children with multiple older siblings were protected from developing seasonal allergy by either measles infection or vaccination. Children from smaller families who were neither vaccinated nor infected with measles had a higher prevalence of allergic rhinitis. This provides further evidence that viral immune stimulation early in life may reduce symptomatic atopic disease.*
S. A. T.
Lewis SA, Britton JR: Measles infection, measles vaccination and the effect of birth order in the aetiology of hay fever. **Clin Exp Allergy** 28:1493-1500, 1998. ♦♦

Gastroesophageal Reflux Is Correlated With Respiratory Symptoms in Asthma Patients

TWENTY-four-hour esophageal pH monitoring is a sensitive and specific technique for the diagnosis of gastroesophageal reflux (GER), which may be a trigger for asthma. Esophageal pH monitoring was performed in asthma patients to correlate respiratory symptoms with esophageal acid events. The retrospective study included 199 asthmatic patients who underwent 24 h esophageal pH testing.

Eighty-two percent of the patients had symptoms of GER. The rate of abnormal results on esophageal pH monitoring was 72% for patients with GER symptoms vs 29% in asthmatic patients without GER symptoms. Of 151 respiratory symptoms occurring during esophageal pH monitoring, nearly 80% were associated with esophageal acid events. About 90% of coughs were associated with esophageal acid. Theophylline treatment had no effect on the esophageal acid findings.

The study is the first to demonstrate a correlation between esophageal acid events and respiratory symptoms in patients with asthma. This association adds to the evidence that GER may serve as an asthma trigger. Gastroesophageal reflux is very common among patients with asthma. In asthma patients without GER symptoms, esophageal testing may be required to make the diagnosis.

COMMENT: *Of 199 asthmatics who qualified for this study, 164 (82%) had reflux symptoms. Asthmatics without reflux symptoms may require esophageal pH testing to detect GER. Most importantly, in asthmatics with GER, this study showed a high correlation of respiratory symptoms with esophageal acid.*
J. B.-M.
Harding SM, Guzzo MR, Richter JE: 24-h Esophageal pH testing in asthmatics: respiratory symptom correlation with esophageal acid events. **Chest** 115:654-659, 1999. ♦♦

Patch Testing Is Most Sensitive for Diagnosis of Cow's Milk Allergy

THREE different diagnostic tests for cow's milk allergy--skin prick testing, patch testing, and measurement of specific IgE antibodies--were compared. The study included 143 infants with skin and/or GI symptoms suggesting cow's milk allergy. All underwent a diagnostic elimination challenge, followed by cow's milk challenge. The results were compared with serum levels of cow's milk-specific IgE by RAST and the response to skin prick and patch testing.

Fifty percent of the cow's milk challenges were positive. Of the 72 positive challenges, 22 were immediate and 50 of delayed onset. Among infants with a positive cow's milk challenge, specific IgE concentrations were elevated in 26%, skin prick testing was positive in 14%, and patch testing was positive in 44%. Thirty-eight percent of patients with a positive cow's milk challenge did not have positive results on either skin testing or RAST. Most patients with a positive patch test had a negative prick test.

In infants with clinically suspected cow's milk allergy, skin patch testing appears to be a more sensitive diagnostic technique than skin prick testing or RAST for cow's milk-specific IgE. Patch testing is therefore ➤➤

likely to improve early detection of cow's milk allergy. For patients with negative test results but clinically suspected food allergy, or in those with positive patch test results, it is essential to confirm the diagnosis. This is most reliably done by elimination-challenge testing.

COMMENT: *The authors evaluated skin tests and the concentration of cow's milk-specific IgE antibodies in 143 infants under 2 years old, as contrasted with oral cow's milk challenge. Many patients with a negative puncture test had a positive patch test to cow's milk. The patch test was more sensitive than puncture test or RAST in detecting cow's milk allergy. The most reliable method was the elimination-challenge procedure.*
E. J. B.

Majamaa H, Moisio P, Holm K: Cow's milk allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. **Allergy** 54:346-351, 1999. ♦♦

Fluticasone Offers Similar Efficacy at Half the Dosage of Budesonide

TWO high-dose inhaled corticosteroid regimens--fluticasone propionate 400 µg/d and budesonide 800 µg/d--were compared for safety and efficacy in asthmatic children. The randomized trial included 333 children, aged 4 to 12 years, with moderate to severe asthma. After a 2-week run-in period, the children received 20 weeks of treatment with fluticasone, 200 µg twice daily via Diskus, or budesonide, 400 µg twice daily via Turbuhaler.

The main outcome measure, peak expiratory flow, improved from 236 to 277 L/min with fluticasone vs 229 to 257 L/min with budesonide. The two treatments offered similar symptom control, with no difference in the need for rescue mediation. There was no difference in serum cortisol suppression, with posttreatment cortisol values of 199 nmol/L with fluticasone and 183 nmol/L with budesonide. Linear growth was reduced by a mean of 6 mm in the budesonide group.

For children with moderate to severe asthma, inhaled fluticasone 400 µg/d is just as effective as budesonide 800 µg/d. Fluticasone yields a better improvement in peak expiratory flow, with equal control of clinical symptoms. The two drugs are similar in terms of serum cortisol suppression and hepatic or renal function. Fluticasone had less effect on linear growth than budesonide in this short term study.

COMMENT: *This study of 333 children with moderate to severe asthma (aged 4 to 12) compares the efficacy and adverse effects of inhaled fluticasone propionate 400 µg/d with those of budesonide 800 µg/d. Fluticasone was as effective as budesonide at half the dose, with improved peak expiratory flow and comparable control of symptoms. Growth was reduced with budesonide compared to fluticasone, but there was no difference in serum cortisol suppression.*
J. B.-M.

Ferguson AC, Spier S, Manjra A, et al: Efficacy and safety of high-dose inhaled steroids in children with asthma: a comparison of fluticasone propionate with budesonide. **J Pediatr** 134:422-427, 1999. ♦♦

Passive Dry Powder Inhaler Achieves Same Bronchodilator Response as Pressurized Inhaler

NEW dry powder inhalers (DPIs) have been developed in response to the phase-out of chlorofluorocarbon (CFC) propellants in pressurized metered-dose inhalers (pMDIs). This randomized, placebo-controlled trial compared a new albuterol DPI, the Clickhaler, with a pMDI in patients with moderate to moderately severe asthma. The 16 patients included in the study all had stable disease with confirmed albuterol reversibility. The bronchodilator response to albuterol 200 µg delivered via Clickhaler DPI at flow rates of 15, 30, and 60 L/min was compared with the response to albuterol via pMDI at 30 L/min and to placebo. Outcome measures included FEV_1, forced vital capacity (FVC), and FEV_1/FVC.

The bronchodilator response to albuterol via Clickhaler was equivalent at all flow rates studied. The response to Clickhaler, at all flow rates, was not significantly different from the response to pMDI. All active treatments were superior to placebo. There were few adverse events with any of the delivery methods studied.

In patients with moderate to moderately severe, stable asthma, albuterol delivered via the Clickhaler DPI achieves a similar bronchodilator response to a pMDI. This is so at a flow rate as low as 15 L/min. In addition to avoiding CFCs, the new DPIs ensure aerosolization of the drug as the patient inhales.

COMMENT: *This new delivery device represents yet another dry-powder delivery system as the industry adapts to the CFC-free mandate. Efficacy independent of inspiratory flow rate may offer an advantage over other systems.*
S. A. T.

Newhouse MT, Nantel NP, Chambers CB, et al: Clickhaler (a novel dry powder inhaler) provides similar bronchodilation to pressurized metered-dose inhaler, even at low flow rates.
Chest 115:952-956, 1999. ♦♦

Salmeterol Plus Low-Dose Fluticasone Is Superior to Increased-Dose Fluticasone

THIS randomized trial compared two treatment approaches for asthma patients who remain symptomatic while taking low-dose fluticasone propionate, 88 µg twice daily. One group stayed on the same dose of fluticasone but added salmeterol, 42 µg twice daily. The other group had their fluticasone dosage increased to 220 µg twice daily. Both treatments continued for ➤➤

24 weeks. The multicenter study included 437 patients, all at least 12 years old. The main efficacy outcome was morning peak expiratory flow. Asthma exacerbations and other adverse events were evaluated as well.

Lung function and symptom control were both significantly better with fluticasone plus salmeterol than with increased-dose fluticasone. Morning peak expiratory flow increased by a mean of 47 L/min in the fluticasone plus salmeterol group, compared with 24 L/min with the higher dose of fluticasone. The percentages of symptom-free days increased by 26% vs 10%, respectively. Patients receiving fluticasone plus salmeterol had fewer adverse events; other adverse events were comparable between groups.

In patients with corticosteroid-resistant asthma, adding salmeterol to low-dose fluticasone is superior to increasing the dose of fluticasone. The addition of salmeterol improves pulmonary function and symptom control without increasing the corticosteroid dosage. Salmeterol plus the lowest recommended dose of fluticasone appears to be an effective treatment option for patients with persistent asthma.

COMMENT: *Previous studies have shown that adding salmeterol to inhaled steroids has a similar therapeutic effect to doubling the dose of inhaled steroids. This study demonstrates that adding salmeterol to fluticasone 44 μg 2 puffs bid is actually superior to increasing the fluticasone dosage to 110 μg 2 puffs bid. The salmeterol-low dose fluticasone group had statistically significant improvements in morning peak flow, FEV_1, symptom-free days and nights, and symptom scores. Although the combination approach is more labor intensive as well as expensive, it provides the win-win results of improving efficacy while reducing steroid dose.*
S. R. W.

Condemi JJ, Goldstein S, Kalberg C, et al: The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma.
Ann Allergy Asthma Immunol 82:383-389, 1999. ♦♦

Extension Trial Supports Long-Term Safety of Zafirlukast

A PREVIOUS 13-week randomized, placebo-controlled trial found zafirlukast to be safe and effective for patients with mild to moderate asthma previously treated with β_2-agonists alone. Four hundred forty-three patients, including 133 who had previously been assigned to placebo, entered a 36-week open-label extension phase. Two hundred twenty-six patients, including 96 originally from the placebo group, completed the extension phase.

Eighty percent of patients reported adverse events during the extension phase, most frequently pharyngitis and headache. However, the adverse event rate during open-label treatment was not significantly different from that reported by patients in the placebo group during the double-blind trial. A few patients developed significant elevations of liver enzymes during zafirlukast treatment, though only 1 was withdrawn from the study for this reason. There were no significant changes in physical examination or ECG findings. By the third week of the extension phase, both groups of patients showed modest but significant improvements in spirometric efficacy assessments, which were maintained throughout zafirlukast treatment. The overall treatment failure rate was 13%; most failures were acute exacerbations managed with oral steroids. Compliance was very high.

Data from this 39-week extension phase support the safety and efficacy of zafirlukast for patients with mild, persistent asthma. The treatment is well tolerated and provides good long-term asthma control. The adverse event rate is similar to that in patients receiving placebo.

COMMENT: *Now that antileukotriene agents have been around for a while, "long-term" (ie, 1-year) safety data are beginning to emerge. This study analyzed 443 adult patients with persistent asthma who entered an open-label extension of a zafirlukast vs placebo study. ALT/AST elevation more than five times the upper limit of normal was seen in 2 patients, but overall the rate of liver function abnormality was not significantly different from placebo. In general adverse event occurrences were no greater than placebo. The treatment failure rate in patients receiving zafirlukast during the trial extension was only 13.1%*
S. R. W.

Grossman J, Smith LJ, Wilson AM, Thyrum PT: Long-term safety and efficacy of zafirlukast in the treatment of asthma: interim results of an open-label extension trial.
Ann Allergy Asthma Immunol 82:361-369, 1999. ♦♦

Trace Element Supplements Improve Humoral Response to Vaccination in Elderly

THIS study examined the effects of long-term supplementation with trace elements or vitamins on the risk of infection among elderly nursing home residents. Seven hundred twenty-five residents of 25 French nursing homes were randomized in double-blind fashion to receive 2 years of supplementation with trace elements, zinc sulfate 20 mg and selenium sulfide 100 μg; vitamins, ascorbic acid 120 mg, beta carotene 6 mg, and α-tocopherol 15 mg; trace elements plus vitamins; or placebo. In addition to infectious morbidity and mortality, the study assessed delayed-type hypersensitivity skin responses to various antigens and the antibody response to influenza vaccine.

By 6 months, the proportions of residents with nutrient deficiencies decreased significantly in the groups receiving active supplementation. These improvements were maintained throughout the study. Delayed-type hypersensitivity skin response was unchanged in any of the treatment groups. Residents receiving trace elements, with or without vitamins, had significantly higher antibody titers in response to influenza vaccination. In contrast, antibody titers were significantly reduced in the vitamin-only group. Residents receiving trace elements were significantly less likely to be free of respiratory tract infections. None of the treatments ➤➤

reduced the risk of urogenital infections or significantly altered survival.

Micronutrient supplementation can correct vitamin and trace element deficiencies in institutionalized elderly patients. The antibody response to influenza vaccine is improved and the risk of respiratory infections reduced in residents receiving zinc and selenium supplementation. Trace element supplementation could have an important benefit in improving resistance to infections among elderly people.

COMMENT: *Antioxidant supplements are thought to improve immunity and thereby reduce infectious morbidity. This randomized, double-blind, placebo-controlled intervention study included 725 institutionalized elderly patients (>65 years) from 25 geriatric centers in France. Patients received an oral supplement of nutritional doses of trace elements (zinc and selenium sulfide) or vitamins (beta carotene, ascorbic acid, and vitamin E) or a placebo with a 2 x 2 factorial design for 2 years. Low-dose supplementation of zinc and selenium provided significant improvement in elderly patients by increasing the humoral response after vaccination. The implications could be very important in reducing morbidity from respiratory tract infections.*
E. J. B.

Girodon F, Galan P, Monget A-L, et al: Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial.
Arch Intern Med 159:748-754, 1999. ♦♦

Peak Expiratory Flow Rate in the ED Does not Predict Asthma Relapses

ADULT patients seeking treatment for acute asthma in the emergency department (ED) were studied to identify variables associated with subsequent asthma relapse. The analysis included 939 patients, aged 18 to 54 years, who had a physician diagnosis of acute asthma, were discharged to home from the ED, and did not have comorbid respiratory conditions. Telephone follow-up was available for 641 patients. An urgent or unscheduled visit to a physician because of worsening asthma symptoms in the 2 weeks after ED discharge was considered a relapse.

Seventeen percent of patients had a relapse during the study period. Peak expiratory flow rate (PEFR) measured in the ED was similar for patients with vs without relapse. Several factors were associated with relapse on multivariate analysis, controlling for age, sex, race, and primary care provider status. These included a history of numerous ED or urgent clinic visits for asthma, odds ratios (ORs) 1.3 and 1.4 per 5 visits in the past year; home use of a nebulizer, OR 2.2; multiple asthma triggers, OR 1.1 per trigger; and longer duration of asthma symptoms, OR 1.5 for symptoms lasting 1 to 7 days.

Several different findings in the patient history can predict the risk of relapse after an ED visit for acute asthma. However, PEFR measured in the ED is not a significant predictor. Future research may determine if patients identified by these criteria would benefit from more aggressive management in the ED.

COMMENT: *Peak expiratory flow rate (PEFR) monitoring in the emergency department is clearly not the solution to preventing "bounce-backs" in inner-city asthma. Of interest, the patients who relapsed more often had recently used inhaled or systemic corticosteroids than those who did not relapse. This observation, together with the huge difference in tendency to have had prior asthma hospitalizations and emergency department visits, suggests that these patient groups may have distinct asthma phenotypes.*
S. A. T.

Emerman CL, Woodruff PG, Cydulka RK, et al: Prospective multicenter study of relapse following treatment for acute asthma among adults presenting to the emergency department. **Chest** 115:919-927, 1999. ♦♦

Low-Level HDI Exposure Does Not Reduce Pulmonary Function

HEXAMETHYLENE diisocyanate (HDI) is partially prepolymerized to the HDI biuret and the HDI trimer in the production of polyurethanes. Like other diisocyanates, HDI can cause occupational asthma. This study examined pulmonary function over time in workers with chronic, low-level exposure to HDI. Starting in 1991, when production of HDI biuret and HDI trimer began at the study plant, workers underwent annual pulmonary function tests. Industrial hygiene monitoring during the study period found that time-weighted exposure to HDI without respiratory protection (about 2 h/d) was 0.5 ppb, with an average daily peak exposure of 2.9 ppb.

Forced vital capacity (FVC) decreased by about 0.026 L/y in exposed workers, compared with 0.025 L/y in controls. Rates of decline in FEV_1 were 0.044 and 0.041 L/y, respectively.

At the low levels measured in this industrial setting, chronic exposure to HDI does not appear to cause an accelerated decline in pulmonary function. Permissible exposure limits for HDI have been based on studies of toluene diisocyanate, which does cause declines in pulmonary function with long-term, low-level exposure.

COMMENT: *Isocyanate exposure remains one of the most important causes of occupational asthma. In this well-controlled prospective, longitudinal study, exposure to HDI in an HDI-manufacturing plant did not result in accelerated loss of pulmonary function. While these authors did not prove complete safety, unprotected exposure to HDI at average levels of 0.5 ppb did not result in change in pulmonary function. These are important, well-studied observations.*
A. M. ➤➤

Hathaway JA, DeWilde A, Shepperly DC, et al: Evaluation of pulmonary function in workers exposed to hexamethylene diisocyanate.
J Occup Environ Med 41:378-383, 1999. ♦♦

Beclomethasone Has a Larger Effect Than Montelukast in Chronic Asthma

THIS randomized trial compared the oral leukotriene receptor antagonist montelukast with inhaled beclomethasone for the treatment of chronic asthma. The study included 895 adult patients with asthma; all had an FEV1 between 50% and 85% of predicted and required daily use of a controller medication. They received 12 weeks of treatment with oral montelukast, 10 mg once daily at bedtime; inhaled beclomethasone, 200 µg twice daily; or placebo. The main outcome measures were daytime asthma symptom score and FEV_1.

Compared with baseline, FEV_1 increased by 13% with beclomethasone vs 7% with montelukast vs 1% with placebo. Daily symptom score decreased by 0.62 with beclomethasone vs 0.41 with montelukast vs 0.17 with placebo. Both active treatments increased peak expiratory flow rates and quality of life and reduced nighttime awakenings and asthma attacks. Both treatments increased the number of days with asthma control while reducing the number of days with asthma exacerbations. The mean clinical benefit was greater with beclomethasone, though the onset of action was faster and the initial effect greater with montelukast. Peripheral blood Eosinophil counts decreased to a similar extent with montelukast and beclomethasone, both of which had a tolerability profile similar to that of placebo.

For patients with chronic asthma, both oral montelukast and inhaled beclomethasone are effective in increasing FEV_1 and reducing daytime symptoms. Both treatments prevent asthma exacerbations. Beclomethasone has a greater clinical effect, while montelukast has a more rapid onset.

COMMENT: *This is one of the pivotal studies comparing inhaled corticosteroids with leukotriene modifiers. In this large well-controlled, multicenter trial in mild to moderate asthmatics, montelukast appeared safe and effective. As previously reported in other studies, beclomethasone responses were greater than those to montelukast. Further studies will be required to determine the precise role of montelukast in chronic asthma.*
A. M.
Malmstrom K, Rodriguez-Gomez G, Guerra J, et al: Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma: a randomized, controlled trial.
Ann Intern Med 130:487-495, 1999. ♦♦

Oral Corticosteroids Reduce Costs in Pediatric Asthma Exacerbations

CORTICOSTEROIDS plus β-agonists reduce hospitalization rates for children and adults with asthma, and oral corticosteroids are an effective outpatient treatment for asthma. This randomized trial compared oral prednisone and IV methylprednisolone, both at 4 mg/kg/day, in the treatment of children hospitalized for acute asthma exacerbations. The 66 study patients received either oral prednisone, 2 mg/kg twice daily, maximum dose 120 mg; or IV methylprednisolone, 1 mg/kg 4 times daily, maximum dose 60 mg.

Length of hospital stay, the main outcome measure, was not significantly different: 70 h in the prednisone group vs 78 h in the methylprednisolone group. Mean time for weaning to β-agonists in 6 h intervals was 59 h in the prednisone group vs 68 h in the methylprednisolone group. Duration of supplemental oxygen administration was also shorter with prednisone, 30 vs 52 h.

In pediatric patients hospitalized for acute asthma exacerbations, oral prednisone is just as effective as IV methylprednisolone. Since IV methylprednisolone is 10 times more expensive, oral prednisone has the potential to reduce hospital costs substantially. The optimal dose and dosage frequency of oral prednisone remain to be determined.

COMMENT: *Finding the most cost-effective approach to the management of status asthmaticus is important since hospitalization is the single highest direct cost item in the disease. Becker et al prove that oral corticosteroids are just as effective as IV corticosteroids in pediatric status asthmaticus. Not only do oral corticosteroids decrease costs, they limit the trauma to the child caused by insertion of an IV line.*
M. S. B.
Becker JM, Arora A, Scarfone RJ, et al: Oral versus intravenous corticosteroids in children hospitalized with asthma. **J Allergy Clin Immunol** 103:586-590, 1999. ♦♦

Asthmatic Airway Inflammation Linked to Reduced Cell Apoptosis

REDUCED apoptosis of immune effector cells plays a key role in the evolution of various chronic inflammatory processes, such as rheumatoid arthritis. This study examined the role of inflammatory cell apoptosis in airway inflammation in asthma.

Apoptosis was analyzed in eosinophils, macrophages, and T-lymphocytes using bronchial biopsy specimens from 30 patients with asthma, 26 patients with chronic bronchitis, and 15 controls. The asthma patients showed reduced numbers of apoptotic eosinophils and macrophages, compared to the patients with chronic bronchitis. Patients with lower numbers of apoptotic eosinophils and macrophages had more severe asthma. Numbers of apoptotic T-lymphocytes were low in all three groups. The B-cell lymphoma leukemia-2 protein appeared to play a role in the enhanced T-cell survival in asthmatic airways.

Airway inflammation in asthma is associated with reduced apoptosis of various inflammatory cells in the airway, leading to enhanced cell survival. Thus cell

apoptosis may play a key role in asthma-associated chronic airway inflammation. Defective cell apoptosis could provide a valuable new target for asthma therapies.

COMMENT: *This article increases our knowledge of apoptosis in asthma inflammation. The authors show a significant relationship of asthma with depressed apoptosis of eosinophils and macrophages in the lungs. These data may lead to novel medical treatments for asthma that "turn on" apoptosis in inflammatory cells.*
M. S. B.
Vignola AM, Chanez P, Chiappara G, et al: Evaluation of apoptosis of eosinophils, macrophages, and T lymphocytes in mucosal biopsy specimens of patients with asthma and chronic bronchitis.
J Allergy Clin Immunol 103:563-573, 1999. ♦♦

Study Examines Costs of and Compliance With Immunotherapy

THERE are few data on the use of immunotherapy in the general population, on patient compliance with this form of treatment, or on the associated costs. Review of an HMO data base found that about 2% of patients with asthma or rhinitis received at least one immunotherapy injection over a 6-year period (2,667 of 122,196 members). Of these, 603 patients met all eligibility requirements, including duration of membership, pharmacy coverage, and availability of automated records. The duration of immunotherapy and the costs of immunotherapy and related care were evaluated.

The patients had a total of 28,266 immunotherapy encounters, with a median of 48 per patient. More than 80% received immunotherapy for multiple allergens, most commonly including ragweed. Duration of therapy was significantly shorter in female patients, patients in their teens, and those for whom the treatment allergen was unknown. Only 33% of patients with sufficient follow-up received the full course of 61 immunotherapy injections. The rate of completed immunotherapy was higher for patients with both rhinitis and asthma and for patients treated with ragweed allergen. In 54% of cases, the decision to discontinue immunotherapy was made by the patient. The cost per person-year of immunotherapy was $438 overall, $698 for those who completed immunotherapy, and $247 for those who failed to complete. Costs for the care of rhinitis and asthma were the factors most strongly affecting the costs of immunotherapy. More than 50% of nonimmunotherapy costs were for prescription drugs; less than 20% were for hospitalization.

This study in a large HMO population finds that only 2% of patients with asthma or rhinitis receive immunotherapy. Rates of completed immunotherapy are low, even when patients are screened to optimize compliance. Patients who complete immunotherapy have more severe disease and accordingly higher costs for nonimmunotherapy care.

COMMENT: *These authors from the Harvard Medical School and Harvard Pilgrim Health Care present objective data on the utilization of immunotherapy for allergic disease. Their findings confirm other observations that immunotherapy appears to be used more commonly in the more severe cases. The results further highlight the problem of noncompliance. Unfortunately, this review does not address the potential long-term costs and benefits of immunotherapy for younger patients with less severe disease.*
A. M.
Donahue JG, Greineder DK, Connor-Lacke L, et al: Utilization and cost of immunotherapy for allergic asthma and rhinitis.
Ann Allergy Asthma Immunol 82:339-347, 1999. ♦♦

Nonfeather Pillows May Increase Rhinitis Risk

THIS survey study examined the effects of cat or dog ownership and type of pillow on the prevalence of rhinitis. A questionnaire was given to 2,555 adult relatives or friends of patients seen at outpatient clinics. The questionnaire asked about the presence of perennial or seasonal rhinitis, defined as having 3 or more symptoms of rhinitis all year or for part of the year, respectively. Respondents were also asked whether they used a feather pillow or synthetic pillow, and whether they had furred pets, currently and during childhood.

About 5% of respondents met the criteria for perennial rhinitis (106 cases) and 230 for seasonal rhinitis (230 cases). Both types of rhinitis were strongly associated with the use of nonfeather pillows. Odds ratios were 1.85 (95% confidence interval 1.43 to 2.5) and 2.63 (1.67 to 5.0), respectively. Seasonal rhinitis was only weakly associated with current dog ownership; childhood pet ownership was not associated with either type of rhinitis.

Contrary to popular belief, the likelihood of perennial and seasonal rhinitis is not increased by use of a feather pillow or ownership of furred pets. Synthetic pillows are strongly associated with an increased risk of rhinitis, perhaps because they harbor higher levels of dust mite antigen than feather pillows. Though this study had a very high response rate, friends and relatives of hospital outpatients are not necessarily representative of the general population.

COMMENT: *Recent studies have demonstrated that, contrary to conventional wisdom, polyester pillows harbor higher levels of house dust mite allergen than do feather pillows. This study suggests that use of nonfeather pillows also increases the risk of developing rhinitis.*
M. S. D.
Frosh AC, Sandhu G, Joyce R, Strachan DP: Prevalence of rhinitis, pillow type and past and present ownership of furred pets.
Clin Exp Allergy 29:457-460, 1999. ♦♦

Children with BHR and High Total IgE Are Vulnerable to Respiratory Effects from Air Pollution

THE effects of air pollution on rates of upper and lower respiratory symptoms were examined ➤➤

in children with bronchial hyperresponsiveness (BHR) and relatively high serum IgE concentrations. The study included 632 Dutch children living in rural or urban areas. Over a 3-month period in the winter, daily recordings were made of upper and lower respiratory symptoms and peak expiratory flow. Children with a serum total IgE concentration higher than the median value (60 kU/L) were considered to have high IgE. Logistic regression was performed to analyze the respiratory effects of airborne particulate matter with a diameter of 10 μm, black smoke, sulfur dioxide, and nitrogen dioxide.

Of 459 children with complete data, 26% had BHR and high serum total IgE, 36% had no BHR and below-median IgE, 15% had BHR and below-median IgE, and 23% had no BHR but high IgE. For children with BHR and high IgE, lower respiratory symptoms increased with increasing air pollution. For this group only, lower respiratory symptoms increased by 32% to 139% for each 100 $\mu m/m^3$ increase in particulate matter, and by 16% to 131% for each 40 $\mu m/m^3$ increase in black smoke, sulfur dioxide, or nitrogen dioxide. The BHR/high IgE group was more likely to have a greater than 10% reduction in peak expiratory flow in association with increased airborne particulate matter and black smoke. None of the other BHR/IgE groups showed any consistent relationship between air pollutant levels and respiratory symptoms or peak expiratory flow.

The results suggest that children with BHR and above-median serum total IgE are at high risk of developing respiratory symptoms in response to high levels of air pollution. Though the size of this effect is not large, about one-fourth of children fall into the BHR/high IgE group. Thus the public health impact is likely to be substantial. Children in this group should be targeted for public health interventions.

COMMENT: *In children with BHR and relatively high total IgE, the prevalence of lower respiratory symptoms increased significantly by between 32% and 139% for each 100 $\mu m/m^3$ increase in particulate, and between 16% and 131% for each 40 $\mu m/m^3$ increase in black smoke, SO_2 or NO_2. Decrease in peak expiratory flow of more than 10% in that group was more common with increased airborne particulate matter and black smoke.*
E. J. B.

Boezen HM, van der Zee SC, Postma DS, et al: Effects of ambient air pollution on upper and lower respiratory symptoms and peak expiratory flow in children. **Lancet** 353:874-878, 1999. ♦♦

Inhaled Budesonide Bolus Reverses Subsensitivity to AMP Bronchoprotection

PREVIOUS reports have suggested that long-acting β_2-agonists be added to low-dose inhaled corticosteroid for asthma control. However, patients taking long-acting β_2-agonists develop subsensitivity to the bronchoprotective and bronchodilator effects of these medications, accompanied by down-regulation of lymphocyte β_2-adrenoreceptors. Systemic corticosteroids can rapidly reverse this subsensitivity. The current study examined the ability of a bolus dose of inhaled corticosteroid to achieve the same effect.

The study included 10 patients with stable, mild to moderate asthma, mean FEV_1 81% of predicted. All patients were taking inhaled corticosteroids. All responded to adenosine monophosphate (AMP)--the provocative concentration producing a 20% reduction in FEV_1 (PC_{20}) was less than 200 mg/mL in each case. In randomized, crossover fashion, the patients completed two 1-week periods of treatment with formoterol dry powder, 24 μg bid. At the end of both treatment periods, the last dose was taken with a single dose of placebo or budesonide, 1,600 μg, via Turbuhaler. Two hours after the first and last formoterol dose, the patients performed an AMP challenge. Before and after formoterol treatment, lymphocyte β_2-adrenoreceptor density was measured.

There was no change in PC_{20} after the first dose of formoterol between the two treatment periods. However, the PC_{20} after the last dose of formoterol was significantly increased when that dose was taken with budesonide vs placebo: 427 vs 99 mg/mL. Lymphocyte β_2 adrenoreceptor density was significantly down-regulated by formoterol plus placebo but not by formoterol plus budesonide.

As reported with systemic corticosteroids, a bolus of inhaled budesonide provides rapid reversal of subsensitivity to AMP bronchoprotection. The associated β_2-adrenoreceptor down-regulation is also reversed. More study is needed to assess the value of giving high-dose inhaled corticosteroids with β_2-agonists during acute episodes of bronchoconstriction.

COMMENT: *A small but convincing study demonstrating that the subsensitivity of airway beta-2-adrenoreceptors seen in asthmatics receiving regular long-acting beta-agonists is rapidly reversed by a single bolus of 1,600 μg of budesonide via Turbuhaler. This requires confirmation in a larger population of patients with rapid-onset asthma to assess whether a higher dose of budesonide might be required to achieve the same result in patients with acute asthma.*
J. B. M.

Aziz I, Lipworth BJ: A bolus of inhaled budesonide rapidly reverses airway subsensitivity and β_2-adrenoreceptor down-regulation after regular inhaled formoterol. **Chest** 115:623-628, 1999. ♦♦

"Allergen-Avoidance" Day-Care Centers Can Reduce Exposure to Pet Allergens

EVEN in public areas where pets are not allowed, pet allergens may accumulate because of transport by individuals who have pets at home. In Sweden, special day-care centers have been established for children with severe atopy, who otherwise would have problems with day-care attendance. This study examined pet allergen levels in 12 allergen-avoidance day-care centers, compared with 22 conventional day-care centers. Settled dust samples were collected for measurement of Fel d 1 and Can f 1 by enzyme-linked immunosorbent assay. Airborne Fel d 1 levels were measured as well. ➤➤

The effects of pet ownership by staff and children on allergen levels were assessed, along with the impact of ventilation and general cleaning routines. Because of the high likelihood of selection bias, health effects were not addressed.

All day-care centers had both cat and dog allergen in settled dust. However, these allergen concentrations were significantly lower in the allergen-avoidance centers. Airborne cat allergen levels were lower as well. Day-care centers with higher air change rates had lower levels of airborne cat allergen, especially centers with no cat owners. Frequency of general cleaning did not appear to affect levels of pet allergen.

Allergen-avoidance day-care centers--in which children and staff are restricted from keeping house pets--can reduce allergen exposure to atopic children. Allergen levels can also be reduced by adequate ventilation, though cleaning routines appear to have no effect. It is probably impracticable to achieve a truly allergen-free environment.

COMMENT: *Several studies have demonstrated that schools and offices can develop significant levels of pet allergen by passive carriage on the clothes of individuals who have pets at home. This study suggests that ventilation systems with greater air exchange rates can reduce levels of Fel d 1 cat allergen*
M. S. D.
Wickman M, Egmar A-C, Emenius G, et al: Fel d 1 and Can f 1 in settled dust and airborne Fel d 1 in allergen avoidance day-care centres for atopic children in relation to number of pet-owners, ventilation, and general cleaning. **Clin Exp Allergy** 29:626-632, 1999. ♦♦

Study Estimates One Percent Prevalence of Nut Allergy

A survey of the general U.S. population was performed to assess the prevalence of allergy to peanuts and tree nuts, one of the major causes of fatal food-induced allergic reactions. The nationwide phone survey reached 4,374 households, representing a participation rate of 67%. The respondents provided information on 12,032 individuals.

The frequency of self-reported peanut or tree nut allergy was 1.4%. Details of the reactions were obtained for 131 individuals. Ten percent were excluded because the reactions lacked the typical features of IgE-mediated reactions: hives, angioedema, wheezing, throat tightness, vomiting, and diarrhea. Of the remaining 118 subjects, 45% reported having more than five such reactions during their lives. However, only 53% had ever seen a physician about the problem, and only 7% carried self-injectable epinephrine.

The investigators clarified their estimate by assuming that subjects who did not provide a description of their reactions would be excluded and correcting for a 7% false-positive rate. This resulted in a final "corrected" 1.1% prevalence of peanut/tree nut allergy, with a 95% confidence interval of 1.0% to 1.4%

Extrapolated to the U.S. population, this estimate suggests that 3 million Americans are allergic to peanuts or tree nuts. Even though they are at risk for frequent, severe reactions, only about half of these patients have ever seen a physician for their problem, while very few carry epinephrine for emergency use.

COMMENT: *There has been increasing awareness of peanut and tree nut allergy in the United States, but the true incidence in the population has not been known. This survey gives the allergy community much-needed information on the high prevalence of this life-threatening condition. It also points out the need to educate the peanut- and tree-nut-allergic patient about the need to be properly evaluated and to carry epinephrine for emergency use.*
M. S. B.
Sicherer SH, Muñoz-Furlong A, Burks W, Sampson HA: Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey.
J Allergy Clin Immunol 103:559-562, 1999. ♦♦

Early IVIG Replacement Improves Outcomes in X-Linked Agammaglobulinemia

THE effects of early, prolonged IV immunoglobulin (IVIG) replacement therapy were reviewed in 31 patients with X-linked agammaglobulinemia (XLA). The patients started IVIG at a median age of 24 months, within 3 months after they were diagnosed as having XLA. They received >0.25 g/kg of IVIG every 3 weeks; mean dose was 390 mg/kg. Median residual IgG level was 700 mg/dL. The patients were followed up for a median of 123 months.

IV immunoglobulin replacement therapy was associated with a significant reduction in the rate of bacterial infections requiring hospital admission: from 0.4 to 0.6 per patient per year. This risk was lower during periods with residual IgG levels of greater than 800 mg/dL. However, there were 3 cases of enteroviral meningoencephalitis, 1 of which was fatal; 3 cases of exudative enteropathy; and 1 case of aseptic arthritis. Thirty patients were still alive at a median age of 144 months. Respiratory function tests and CT scans in 23 patients revealed chronic sinusitis in 20, bronchiectasis in 6, and an obstructive syndrome in 3.

The results support the use of early IVIG replacement therapy for patients with XLA. Replacement therapy achieving IVIG levels of greater than 500 mg/dL reduces the rate of severe bacterial infections and pulmonary insufficiency. However, the IVIG replacement regimen used in this study was not sufficiently intensive to prevent bronchiectasis, chronic sinusitis, and enteroviral and other nonbacterial infections. More study is needed to optimize IVIG replacement therapy for XLA, with particular attention to treatment adherence and quality of life.

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COMMENT: *In 31 children with X-linked agammaglobulinemia, IVIG replacement therapy initiated within 3 months of diagnosis yielded residual serum IgG levels of greater than 500 mg/dL. This treatment was effective in preventing acute bacterial infections, diffuse bronchiectasis, and pulmonary insufficiency. However, most patients had chronic sinusitis and a few had serious nonbacterial infections, including potentially fatal enteroviral meningoencephalitis. Further studies are needed to determine whether more intensive replacement therapy would improve outcome further.*
J. B.-M.
Quartier P, Debré M, De Blic J, et al: Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. **J Pediatr** 134:589-596, 1999. ♦♦

Fluticasone Has Higher Systemic Potency Than Budesonide or Beclomethasone

A study was performed in 16 healthy volunteers to assess the systemic bioavailability of budesonide, 4 mg, given by inhalation via metered-dose inhaler (MDI) alone, MDI with a 750 mL spacer, dry powder inhaler, and nebulizer. Bioavailability, assessed in terms of cortisol suppression, was also measured after oral administration of budesonide 4 mg. In addition, the systemic potencies of three inhaled steroids given by MDI with a large-volume spacer were compared. For this comparison, each subject took 4 mg of budesonide, fluticasone, and beclomethasone and 2 mg each of budesonide and fluticasone.

The percentage suppression of morning cortisol produced by budesonide 4 mg was 73% with MDI alone and 72% with dry powder inhaler, compared to 42% with MDI and a spacer, and 14% with oral administration. An insignificant increase in morning cortisol was noted after nebulized budesonide. When given by MDI with a spacer, fluticasone produced 86% suppression at a 4 mg dose and 72% suppression at a 2 mg dose. Budesonide produced only 43% suppression at a 4 mg dose and 25% suppression at a 2 mg dose.

In healthy volunteers as in asthma patients, fluticasone has substantially higher systemic potency than budesonide or beclomethasone when all are given at microgram-equivalent doses. The findings suggest that fluticasone and budesonide have a similar therapeutic index if given in equipotent doses. The bioavailability of budesonide is greatly affected by the inhaler device used.

COMMENT: *This study in healthy, nonsmoking volunteers uses extremely high doses of inhaled corticosteroids to compare the systemic bioavailability of fluticasone and budesonide. Despite known differences in potency and absorption across mucosal surfaces, when clinically equivalent doses are administered, these drugs appear to have comparable overall systemic bioavailabilities.*
S. A. T.
Wales D, Makker H, Kane J, et al: Systemic bioavailability and potency of high-dose inhaled corticosteroids: A comparison of four inhaler devices and three drugs in healthy adult volunteers.
Chest 115:1278-1284, 1999. ♦♦

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