

## PATHOPHYSIOLOGY

### A RANDOMIZED CONTROLLED TRIAL OF THE EFFECT OF PERTUSSIS VACCINES ON ATOPIC DISEASE

Nilsson L, Kjellman M, Bjorksten B. *Arch Pediatr Adolesc Med.* 1998;152:734–738

*Purpose of the Study.* The development of allergy has been linked to a variety of factors, including genetic predisposition, environment, smoke exposure, and infection. Pertussis is known to act as an adjuvant to the development of sensitization in laboratory animal models. This observation was the background for this study, the purpose of which was to determine if pertussis vaccination was associated with allergen sensitization and the development of allergic disease in children.

*Study Population.* The 669 children participating were part of the larger Swedish vaccine trial. This study was a randomized, double-blinded comparison of the effects of the 2-component acellular pertussis vaccine, the 5-component acellular pertussis vaccine, whole-cell pertussis vaccine, and DT vaccine used as a placebo.

*Methods.* The children were followed from 2 months until 2½ years of age. They were evaluated initially 1 month after the third immunization and again at 2½ years. Questions were asked of the caretakers regarding smoke, dampness, pets, feeding history, and allergic symptoms of the skin, nose, or lower airway. Skin testing to milk, egg white, and cat was done at the 7-month visit. At 2½ years the children were again tested to egg, cat, dog, dust mite, timothy grass, and birch tree pollen. Diagnostic criteria were set for asthma, atopic dermatitis, allergic rhinitis, and urticaria.

*Results.* Allergic disease developed in 201 of the 699 children (28.8%). Atopic dermatitis occurred in 140 (21%), asthma in 67 (10%), allergic rhinitis in 14 (2%), urticaria in 15 (2%), and food allergy in 12 (2%). One or more positive skin tests occurred in 91 (14%) at 7 months and 63 (9%) at 2½ years. The cumulative incidence of atopic disease at age 2½ as well as individual manifestations of allergy were similar in the three pertussis vaccination groups and the DT group. The cumulative incidence of positive skin prick tests at both ages did not differ significantly between the groups. There were no differences in the prevalence of smoke, dampness, pets, preterm births, or gender in all four groups. There were 47 children who developed pertussis—25 in the DT group. The occurrence of pertussis was associated with an increased cumulative incidence of bronchial asthma (19% vs 9% in uninfected children).

*Conclusions.* This study showed that the incidence and manifestations of allergy during the first 2½ years of life was not increased after pertussis vaccination.

*Reviewer's Comments.* There has always been a concern that pertussis vaccines may augment the occurrence of allergy. While previous studies using smaller numbers of children have suggested an association, this larger study has shown that the pertussis vaccine did not cause an increase in allergy. This study is a solid contribution to the issue of allergy development and should help in counseling parents regarding preventative health care measures.

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### ARYLAMINE N-ACETYLTRANSFERASE (NAT2) GENE MUTATIONS IN CHILDREN WITH ALLERGIC DISEASES

Zielinska E, Wojciech N, Bodalski J, Stanczyk A, Bolanowski W, Rebowski G. *Clin Pharmacol Ther.* 1997; 62:635–642

*Purpose of the Study.* A case control study was performed to determine the differences in the distribution of mutation frequency and genotypes that encode normal and defective activity of *N*-acetyltransferase in children with atopic allergies compared with healthy children. Previous studies in persons with chronic allergic rhinitis have shown an overrepresentation of phenotypically slow acetylators. This was the first time *NAT2* genotype, which unlike the acetylation phenotype is not affected by environmental factors, has been used to evaluate the role of the genetic amine acetylation defect in the pathogenesis of allergic disease.

*Study Population.* Genotypes were determined from 56 children with documented inhalation, food, or mixed allergies and from 100 healthy control children with no clinical or laboratory signs of allergy. All subjects were white children from central Poland with a mean age of  $3.89 \pm 6.4$  years.

*Methods.* DNA was isolated from 1- to 2-mL samples of blood. Polymerase chain reaction followed by analysis of restriction fragment length polymorphism identified genotype coding for *N*-acetyltransferase. To disclose genotypes that determine fast and slow acetylation phenotypes in white individuals, four of seven known *NAT2* gene mutations were identified. The three other mutations in this region either have not yet been found in white individuals or occur in tandem with one of the identified mutations.

*Results.* Among the total population ( $n = 156$ ) 351 mutations were found in the *NAT2* gene. A statistically significant difference in the distribution of the frequency of mutated alleles between the case and control groups was shown. Ninety-one percent of children from the case group had genotypes that determined slow acetylation phenotypes. In contrast, 38% of the control group had rapid acetylation genotypes (normal *NAT2* activity) and 62% had genotypes with mutated alleles (homozygous or heterozygous).

*Conclusions.* The majority of subjects studied had genotypes that included mutated alleles of the *NAT2* gene. The authors remind us *NAT2* mutations are associated with acetylation defects, and acetylation has been hypothesized to play an important role in the inactivation of excessively released histamine, the primary mediator of atopic allergic reactions. They conclude that genetic defect of acetylation may be treated as a marker of atopic predisposition.

*Reviewer's Comments.* As the authors acknowledge in their discussion, histamine is only one of many inflammatory process mediators released in allergic reactions. Additional studies are needed to evaluate the importance of their findings in relation to clinical manifestations.

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### SECONDHAND SMOKE IS AN ADJUVANT FOR T HELPER-2 RESPONSES IN A MURINE MODEL OF ALLERGY

Seymour BWP, Pinkerton KE, Friebertshausen KE, Coffman RL, Gershwin LJ. *J Immunol.* 1997;159:6169–6175

**Background.** Secondhand smoke, also known as environmental tobacco smoke (ETS), has been implicated as a contributing factor to asthma, allergy and elevated immunoglobulin E (IgE) levels. In all asthmatic and allergic children, the T-Helper cells designated as T helper-2 (Th2) are increased. These specific T-cells are responsible for the cytokines that drive the allergic and asthmatic responses (eg, IL-4, IL-5, IL-13). In this study mice sensitized to egg protein develop allergy and elevated Th-2 cells and then are exposed to ETS (at levels found in homes of smokers) or ambient air.

**Methods.** Balb/c mice were immunized to egg protein using standardized techniques. Once sensitized the study mice were exposed to sidestream cigarette smoke from a smoking machine for 6 hours/day 5 days/week for 47 days. Control mice were only exposed to ambient air. IgE was measured serially. Lung cytokines were measured. Mice without egg protein sensitization exposed to ambient air and ETS were also included.

**Results.** Serum IgE was significantly highest in the egg-sensitized, ETS-exposed mice and was sustained for the entire protocol. The nonsensitized, ETS-exposed mice had no change in IgE levels. The egg-sensitized, ambient air mice developed elevated IgE, which was not sustained. IL-4, the Th-2 cytokine partially responsible for regulating IgE, was found to be significantly highest in the mice egg-sensitized and ETS-exposed.

**Conclusions.** Serum IgE, a well recognized marker for atopy, and the cytokine that regulates IgE production, IL-4, were increased in mice sensitized to egg protein and then exposed to ETS.

**Reviewer's Comments.** In this study ETS provided potentiation to the production of IgE in mice sensitized to egg. This would suggest that children with allergic rhinitis and asthma might produce more IL-4 and make more IgE when they are exposed to ETS. As if it wasn't bad enough without the smoke exposure!

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## EOSINOPHILS BIND RHINOVIRUS AND ACTIVATE VIRUS-SPECIFIC T CELLS

Handzel ZT, Busse WW, Sedgwick JB, et al. *J Immunol.* 1998;160:1279–1284

**Background.** Infection with rhinovirus (RV) is a potent trigger for the exacerbation of asthma. RV may act to augment allergic inflammation in the lung, especially eosinophilic inflammation.

**Study Population.** Eosinophils (EOS) were recovered from 13 allergic rhinitis and 8 atopic asthmatic subjects. All subjects were skin test positive.

**Results.** Radiolabeled RV 16 did not bind to isolated EOS. When EOS were first stimulated with granulocyte-macrophage colony-stimulating factor (GM-CSF), which upregulates ICAM-1 (a surface marker) on EOS, RV was bound to EOS. This could be blocked with anti-ICAM. RV alone did not increase ICAM expression on EOS. T-cells previously sensitized to RV were stimulated to proliferate when further exposed to the EOS with bound RV, and these T-cells produced large amounts of interferon-gamma.

**Conclusions.** Eosinophils may contribute to asthma exacerbations by acting as antigen presenting cells to T-cells, which activate antiviral processes that increase lung inflammation, a detriment to asthmatics.

**Reviewer's Comments.** Viral illnesses account for most acute exacerbations of asthma in children. RVs are the most

common viruses implicated. Effective strategies to reduce the consequences of viral-induced pulmonary inflammation in asthma would have a great impact on asthma care.

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## ENVIRONMENTAL ALLERGENS

### CAT ALLERGEN (FEL D 1) LEVELS ON SCHOOL CHILDREN'S CLOTHING AND IN PRIMARY SCHOOL CLASSROOMS IN WELLINGTON, NEW ZEALAND

Patchett K, Lewis S, Crane J, et al. *J Allergy Clin Immunol.* 1997;100:755–759

**Purpose of the Study.** Exposure to environmental allergens can contribute to the clinical expression of atopic illness, and may play a role in the increasing prevalence of asthma. Domestic cat ownership is high in both New Zealand and the United States. Studies have demonstrated significant cat allergen (Fel d 1) content in cat-free homes and public buildings, perhaps in part attributable to allergen transport on clothing. As young children spend prolonged periods at school, the authors sought to determine the level of cat allergen exposure in the classroom environment.

**Study Population.** Eight-year-old children from classrooms in 10 primary schools in the Wellington area were enrolled. Eleven school rooms and 202 articles of clothing were examined. Rooms were similar in construction and had independent heating units.

**Methods.** Flooring was sampled by vacuuming at the entrance and the center of each room. Children's outer garments were identified by fabric and vacuumed in a standardized fashion. The dust obtained was assayed for Fel d 1 content by a monoclonal antibody enzyme-linked immunosorbent assay technique.

**Results.** There was a strong positive correlation ( $r^2 = 0.93$ ) between classroom floor Fel d 1 and pupil cat ownership. Classrooms with carpeted floors had markedly higher cat allergen levels, particularly in the center of the rooms. More than half (55%) had a level greater than 8  $\mu\text{g}/\text{m}^2$ , quoted as high enough to provoke symptoms in allergic individuals. Ownership was the major determinant of clothing Fel d 1, and 63.4% of children came from homes where a cat was regularly indoors. Clothing levels were lower if the cats stayed out of the bedroom, and higher if the home had several cats, or if the garment was made of fleece or wool. Curiously, allergen levels were three times higher on girl's clothing, even controlling for the factors previously mentioned. A correlation between levels of allergen on clothing and on classroom floors was not found.

**Conclusions.** The authors found a linear correlation between classroom cat allergen content and prevalence of cat ownership among pupils. High levels of Fel d 1 found on clothing suggests allergen transfer from contaminated homes.

**Reviewers' Comments.** The first step in reducing secondary exposure to Fel d 1 is identifying sources and reservoirs of this seemingly ubiquitous allergen. Previous studies have found similar or higher levels in classrooms in other countries. Although a "school cat" was present in two of the schools included, and one did enter a classroom infrequently ("less than once a week"), these schools did not have the highest allergen levels. Ease of cleaning may explain the variation in levels between fabrics. Perhaps the use of frequently washed cotton outfits and minimal amounts of carpeting may reduce classroom levels of Fel d

1. In addition, by uncovering such substantial and obligatory exposure to cat allergen, this study suggests cat immunotherapy merits greater consideration in cat allergic youngsters with persistent allergic disease. By reserving immunotherapy merely for those with obvious contact with cats, we may be omitting many children who may well benefit.

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### DOMESTIC ALLERGENS IN PUBLIC PLACES III: HOUSE DUST MITE, CAT, DOG AND COCKROACH ALLERGENS IN BRITISH HOSPITALS

Custovic A, Fletcher A, Pickering CAC, et al. *Clin Exper Allergy*. 1998;28:53–59

**Purpose of the Study.** To investigate the levels of major indoor allergens in the settled dust and air in hospitals and determine the effects of regular vacuuming on allergen levels in hospital chairs.

**Methods.** House dust mite (Der p 1), cat (Fel d 1), dog (Can f 1), and cockroach (Bla g 2) allergen levels were measured in dust collected from 83 carpeted floors, 69 mattresses, and 42 upholstered chairs in 14 British hospitals. The hospitals included six private and eight public hospitals that provided both adult and pediatric care. Airborne samples were also collected from the outpatient department of one of the participating hospitals. Samples were collected using standard techniques and allergen levels were measured by enzyme-linked immunosorbent assays (ELISA). To compare the effects of vacuuming on dog and cat allergen levels, dust samples were collected from 36 upholstered chairs on four separate occasions at 4 weekly intervals from a busy outpatient chest clinic. During the 12 intervening weeks, 18 of the chairs (active group) were cleaned by vacuuming for 1 minute using a vacuum cleaner with a high efficiency particulate air (HEPA) filter. The remaining 18 chairs served as controls. There was no significant difference in baseline levels of cat or dog antigen in the controls versus the active chairs.

**Results.** Dust mite, cat, and dog allergen levels were significantly higher in upholstered chairs than in carpets or mattresses. There was no correlation between the age of the carpet, mattresses, or chairs and the levels of antigen detected. Cockroach allergen was below the detection limit of the assay in all the dust samples from the hospitals. No differences were found among the sampling sites from the different hospitals. Dog antigen was found in the air using high-volume samplers on 10 separate days in the outpatient department of one of the hospitals. Detectable cat antigen was found on 7 out of 10 days, but no measurable airborne dust mite or cockroach antigen was found. Repeated vacuuming of upholstered chairs in the outpatient clinic significantly reduced the settled dust levels of both cat and dog antigen in the active group versus the control group. For example, dog allergen levels decreased from a mean of 8.4  $\mu\text{g}/\text{chair}$  at baseline to 0.5, 0.2, and 0.15  $\mu\text{g}/\text{chair}$  at weeks 4, 8, and 12, respectively. Cat allergen levels decreased from a baseline mean of 6.9  $\mu\text{g}/\text{chair}$  to 0.4, 0.3, and 0.3  $\mu\text{g}/\text{chair}$ , respectively, with regular vacuuming.

**Discussion.** The low levels of dust mite in the hospitals was thought to be related to the typically low humidity in the UK hospitals, found in one hospital studied to be consistently <45%. Hospital ward carpets were also vacuumed daily and hospital mattresses are encased in vinyl covers that are impermeable to dust mites. High levels of

cat and dog allergen measured in upholstered hospital chairs were probably brought in on the clothing of cat and dog owners. The cost effectiveness of additional cleaning techniques required to reduce allergen levels would have to be weighed against the cost of more suitable furnishings and flooring.

**Conclusion.** Upholstered chairs in hospitals may constitute a significant reservoir for cat and dog allergen. Thorough vacuuming of chairs could reduce the levels of cat and dog antigen.

**Reviewer's Comments.** This study supports findings from other studies that cat and dog allergens are ubiquitous, having been found in various public buildings, schools, day care centers, homes, and now hospitals. The fact that levels of antigen in vinyl encased hospital mattresses were relatively low is encouraging, although the high levels of antigen in upholstered chairs should discourage their use, particularly in clinical areas where potentially sensitive asthmatic patients are cared for. Regular vacuuming of upholstered chairs seems a reasonable alternative although no mention was made of the effects of vacuuming on airborne allergen levels, which are most important in causing symptoms.

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### PREDICTION AND PREVENTION

#### INCREASING PREVALENCE OF HAY FEVER AND ATOPY AMONG CHILDREN IN LEIPZIG, EAST GERMANY

von Mutius E, Weiland SK, Fritzsck C, Duhme H, Keil U. *Lancet*. 1998;351:862–866

**Purpose of the Study.** Surveys indicate that the prevalence of asthma and allergic diseases in children and adults is lower in eastern Europe than in western countries, suggesting that the "western lifestyle" may be an important risk factor. This study investigates time trends in the prevalence of asthma and allergic diseases among children in the eastern part of Germany in association with the tremendous changes toward western lifestyles that have occurred since unification in 1991.

**Study Population.** In 1995–1996, 2334 (87.5%) fourth grade school children (ages 9 to 11) in Leipzig, Germany (formerly East Germany), were surveyed. Data from this cohort were compared with similar data from 1517 (81.8%) Leipzig children in 1991–1992. Substantial migration within the Leipzig population did not occur between sampling periods. The main changes affecting the population resulted from unification of Germany in 1991. Children surveyed in 1995–1996 spent their first 3 years of life under eastern living conditions and were subsequently exposed to a western lifestyle. Data from both time periods were compared with control groups in Munich, Germany, a consistent western environment.

**Methods.** Surveys assessing the frequency of allergic diseases (hay fever and atopic dermatitis) were sent to 44 schools of Leipzig, Germany for completion by parents of all children in the fourth grade. The children underwent skin testing to six aeroallergens (*Dermatophagoides pteronyssinus*, grass pollen, birch and hazel pollen, and cat and dog dander), pulmonary function testing, and morning bronchial challenge at school.

**Results.** Prevalence of asthma and related symptoms did not increase between surveys. Frequency of bronchial hyperresponsiveness was virtually the same. Hay fever prevalence significantly increased from 2.3% to 5.1% be-



tween surveys. Prevalence of atopic sensitization demonstrated by skin test results increased significantly; the greatest increase occurred to pollens (14.3%–21.5% to at least one pollen) and dust mite (4.6%–8.1%). Significant changes were observed in potential risk factors: coal/wood home heating and indoor dampness decreased; while central heating, indoor gas appliances, passive cigarette smoke exposure, wall-to-wall carpeting, and cat and dog ownership all increased. First degree relatives with hay fever or eczema increased (22.7%–26.6%). First degree relatives with asthma did not increase. No significant differences were found between surveys in number of siblings, day care attendance, or breastfeeding. Increases in hay fever and atopy could not be explained by any single variable or combination of variables.

**Conclusions.** At the same time school children were exposed to a change from an eastern to a western lifestyle, allergic diseases increased while asthma prevalence remained unchanged. The changes occurred after the children were at least 3 years old. This suggests that factors associated with a “western lifestyle” can influence the development of allergic diseases even when presented after a child’s third birthday. The prevalence of childhood asthma will not be similarly affected by such changes if they occur after the third birthday.

**Reviewers’ Comments.** There is ongoing research and discussion regarding at what point a child develops asthma as opposed to allergic diseases in general. This study reinforces the belief that events influencing the inception of childhood asthma occur before a child is 3 years old, and that risk factors for the development of atopy can be dissociated from risk factors for the development of asthma after the age of 3 years.

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#### ALLERGIC FACTORS ASSOCIATED WITH THE DEVELOPMENT OF ASTHMA AND THE INFLUENCE OF CETIRIZINE IN A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL: FIRST RESULTS OF ETAC

ETAC Study Group. *Pediatr Allergy Immunol.* 1998;9:116–124

**Purpose of the Study.** The “atopic march” is the common progression of allergic disorders in children from atopic dermatitis to allergic asthma. The aim of the study was to determine whether an 18-month course of cetirizine, an antihistamine with several antiallergic properties, could prevent the development of airway inflammation and asthma in infants with atopic dermatitis.

**Methods.** Over a 2-year period, 817 infants <2.5 years of age with atopic dermatitis, no history of wheezing, and at least one parent or sibling with a history of atopic disease were included in the ETAC (Early Treatment of the Atopic Child) trial, a multicountry, double-blind, randomized, placebo-controlled trial. Total and specific immunoglobulin E (IgE) [grass pollen, cow milk, egg, dust mite, and cat dander] were determined at entry, and after 3, 12, and 18 months. Infants were treated for 18 months with either cetirizine (0.25 mg/kg bid) or placebo, and the number of infants developing asthma was compared between the two groups.

**Results.** Overall, there was no difference between the cetirizine- and placebo-treated groups in the number of infants developing asthma. However, in patients with increased total IgE ( $\geq 30$  kU/l) or specific IgE ( $\geq 0.35$  kUA/l)

for grass pollen, dust mite, or cat dander, the relative risk (RR) for developing asthma was elevated (RR between 1.4 and 1.7). Compared with placebo, cetirizine significantly reduced the incidence of asthma for patients sensitized to grass pollen (RR = 0.5) or to house dust mite (RR = 0.6). The adverse events profile was similar in the two treatment groups.

**Conclusion.** In infants with atopic dermatitis, elevated levels of total IgE or specific IgE to grass pollen, house dust mite, or cat dander were predictive of subsequent asthma. In this “high-risk” group, cetirizine halved the number of children developing asthma after 18 months of treatment. In view of the proven safety of the drug, the authors propose treating such “high risk” infants with cetirizine to prevent the development of asthma.

**Reviewer’s Comments.** These preliminary findings of the ETAC group are obviously of great interest and worth tracking. The follow-up period is too short to conclude that this pharmacologic intervention is going to be successful in preventing asthma, but it does raise the exciting possibility that we may be able to do something other than watch 50% to 60% of infants with atopic dermatitis progress on to asthma. The mechanism of this apparent prophylactic effect remains to be elucidated, and it is possible that other antihistamines, eg, loratidine and ketotifen, may be even more effective. Stay tuned.

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#### LONG-LASTING SENSITIZATION TO FOOD DURING THE FIRST TWO YEARS PRECEDES ALLERGIC AIRWAY DISEASE

Kulig M, Bergmann R, Tacke U, Wahn U, Guggenmoos-Holzmann I, MAS Study Group. *Pediatr Allergy Immunol.* 1998;9:61–67

**Purpose.** The aim of this study was to investigate whether the duration of sensitization to food allergens during early childhood was predictive of the later development of immunoglobulin E (IgE) mediated hypersensitivity to inhalant allergens, allergic rhinitis, and asthma.

**Methods.** The prospective birth study cohort was derived from five German cities and consisted of 499 infants at “high-risk” for atopic disease and 815 infants without risk factors for atopic disease. The children were followed through 5 years of age and of these, serum samples were available on 508 children. Specific sensitizations to food (milk, egg, soy, and wheat) and inhalant (dust mite, cat dander, grass pollen, and birch pollen) allergens were determined at 1, 2, and 5 years of age with the CAP-RAST FEIA (Pharmacia & Upjohn; Uppsala, Sweden). History and physical examination were used to establish the diagnosis of subsequent allergic airway disease.

**Results.** Children with a long-lasting sensitization to food allergens (persistently sensitized for more than 1 year) had significantly greater total IgE and specific IgE concentrations than children who were food-sensitized only transiently in the first 2 years of life. Children with persistent sensitivity to food had a 3.4-fold greater risk of developing allergic rhinitis and a 5.5-fold greater risk of developing asthma than infants who were only transiently sensitized to foods.

**Conclusion.** Persistent food sensitization in young children with a positive atopic family history is a strong predictor for the development of allergic rhinitis and asthma by 5 years of age, up to 50%, and 67%, respectively. Persistently detectable IgE antibodies to a food over more than 1 year in early childhood is a strong prognostic indicator of

subsequent allergic airway disease. Persistently food-sensitized children, especially in atopic families, have to be regarded at high-risk for respiratory allergy and should be considered for preventive measures.

*Reviewer's Comments.* With the increasing prevalence of allergic disease in westernized societies, investigators are trying to identify simple screening measures to distinguish children at "risk." This study suggests that identifying children with IgE antibodies to any of a few common foods (presumably by prick skin tests or radioallergosorbent tests) will provide a simple, inexpensive way to identify children at risk for later allergic respiratory disease, who then might benefit from prophylactic measures.

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## FOOD ALLERGY

### PERSISTENT COW MILK PROTEIN INTOLERANCE IN INFANTS: THE CHANGING FACES OF THE SAME DISEASE

Iacono G, Cavataio F, Montalto G, Soresi M, Notarnartolo A, Carroccio A. *Clin Exp Allergy*. 1998;28:817-823

*Purpose of the Study.* To investigate the natural history of cow milk protein intolerance (CMPI) in infants.

*Study Population.* Twelve infants (6 boys and 6 girls) with persistent CMPI were followed from birth until a median age of 5 years. Controls were 26 children (12 boys, 14 girls), median age 6 years, with CMPI that resolved within 1 to 2 years.

*Methods.* A retrospective chart review of patients with CMPI followed over a period of 7 years. Clinical suspicion of CMPI was confirmed by a double-blinded, placebo-controlled, food challenge (DBPCFC), within 4 to 6 weeks after onset of symptoms, after the patients had followed a CMP-free diet. The immunologic status of the study subjects was evaluated at baseline, including total serum immunoglobulin E, IgG anti- $\beta$ -lactoglobulin, and radioallergosorbent tests (RASTs) for whole cow milk,  $\beta$ -lactoglobulin,  $\alpha$ -lactalbumin, and casein. At the end of the study these tests were repeated, and in addition RASTs and skin tests were performed for other foods and environmental allergens.

*Results.* Family history of allergic disease was significantly more frequent in patients (11/12) than in the controls (10/26),  $p < .01$ . In all the studied subjects symptoms regressed during CMP-free diet. Clinical reactions to CMP challenge after 9-12 months of CMP-free diet in 5/12 patients with persistent CMPI were different than the ones present at diagnosis. There was an increase in respiratory reactions (wheezing), which occurred in 6/12 patients, compared with 1/12 at the initial diagnosis, and there was a growing tendency to reactions being delayed. At diagnosis only 2/12 patients had delayed reaction, while at the final challenge 9/12 had reactions that occurred >48 hours after the challenge. At diagnosis 5/12 patients with persistent CMPI had a positive RAST to CM antigens, compared with 6/26 controls. At the end of the study there was no increase in frequency of positive RASTs in patients with persistent CMPI but there were no controls with positive RASTs to CM antigens. A total of 11/12 patients with persistent CMPI showed intolerance to other foods (egg-10, tomato-3, banana-3, orange-2, chicken-2, cocoa-1) confirmed by DBPCFC. In the controls the frequency of multiple food intolerance was 3/26 (soy-2, egg-1). During the study other atopic disease was frequently observed in children with persistent CMPI: asthma (8/12), rhinitis

(1/12), eczema (1/12). In controls only 2/26 infants showed other atopic disease.

*Conclusions.* Persistent CMPI forms are characterized by considerable importance of familial atopic disease, change in CMPI manifestations over time, more prolonged delay between CMP consumption and manifestation of symptoms, and very high frequency of multiple food intolerance and atopic disease.

*Reviewers' Comments.* Some authors indicate that CMPI symptoms regress within 3 years in majority of patients, while others find that 33% to 44% of infants are still intolerant at 4 years of age. This study confirms that infants with CMPI are a heterogeneous group of patients. In this study approximately 2/3 of infants outgrew their intolerance within 12 months after institution of strict CMP elimination diet. These infants in general did not have the tendency towards other forms of allergic disease, which may suggest that in their case CMPI was a manifestation of gastrointestinal tract immaturity. However, one third of infants had persistent CMPI at 5 years of age despite strict avoidance. They also frequently developed other food, respiratory, or skin allergic disease. It appears that in this subset of patients with positive family history, food allergy is the first manifestation of atopy. These patients should be followed closely with careful introduction of new foods and monitoring for the development of new food and environmental allergies.

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### RANDOMIZED CONTROLLED TRIAL OF ADVICE ON AN EGG EXCLUSION DIET IN YOUNG CHILDREN WITH ATOPIC ECZEMA AND SENSITIVITY TO EGGS

Lever R, MacDonald C, Waugh P, Aitchison T. *Pediatr Allergy Immunol*. 1998;9:13-19

*Purpose of the Study.* The role of exclusion diets in the management of atopic dermatitis (AD) in young children remains controversial. The aim of this randomized, controlled trial was to evaluate the effect of excluding egg from the diet in young children with AD and sensitivity to eggs.

*Methods.* Fifty-five children with AD and egg sensitivity were randomized either to a 4-week egg exclusion diet (diet group,  $n = 28$ ) or no diet (control,  $n = 27$ ). The mothers of all children were given advice on the general care of eczema. Randomization for the dietary phase took place only after optimal control of the eczema was achieved and the child was stable on maintenance treatment (mean = 3.5 months). Disease activity was assessed by estimates of the surface area affected by eczema and by an arbitrary severity score. Possible egg sensitivity was identified by radioallergosorbent test (RAST) before randomization and after the trial by double-blind, placebo-controlled egg challenge.

*Results.* Overall, two thirds of the children with positive RAST results to egg experienced a positive reaction during double-blind challenge. After the dietary period, the dietary group experienced a significantly greater mean reduction in surface area affected by eczema than the control group ( $P = .02$ ); from 19.6% to 10.9% area affected in dietary group compared with the 21.9% to 18.9% reduction in the control group. A significant improvement also was seen in the severity score ( $P = .04$ ); from 33.9 to 24.0 units for the dietary group compared with a decrease from 36.7 to 33.5 in the control group. Egg-sensitive patients in the

control group were then placed on a 4-week egg exclusion diet and also showed significant improvement in their severity scores.

**Conclusions.** The authors concluded that advice on the dietary exclusion of eggs is useful as part of the overall management of young children with atopic eczema and sensitivity to eggs.

**Reviewer's Comments.** Allergists and dermatologists continue to disagree over the role of allergic inflammation in children with AD. A recent study demonstrated that almost 40% of children presenting to a university dermatology clinic with moderate to severe AD have food hypersensitivity (see below). This study by Dr Lever and her dermatology colleagues demonstrates that removal of a food allergen from the diet of a food allergic patient leads to improvement in eczematous symptoms. In fact, it is somewhat remarkable that significant differences were observed in this relatively small number of patients, in such a short period of time, with the exclusion of a single food after an intensive topical steroid regimen. It would have been interesting to see whether a more complete dietary assessment and longer follow-up would have produced even more striking results, and information on whether a significant reduction in medication requirements occurred in the dietary group.

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#### PREVALENCE OF IGE-MEDIATED FOOD ALLERGY AMONG CHILDREN WITH ATOPIC DERMATITIS

Eigenmenn PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. *Pediatrics*. 1998;101(3). URL: <http://www.pediatrics.org/cgi/content/full/101/3/e8>

**Purpose of the Study.** Although it is clear that food allergy may play an important role in atopic dermatitis (AD) in selected populations, its overall prevalence in children with eczema is still not fully established. This study was designed to study the prevalence of immunoglobulin E (IgE)-mediated food allergy in children with atopic dermatitis being seen in a pediatric dermatology clinic.

**Study Population.** Sixty-three patients with AD, ranging in age from 0.4 to 19.4 years (median, 2.8 years).

**Methods.** Each patient's AD was scored by a standardized protocol and serum was screened for food-specific IgE antibodies to six foods (milk, egg, wheat, soy, peanut, and fish). Those with CAP radioallergosorbent (RAST) tests greater than 0.7 kIUa/L underwent further evaluation and were considered to be food allergic if they had: 1) a positive food challenge; 2) a convincing history of reacting to the food to which the RAST was positive; and 3) a CAP RAST level greater than the 95% confidence interval predictive for a positive challenge.

**Results.** Of the 63 patients, 22 had negative CAP values and were considered to not be food allergic. Of the 41 with one or more positive tests, 31 were evaluated further, including a total of 50 food challenges in 19 patients. Overall, 23 of the 63 (37%) patients were found to have a clinically significant food allergy.

**Conclusions.** Approximately one third of children with moderate to severe AD have IgE-mediated clinical reactivity to one or more of the six food allergens tested. An evaluation for food allergy should be considered in all patients with difficult to control AD.

**Reviewer's Comments.** Previous studies looking at the relationship between food allergy and AD have primarily been performed in patients referred to an allergy clinic and therefore may have been biased toward a more allergic

population. This study, conducted in a dermatology clinic, helps to confirm the high prevalence of food allergy in children with significant AD, no matter where they are being seen. An evaluation for food allergy in this population has a high yield and should not be overlooked. It should also be noted that screening for food allergy is a relatively simple process, as described in the abstract below, while making a definitive diagnosis of food allergy can be a complicated process that will require referral to an allergist experienced with food allergy and capable of performing food challenges.

ROBERT A. WOOD, MD  
Baltimore, MD

#### ATOPIC DERMATITIS AND FOOD HYPERSENSITIVITY REACTIONS

Wesley Burks A, James J, Heigel A, et al. *J Pediatr*. 1998;132:132-136

**Purpose of the Study.** The authors set out to determine the role and appropriate evaluation of food hypersensitivity in atopic dermatitis, using prick tests with a limited number of foods.

**Study Population.** One hundred sixty-five children, ages 4 months to 21.9 years, who met the criteria for a diagnosis of atopic dermatitis (AD), were enrolled in the study conducted in the pediatric allergy clinic of a teaching hospital.

**Methods.** Precise histories were obtained as well as complete physical examinations. All patients underwent allergy prick tests with at least 12 common food antigens plus other foods that the parents thought caused symptoms. Food challenges were carried out on the basis of a positive skin test after the suspected food was eliminated for 2 to 3 weeks. A double-blind, placebo-controlled, food challenge (DBPCFC) was the method used. No child with a convincing history of a major anaphylactic reaction to a specific food was challenged with that food.

**Results.** A staggering 92% of these children had a family history of allergic rhinitis, asthma or AD! There were 2061 prick tests to foods performed with 323 (15.6%) read as positive. Ninety-eight patients had at least 1 positive test while 67 were completely negative. A total of 266 DBPCFC were performed and 88 were positive, plus an additional 22 were not performed because of a history of anaphylaxis. The results showed that a positive skin test had 100% sensitivity, 66% specificity, 65% positive predictive value, and 100% negative predictive value. The seven foods that accounted for 89% of the positive challenges were milk, egg, peanut, soy, wheat, cod/catfish, and cashew.

**Conclusion.** Any child with significant AD who has been treated with the standard topical protocols plus systemic antihistamines and who fails to adequately respond should be considered for limited food prick skin testing, eg, the seven above. Elimination and challenge should be tried and if positive, an elimination diet should be instituted.

**Reviewer's Comments.** We all encounter those children with tough to treat AD. The authors most convincingly present their case for a limited food skin test screening program. Your local friendly allergist may therefore be the best person to consult regarding your next troublesome AD patient. Rubbing "stuff" on and gulping pills does have it's limits, especially with the dramatic benefits that can be observed when food allergies are identified and appropriate diets are instituted.

THAD JOOS, MD  
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## CLINICAL FEATURES OF ACUTE ALLERGIC REACTIONS TO PEANUT AND TREE NUTS IN CHILDREN

Sicherer SH, Burks AW, Sampson HA. *Pediatrics*. 1998; 102(1). URL: <http://www.pediatrics.org/cgi/content/full/102/1/e6>

**Purpose of the Study.** To describe the clinical features of acute reactions during initial and subsequent allergic reactions to peanut and tree nuts.

**Study Population.** One hundred twenty-two children with a median age of 8 years at the time of the study were included.

**Methods.** All patients completed a detailed questionnaire and had serum analyzed for specific IgE to peanut and a panel of tree nuts by the CAP radioallergosorbent test (RAST) system.

**Results.** Sixty-eight children had reactions only to peanut, 20 had reactions only to tree nuts, and 34 had reactions to both peanut and tree nuts. Of those reacting to tree nuts, 34 had reacted to 1, 12 had reacted to 2, and 8 had reacted to 3 or more types of nut. Initial reactions most often occurred at home and were considered to have occurred with the first exposure in 72% of cases. The median age of the initial reaction was 24 months for peanut and 62 months for tree nuts. Eighty-nine percent of initial reactions involved the skin, 52% the respiratory tract, and 34% the gastrointestinal tract; 2 organ systems were affected in 31% of initial reactions and all 3 systems were affected in 21%. Subsequent accidental reactions had occurred in 55% of peanut-allergic children and 30% of tree nut-allergic children over a median period of 5.5 years. Overall, symptoms with subsequent reactions were similar to those observed in the initial reactions.

**Conclusions.** Allergic reactions to peanut and tree nuts frequently occur on the first known exposure and may be life-threatening. Allergies to tree nuts occur in approximately one third of peanut allergic children. Accidental exposures are common after diagnosis, especially outside the home, and often require emergency treatment. Early diagnosis followed by education on avoidance and treatment is imperative.

**Reviewer's Comments.** This is an important study that really brings home the tendency for allergic reactions to peanut and tree nuts to occur early and to be severe, even life-threatening, from the start. All of these children must be equipped with epinephrine and a clear plan as to how and when it is to be used.

ROBERT A. WOOD, MD  
Baltimore, MD

## RESOLUTION OF PEANUT ALLERGY: CASE-CONTROL STUDY

Hourihane J, Roberts S, Warner J. *Br Med J*. 1998;316: 1271-1275

**Purpose of the Study.** To determine whether there are any differences between children who remain mildly or moderately allergic to peanut and children with similar histories but a negative reaction on challenge with peanut.

**Study Population.** One hundred fifty-five children from Southampton and 75 children from south Manchester referred to the regional pediatric allergy clinic for evaluation of suspected peanut allergy between April 1995 and December 1996.

**Methods.** Children were determined allergic to peanuts with a constellation of typical symptoms 3 years before presentation. Patients were selected for challenges accord-

ing to the clinical needs in each case. Some were because of negative skin tests despite convincing histories. Those with positive skin tests were challenged because of remoteness of their last reaction or parental request. Those with history of life-threatening reactions were not challenged. Resolvers were children considered no longer allergic if they a) had a clear history of prior reaction to peanut, and b) had a negative formal open challenge. Case controls were matched for age and sex. In addition to skin testing, total serum immunoglobulin E (IgE) was measured using enzyme-linked immunosorbent assay.

**Results.** A total of 120 subjects were challenged with peanut. Twenty-two cases of resolved peanut allergy were identified but only 15 had suitable positive controls. Allergy to other foods was less common in resolvers (2/15) than persisters (9/15) ( $P = .02$ ). Skin tests were available for 13/15 resolvers and 14/15 persisters. The two resolvers without skin tests had raised IgE levels of 34 and 280 IU/ml. Eight resolvers had negative skin tests. No persister had negative skin tests. None of the five resolvers with positive prick skin tests had a wheal of  $>5$  mm compared with 17/21 persisters,  $P < .0001$ . With cutoff of 6 mm for skin tests, positive predictive value was 100% and negative predictive value was 80%. Total IgE and peanut specific IgE concentrations did not differ between groups. Follow-up for 2 years after challenge showed that 12/14 had not eaten peanuts since challenge. Five of the 12 had eaten them but disliked them. Six ate peanuts without problems, and one resolver vomits after peanuts but still enjoys them despite vomiting. Two persisters who were rechallenged had similar reactions.

**Conclusion.** Appropriately trained clinicians must be prepared to challenge children with peanut as some will be tolerant despite a history of reactions and positive skin tests. Peanut allergy in a small but significant proportion of young children may resolve much like egg or cow milk allergy. Skin wheal size to peanut predicts reactivity but not severity.

**Reviewers' Comments.** This analysis is the first report of resolution of apparent peanut allergy and offers some hope to patients given this diagnosis early on in life. However, the small final sample size does not allow one to make accurate predictions based on skin tests or IgE levels as far as who will become resolvers. It seems that finding appropriate positive controls was difficult. Furthermore, many of these resolvers may have never had true peanut allergy to begin with. Large populations of these patients must be analyzed to define the true natural history of peanut allergy. However, this is an important study in regards to new awareness of the possibility of resolution of peanut allergy in selected patients.

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ROBERT A. WOOD, MD  
Baltimore, MD

## PRIMARY EOSINOPHILIC ESOPHAGITIS IN CHILDREN: SUCCESSFUL TREATMENT WITH ORAL CORTICOSTEROIDS

Liacouras CA, Wenner WJ, Brown K, Ruchelli E. *J Pediatr Gastroenterol Nutr*. 1998;26:380

**Purpose of the Study.** To describe a group of children with gastroesophageal reflux disease (GERD) and persistent esophageal eosinophilia despite traditional antireflux therapy.

**Study Population.** From a total of 1809 children evaluated prospectively over a 2.5-year period for symptoms of GERD, 20 were identified with persistent symptoms and

esophageal eosinophilia despite aggressive therapy with omeprazole and cispamide.

**Methods.** The 20 children were treated with 1.5 mg/kg/d of oral methylprednisolone for 4 weeks. All patients underwent an extensive evaluation before treatment, including questionnaires about symptoms, blood counts, serum chemistries, immunoglobulin E (IgE) level, pH probe, and endoscopy. After treatment the questionnaires and endoscopy with biopsies of the esophagus, stomach, and duodenum were repeated.

**Results.** Histologic findings in pretreatment esophageal biopsies in the 20 children diagnosed with primary eosinophilic esophagitis revealed significantly greater eosinophilia ( $34.2 \pm 9.6$  eosinophils per high power field [HPF]) compared with biopsies from children with GERD who responded to medical therapy ( $2.26 \pm 1.16$  eosinophils per HPF,  $P < .001$ ). After corticosteroid therapy, 19 of 20 children with primary eosinophilic esophagitis had dramatic clinical and histological improvement ( $1.5 \pm 0.9$  eosinophils per HPF). After 12 months of follow-up, 10 patients had remained asymptomatic and 9 redeveloped symptoms. In those with a recurrence of symptoms, treatment with an elemental diet led to an improvement in 7, while 2 remained symptomatic and required further corticosteroid therapy.

**Conclusions.** Children with GERD who were unresponsive to aggressive medical treatment and who displayed significant esophageal eosinophilia had both clinical and histologic improvement after oral corticosteroid therapy.

**Reviewer's Comments.** This is a very useful study from a large pediatric gastroenterology clinic. It points out that the presence of significant eosinophilia in the esophagus may be a very different entity than standard GERD. Although the major conclusion that corticosteroids are helpful in this population is justified, from an allergist's viewpoint I would rather look for a dietary cause before embarking on a course of steroids. Their approach, however, of looking for food allergy only in those whose symptoms recurred after steroid therapy is also reasonable, especially because they found that a relatively short course of corticosteroid therapy was effective. In any event, we should not lose sight of the fact that the presence of significant eosinophilia is commonly associated with allergy, no matter where the eosinophils are located.

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Baltimore, MD

#### SAFE ADMINISTRATION OF INFLUENZA VACCINE TO PATIENTS WITH EGG ALLERGY

James JM, Zeiger RS, Lester M, et al. *J Pediatr.* 1998;133:624-628

**Purpose of the Study.** Although egg allergy is viewed as a contraindication for the administration of the influenza vaccine, this recommendation is based on relatively little data. This study sought to determine the safety of influenza vaccine in patients with egg allergy and to evaluate the value of skin testing with the influenza vaccine before administration.

**Study Population.** Eighty-three subjects with egg allergy and 124 control subjects were recruited by the investigators between 1994 and 1997.

**Methods.** The diagnosis of egg allergy was confirmed by history, skin testing, and, if possible, oral challenge. Patients with egg allergy received the vaccine in 2 doses, 30 minutes apart. The first dose was  $\frac{1}{10}$  and the second dose was  $\frac{2}{10}$  of the recommended dose as determined by age.

Controls received one age-appropriate dose of the vaccine. Skin prick tests with the influenza vaccine were performed on all subjects and the content of egg allergen in the vaccines was measured by an inhibition ELISA.

**Results.** All subjects tolerated the vaccination protocol without any significant allergic reactions. Skin prick tests were positive in 4 subjects with egg allergy and in one control subject. The content of ovalbumin/ovomuroid was 0.1, 1.2, and 0.02 micrograms/mL in the 1994-1995, 1995-1996, and 1996-1997 vaccines, respectively.

**Conclusions.** Patients with egg allergy can safely receive the influenza vaccine in a 2-dose protocol when the vaccine preparation contains no more than 1.2  $\mu\text{g/mL}$  of egg protein.

**Reviewer's Comments.** Now that the issue of the measles, mumps, rubella (MMR) vaccine and egg allergy has been settled, the authors have taken on the task of answering the same question for the influenza vaccine. Although these results are very encouraging, it is still not possible to provide complete reassurance in this regard (as has essentially been done with the MMR vaccine). Although the MMR vaccine has a single manufacturer and therefore relatively consistent egg content, with the influenza vaccine the authors found that some vaccine preparations (that were not studied in this protocol) contained significantly higher amounts of egg protein (42  $\mu\text{g/mL}$  in one preparation). Therefore, unless the egg content of the specific vaccine is known, caution must still be exercised when it comes to the egg-allergic patient and the flu vaccine.

ROBERT A. WOOD, MD  
Baltimore, MD

#### URTICARIA AND ANGIOEDEMA

##### ACUTE URTICARIA IN INFANCY AND EARLY CHILDHOOD: A PROSPECTIVE STUDY

Mortureux P, Leaute-Labreze C, Legrain-Lifermann V, Lamireau T, Sarlangue J, Taieb A. *Arch Dermatol.* 1998;134:319-323

**Purpose of the Study.** This study sought to define the clinical, etiologic, and prognostic features of acute urticaria in infancy and early childhood.

**Study Population.** Fifty-seven infants and children between the ages of 1 and 36 months with acute urticaria.

**Methods.** This was a prospective study of 57 consecutive infants who were admitted to a pediatric hospital with acute urticaria over a 2-year period. All children underwent an extensive evaluation including blood counts, bacterial cultures, cultures and titers for viral pathogens, and allergy tests for penicillin and foods where indicated. Follow-up was attempted 2 months and 1 to 2 years after the initial presentation.

**Results.** Hemorrhagic lesions were observed in 28 patients (49% of cases) and angioedema was present in 34 (60%). An underlying cause was suspected or identified in 52 patients (91%). Infection, either alone or associated with drug intake, was determined to be the cause in 46 patients (81%) and foods were the cause in 6 (11%). Twenty-nine children were taking antibiotics, although none of the 9 children who had penicillin allergy testing performed were positive. Hemorrhagic lesions and associated articular symptoms were more common in urticaria caused by infection. There was a history of atopy in the family or the patient in 33 cases (58%) and a history of atopic dermatitis was particularly associated with urticaria caused by food. One- to 2-year follow-up was available in 40 of the 57



children, revealing that 12 (30%) had chronic (3 cases) or recurrent (9 cases) urticaria.

**Conclusions.** Viral illnesses, often associated with antibiotic therapy, were by far the most common cause of acute urticaria in infants and young children.

**Reviewer's Comments.** This is an excellent study of a common and frustrating condition. I am particularly fond of this study because it confirms my long held bias that viral infection is the most common cause of acute urticaria in children. The main drawback of the study is that it only included hospitalized children and may therefore not be completely representative of all childhood urticaria.

ROBERT A. WOOD, MD  
Baltimore, MD

## ANGIOEDEMA ATTRIBUTED TO THE USE OF LOSARTAN

van Rijnsoever EW, Kwee-Zuiderwijk WJ, Feenstra J. *Arch Intern Med.* 1998;158:2063–2065

**Purpose of the Study.** Angioedema is a well-known adverse effect of angiotensin-converting enzyme inhibitors. The bradykinin accumulation as a result of the decreased degradation of bradykinin is thought to be the causal mechanism. Angiotensin II antagonists seem to have no effect on the degradation of bradykinin. Therefore, it was expected that angioedema would not occur during treatment with losartan potassium, the first orally active angiotensin II antagonist.

**Study Population and Methods.** They reviewed the 13 case reports of angioedema associated with the use of losartan reported to Lareb (Netherlands Pharmacovigilance Foundation, Den Bosch) and to the Drug Safety Unit of the Inspectorate for Health Care, Ryswyh, in the Netherlands since the introduction of losartan in 1995 until May 1997.

**Results.** In all 13 cases, a diagnosis of angioedema attributed to the use of losartan seems to be very plausible. In 7 cases the diagnosis could not be confirmed by a physician because the symptoms had already been resolved, but the signs and symptoms clearly indicated angioedema. The adverse reactions occurred within 24 hours to 16 months after the initiation of losartan therapy. Three patients had previously experienced angioedema during treatment with an angiotensin-converting enzyme inhibitor. Eleven of the patients involved were women and 2 were men.

**Conclusions.** These observations strongly suggest that the onset of angioedema was associated with the use of losartan. Physicians and pharmacists should be aware of this potentially life-threatening complication. It may be advisable not to prescribe angiotensin II antagonists to patients with a history of angioedema (of whatever origin).

**Reviewer's Comments.** I have seen a few cases of angioedema that I felt were attributable to angiotensin II receptor antagonists. Losartan (Cozaar) is one of 4 angiotensin II receptor antagonists currently available in the United States. All block the binding of angiotensin II to type 1 angiotensin II receptors. Angiotensin-converting enzyme (ACE) inhibitors block conversion of angiotensin I to angiotensin II. In addition, ACE inhibitors block the breakdown of bradykinins and substance P, which accumulate and may cause adverse effects such as cough. ACE inhibitors can cause angioedema, and case reports such as this suggest that this may also occur with angiotensin II receptor antagonists.

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## ANAPHYLAXIS

### EPINEPHRINE ABSORPTION IN CHILDREN WITH A HISTORY OF ANAPHYLAXIS

Simons FER, Roberts JR, Gu A, Simons KJ. *J Allergy Clin Immunol.* 1998;101:33–37

**Purpose of the Study.** To study the clinical pharmacology of epinephrine in allergic children with a history of anaphylaxis.

**Study Population.** A total of 17 children, ages 4 to 12 years old, with a history of severe allergies and systemic anaphylaxis.

**Methods.** This was a randomized, single-blind, single-dose, parallel-group study. Subjects received either a subcutaneous injection of 0.01 mL/kg (maximum 0.3 ml [0.3 mg]) epinephrine solution or an intramuscular injection of 0.3 mL (0.3 mg) of epinephrine via an EpiPen Auto-Injector (Dey; Napa, CA). Before injection and at timepoints up to 180 minutes afterwards, blood samples were collected for plasma epinephrine measurement. Heart rate, blood pressure, and rhythm strip monitoring were also performed during the same intervals. Plasma epinephrine concentrations were measured with a high-performance chromatography (HPLC) reverse-phase system with electrochemical detection.

**Results.** Nine subjects were randomized to the subcutaneous epinephrine group (epinephrine solution) and 8 to the intramuscular injection group (EpiPen Auto-Injector). The mean peak plasma epinephrine concentration in the subcutaneous group was  $1802 \pm 214$  pg/mL. The mean time to reach maximum plasma concentrations was  $34 \pm 14$  minutes in this group, with only 2 subjects achieving maximum concentration by 5 minutes. In contrast, the mean peak maximum plasma epinephrine concentration in the intramuscular group was  $2136 \pm 351$  pg/mL. The mean time to reach maximum plasma concentration was  $8 \pm 2$  minutes ( $P < .05$ , compared to subcutaneous group), with 6 achieving the peak concentration by 5 minutes. No serious adverse effects were reported in either group.

**Conclusions.** Epinephrine has a delayed absorption when given via the subcutaneous route compared with the intramuscular route in children.

**Reviewer's Comments.** Although a small sample size, this study of the pharmacologic dynamics of epinephrine delivery in children has great implications. Epinephrine remains the drug of choice for the treatment of acute systemic anaphylaxis, yet epinephrine dosing in children is currently recommended on the basis of findings in adult populations and anecdotal reports. This study is the first to demonstrate the pharmacokinetics of epinephrine in children. The authors clearly demonstrate delayed absorption and lower peak plasma concentrations when epinephrine is given via the subcutaneous route compared with the intramuscular route. These findings have important clinical implications for use of epinephrine in all settings of systemic anaphylaxis, indicating that intramuscular delivery of epinephrine may be preferable.

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### ANAPHYLAXIS IN SCHOOLS AND OTHER CHILD CARE SETTINGS

AAAAI Board of Directors. *J Allergy Clin Immunol.* 1998; 102:173–176

**Purpose of the Study.** This physician's statement is published to better identify the problem of anaphylaxis in

schools and other child care settings with an emphasis on avoidance, treatment strategies, and making available emergency health care plans.

*Study Population/Methods.* Do not apply to this review.

*Findings.* This critically important statement is an excellent guide for primary care providers to deal with anaphylaxis. The diagnosis of allergy with a risk of anaphylaxis is made based on the patient's history and confirmed with skin or blood tests performed by appropriately trained allergy specialists. It also identifies the fact that school personnel should develop a system of identifying children with life-threatening allergies to prevent anaphylactic reactions, and school personnel should be prepared to deal with these reactions. When prescribed, every student should also have an epinephrine auto injector device clearly labeled with his or her name and classroom number. School personnel should be instructed about the location of the medication and expiration dates should be checked carefully. This physician's statement makes comments about the avoidance of foods, especially dealing with the student who is going to eat from the cafeteria menu. The child's parents should inform the cafeteria staff in writing about foods to be avoided and suggest safe substitutions. All food service personnel should be instructed of the student's allergies. The physician's statement also deals with treatment strategies. Treatment protocols need to be prescribed by a physician. School staff should have written instructions. Epinephrine should be the first drug that should be used in the emergency management. All individuals receiving emergency epinephrine should be immediately transported to a hospital even if symptoms appear to have resolved. Additional epinephrine should be available during transport if necessary. All individuals entrusted with the care of children need to have familiarity with basic first aid and resuscitative techniques. The physician's statement also nicely defines the common symptoms and signs of an allergic reaction, and has an excellent emergency health care plan sample which includes a form that could be readily used by schools and other facilities taking care of children who may have the potential for anaphylaxis.

*Editor's Note.* Although not a research paper, this article was included because of its great relevance to pediatricians.

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## DRUG ALLERGY

### DIAGNOSIS OF PENICILLIN, AMOXICILLIN, AND CEPHALOSPORIN ALLERGY: RELIABILITY OF EXAMINATION ASSESSED BY SKIN TESTING AND ORAL CHALLENGE

Pichichero ME, Pichichero DM. *J Pediatr.* 1998;132:137-143

*Purpose of the Study.* The major aims were to 1) assess the reliability of pediatrician-diagnosed allergic reactions to commonly used  $\beta$ -lactam antibiotics based on the examination at the time of reaction followed by elective skin testing and oral challenge, and 2) monitor prospectively the predictive value of negative skin testing for subsequent reactions to antibiotics administered.

*Study Population.* Children and adolescents ( $n = 247$ ) experiencing an adverse reaction to penicillin, amoxicillin, and/or an oral cephalosporin sufficient to lead to the recommendation to avoid further use of the drug.

*Methods.* Skin testing with penicillin G, commercial benzylpenicilloyl phosphate (Pre-pen), penicillin minor determinant mixture (MDM), ampicillin, cefazolin, cefuroxime, and/or ceftriaxone was performed according to the suspected cause of the reaction. This was followed by an oral challenge, repeat testing, and prospective follow-up if no reactions were observed.

*Results.* Overall, 84 (34%) of 247 patients had an immunoglobulin E (IgE)-type reaction on skin testing or oral challenge. Twenty-seven (32%) of 85 suspected penicillin reactions, 53 (34%) of 156 suspected amoxicillin reactions, and 13 (50%) of 26 suspected cephalosporin reactions were felt to be IgE-mediated. Positive skin tests were observed in 20 patients with non-IgE-type adverse reactions, including 15 patients with only a pruritic polymorphous rash. No reactions to oral challenge were severe after negative skin testing. One hundred sixty-three patients received multiple treatment courses with  $\beta$ -lactam antibiotics after a negative skin test and oral challenge and 3 (1.8%) had adverse IgE-type reactions, all of which were mild.

*Conclusions.* Physician-diagnosed allergic reactions to  $\beta$ -lactam antibiotics based on the examination at the time of the reaction is more accurate than patient history alone, but still overestimates the rate of true allergy in 66% of patients. Elective penicillin, amoxicillin, and cephalosporin skin testing and oral challenge protocols are necessary to identify patients at risk.

*Reviewers' Comments.* How often (ie, monthly, weekly, or even daily) do you encounter a patient with a history of a  $\beta$ -lactam allergy? In our current era of emerging antibiotic resistance, this clinical issue has reached an even greater degree of importance. This article addressing the diagnosis of  $\beta$ -lactam allergy should strike a cord with both pediatricians and allergy/immunology specialists. There are several useful "take home" messages. First, examination of the patient at the time of the adverse antibiotic reaction accurately diagnosed an IgE-mediated reaction only 30% of the time. Second, young and middle-aged adults (ages 20-49) seemed to have the greatest risk of acute allergic reactions to antibiotics. Third, this investigation confirms the safety of testing for penicillin allergy with penicillin G, Pre-pen, and MDM, as well as with cephalosporin skin testing reagents. Fourth, after negative skin testing, use of an oral challenge is the safest method of confirming the negative result. Fifth, while a potential for increased hypersensitivity to first-generation cephalosporins exists in those patients who have histories of penicillin, second- and third-generation cephalosporins have a lower incidence of allergic reactions. Finally, patients observed during subsequent, multiple treatment courses with  $\beta$ -lactams after negative testing and oral challenge rarely had mild IgE-mediated reactions.

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### INHIBITION OF TOXIC EPIDERMAL NECROLYSIS BY BLOCKADE OF CD95 WITH INTRAVENOUS IMMUNOGLOBULIN

Viard I, Wehrli P, Bullani R, et al. *Science.* 1998;282:490-493

*Purpose of the Study.* Toxic epidermal necrolysis (TEN) is a severe, drug-induced skin disease characterized by epidermal cell death leading to loss of skin. TEN is most frequently induced by sulfonamides, anticonvulsants, or nonsteroidal antiinflammatory drugs and occurs in 0.8 cases per million with a mortality of 30%. Keratinocyte apoptosis (programmed cell death) is abnormally in-

creased in TEN but the mechanism for the increase is unknown. This study evaluated the role of the "death receptor," fas (CD95), and its ligand, fas ligand (FasL), in TEN and the possible therapeutic use of intravenous gammaglobulin (IVIg) for this disorder.

**Study Population.** Seven patients (adults and children) with TEN, 4 controls with drug-induced maculopapular rashes, and 7 healthy controls were evaluated.

**Methods.** Enzyme-linked immunosorbent assay was used to measure serum concentration of soluble FasL; immunohistochemical staining of skin biopsy tissue was used to detect keratinocyte expression of Fas and FasL. The lytic capacity of keratinocyte FasL was evaluated using Fas-sensitive Jurkat cells overlaid on the skin frozen sections. Keratinocyte apoptosis was evaluated by flow cytometric methodology.

**Results.** Patients with TEN had elevated serum sFasL (concentrations were virtually undetectable in control groups). Keratinocytes expressed increased FasL but similar amounts of Fas compared with controls. The lytic capacity of FasL expressed on keratinocytes was greatly increased, but could be blocked completely by incubation with FasL-blocking antibody. Apoptosis was inducible in human keratinocytes by recombinant sFasL. However, preincubation of keratinocytes with IVIg prevented recombinant sFasL-induced apoptosis. Conversely, incubating the recombinant sFasL with IVIg did not inhibit apoptosis (implicating blockade of Fas receptor as the rescue mechanism). Depletion of anti-Fas immunoglobulin from the IVIg (on an affinity column) also abrogated the ability of IVIg to block Fas-mediated keratinocyte cell death.

In an open, noncontrolled pilot study, 10 patients with TEN received IVIg at doses ranging from 200 to 750 mg/kg/day for 4 days. The progression of skin disease was interrupted in all 10 within 2 days. All experienced healing and a favorable outcome.

**Conclusions.** Fas-FasL interactions are directly involved in TEN, a disease in which keratinocyte apoptosis is increased and lytic FasL is up-regulated. IVIg, by blocking the Fas receptor, may be an effective treatment.

**Reviewer's Comments.** This study is a wonderful example of research moving from bedside to bench back to bedside. Controlled studies are needed, but an additional indication for IVIg may be on the horizon. In addition, more specific therapies for this disorder, and possibly others, are likely to be developed now that the immunologic mechanism has been elucidated.

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## SUDDEN INFANT DEATH SYNDROME

### SUDDEN INFANT DEATH SYNDROME: A SEARCH FOR ALLERGEN HYPERSENSITIVITY

Hagen LL, Goetz DW, Revercomb C, Garriott J. *Ann Allergy Asthma Immunol.* 1998;80:227-231

**Purpose of the Study.** Sudden infant death syndrome (SIDS) remains a diagnosis of exclusion with few clues as to its cause. Previous evaluations regarding anaphylaxis and SIDS are few and limited. The purpose of this study is to analyze forensic blood samples for evidence of anaphylaxis in children dying of SIDS against age-matched controls who died from defined nonanaphylactic causes.

**Study Population.** 21 infants (13 males and 8 females) who died from SIDS were selected from a population of deaths investigated by the Bexar County Medical Examiner's Office between 1990 and 1995. Thirteen age-matched

controls (9 males and 4 females) were identified who died from defined, nonanaphylactic causes.

**Methods.** Frozen forensic blood specimens from these subjects were evaluated for the following: 1) total immunoglobulin E (IgE) (IU/mL); 2) latex, cat, dust mite, milk, soy, wheat, peanut, egg, and tomato specific-IgE radioallergosorbent (RAST) testing; and 3) serum tryptase levels (U/L). RAST test results were considered positive and potentially significant at measured counts >500.

**Results.** The 21 SIDS cases (median age, 3 months) and the 13 control cases (median age, 4 months) demonstrated similar total IgE levels of  $9.8 \pm 1.1$  IU/mL and  $19.9 \pm 2.8$  IU/mL, respectively, ( $P = .59$ ). The frequency of detectable (0.5 U/L) serum tryptase levels among SIDS cases (10/51) were similar to controls ((3/13),  $P = .72$ ). The frequency of positive RAST tests was 39% (20/51) in SIDS and 38% (5/13) in controls ( $P = .99$ ). Differences in frequencies of positive RAST tests in SIDS and control cases were not statistically significant for any allergen that was tested. The most frequently detected allergen-specific IgE was to milk and was similar in the SIDS (22%) subjects and the controls (31%,  $P = .48$ ).

**Conclusions.** Elevated tryptase levels and allergen-specific IgE (milk, soy, wheat, peanuts, egg, tomato, dust mites, cat, and latex) were demonstrated in some of the infants who died from SIDS but were no more common than age-matched controls. It is therefore unlikely that anaphylaxis is a common cause in SIDS.

**Reviewers' Comments.** There has been much study and debate over possible causes for the tragedy of SIDS. The anaphylaxis hypothesis has been put forth in several studies but never substantiated. This study relates that allergen hypersensitivity and anaphylaxis is unlikely to be a factor in this entity. However, one must realize that total and specific IgE levels in infants are usually low compared with adults, and reference values for infant RAST interpretations are not standardized. Furthermore, tryptase often can be undetectable in cases of anaphylaxis and is not a definitive diagnostic tool. Nevertheless, this is a nice analysis of an important question. The authors propose that further study is required and desirable.

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## The Upper Airway

### MEASURING QUALITY OF LIFE IN CHILDREN WITH RHINOCONJUNCTIVITIS

Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR, Math B. *J Allergy Clin Immunol.* 1998;101:163-170

**Purpose of the Study.** To develop, pretest, and validate a questionnaire to measure quality of life in children with seasonal allergic rhinoconjunctivitis (SAR).

**Study Population.** Children, ages 6 to 12 years, with a history of SAR and troublesome symptoms during the previous month.

**Methods.** Two studies in different locations were conducted to develop the Paediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ). Study 1 was the "development" phase in which PRQLQ questions were developed and modified in 34 children with SAR. Forty-eight items in 8 initial domains were reduced to 23 ques-



tions in 5 domains (nose symptoms, eye symptoms, other symptoms, practical problems, and activity limitations) to establish the final PRQLQ. Ten children were pretested with the PRQLQ using a 7-point response option scale. Study 2 was the "validation" phase in which 83 children with SAR were tested with the PRQLQ in a 3-week, single cohort study conducted during the fall pollen season of 1996. Children were seen at enrollment and after 1 and 3 weeks. Subjects completed a symptom diary twice daily for 1 week before each visit. At the 1-week visit, medication was prescribed for the child's symptoms. The PRQLQ was given at each visit and results analyzed with symptom profiles.

**Results.** Study 1 established the PRQLQ format of 23 questions in 5 domains. Study 2 tested the instrument in 83 children. Of the 83 children enrolled, 75 children completed the analysis with a mean age of 9.8 years (40% female, 76% white, 11% black). The reliability and validity of the PRQLQ were found to be very consistent in the population tested. Good evidence was found for cross-sectional correlations between quality of life and diary symptom scores. The PRQLQ was also able to detect difference in those subjects who remained clinically stable and those who changed clinically. Responsiveness data showed that children did not have trouble understanding the 7-point scale used. The only problem encountered was the apparent difficulty of some children understanding the time specification. Some younger children had problems understanding the concept of "during the last week."

**Conclusions.** The PRQLQ can be completed reliably in children 6 to 12 years old. The instrument demonstrates good measurement properties and can be used with confidence in clinical studies.

**Reviewer's Comments.** Once again, Juniper and colleagues have developed a validated, reliable quality of life instrument for children with chronic disease. This tool will be useful in the assessment of children with rhinoconjunctivitis, especially with regard to clinical studies. The authors recognize some limitation to their study, primarily that the instrument development was conducted in one population and validated in another. This problem was minimized by inclusion of a wide range of disease severity in the test population. Further use of the PRQLQ in pediatric patients will be helpful and will likely strengthen these findings.

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## META-ANALYSIS OF OUTCOMES OF PEDIATRIC FUNCTIONAL ENDOSCOPIC SINUS SURGERY

Hebert RL, Bent JP. *Laryngoscope*. 1998;108:796-799

**Purpose of the Study.** Functional endoscopic sinus surgery (FESS) has been accepted as a useful treatment for children with chronic sinusitis refractory to medical therapy. The authors attempted to create a consensus of published outcomes of pediatric FESS, assessing the effectiveness and safety of this surgery in children.

**Study Population.** Eight articles on pediatric sinus surgery were analyzed, which reported on 832 children (age range, 11 months-18 years) who underwent FESS for computed tomography-proven chronic sinusitis. These articles were published between 1986 and 1996. An additional 50 children underwent FESS at the authors' institution between 1991 and 1996. Patients were followed for an average of 3.7 years. Two of the eight articles reported separately on FESS in children with

underlying medical conditions such as cystic fibrosis or immunodeficiency.

**Methods.** A retrospective review was performed to determine the outcome of pediatric FESS at the authors' institution using a telephone survey. This series was used as unpublished data in the meta-analysis to control for the tendency towards overrepresentation of positive findings in the published literature.

The meta-analysis included articles retrieved from a MEDLINE search that reported new patient data on outcomes in pediatric FESS. Articles were rated by a scoring system that assessed number of patients per study, length of follow-up, prospective versus retrospective design, and exclusion or separation of patients with severe underlying systemic diseases. Eight articles, as well as the unpublished data, met the rating criteria for inclusion. Outcome was categorized simply as "positive" or "not positive" based on questionnaire responses or clinic visit documentation of overall satisfaction and degree of improvement.

**Results.** Positive outcomes of pediatric FESS in the eight publications chosen for the meta-analysis ranged from 77% to 100% with a "pooled" positive outcome in 88.4% of children. The positive outcome for FESS in the unpublished series of children was 92%. The two papers that separately analyzed FESS in children with immunodeficiency or cystic fibrosis reported less favorable outcomes, with 0% and 57% positive outcomes reported. These patients tended to require multiple procedures. The major complications of FESS in children in the pooled analysis were hemorrhage requiring blood transfusion ( $n = 2$ ) and meningitis ( $n = 2$ ), yielding a complication rate of 0.6%.

**Conclusions.** Endoscopic sinus surgery is a safe and effective treatment of refractory chronic sinusitis in children, with >88% of children having a positive outcome and <1% of children experiencing a major complication. Children with sinusitis accompanied by chronic illnesses such as cystic fibrosis and immunodeficiency have poorer outcomes with FESS, and often require multiple surgical procedures.

**Reviewers' Comments.** The authors used meta-analysis to assess outcomes of children with refractory chronic sinusitis treated with FESS. They report a positive outcome of 88.4% and a major complication rate of 0.6%. In the absence of a large prospective trial, this approach enables the pooling of data from multiple studies. However, one must note that 500 out of 882 patients included in this meta-analysis were derived from a single large series.

As medical literature tends to be dominated by positive results, the authors have included an unpublished retrospective series of 50 patients from their own institution to control against "publication bias." The results of FESS assessed in this unpublished series agree with those of the eight published studies that were analyzed.

The meta-analysis in this article has several limitations. Eight of 9 of the patient series included in the analysis used a retrospective design. Objective, standardized measurements of surgical outcomes have not been used. The patient population being treated with FESS may be heterogeneous, as each series varies with regard to patient selection criteria, severity of sinusitis (no staging system has been uniformly used), and presence of underlying systemic disease. The type of surgery performed varies from child to child and from series to series, as most children are treated with middle meatal antrostomy and anterior ethmoidectomy, while other children may have more extensive sinus surgery. Few studies have prospectively compared FESS with prolonged medical therapy. A prospective study of long-term surgical outcomes of pedi-

atric FESS is needed, as well as a better understanding of the natural history of chronic sinusitis in children.

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### INTRANASAL BECLOMETHASONE AS AN ADJUNCT TO TREATMENT OF CHRONIC MIDDLE EAR EFFUSION

Tracy J, Demain J, Hoffman K, Goetz D. *Ann Allergy Asthma Immunol.* 1998;80:198–206

*Purpose of the Study.* Following otitis media, 10% to 50% of children develop residual middle ear effusions. Prophylactic antibiotics and tympanotomy tubes are currently recommended treatments. The purpose of this study was to assess the effectiveness of topical intranasal beclomethasone as an adjunct to prophylactic antibiotic therapy.

*Study Population.* Sixty-one children aged 3 to 11 years with persistent middle ear effusion >3 months were recruited from a military dependant population referred to the Wilford Hall Medical Center Pediatric Chronic Ear Clinic between October 1991 and June 1992.

*Methods.* The study used a double-blind, placebo-controlled, randomized design. The subjects were randomized into three 12-week treatment groups: 1) prophylactic antibiotics; 2) prophylactic antibiotics plus intranasal beclomethasone (336 µg/day); and 3) prophylactic antibiotics plus intranasal placebo. At entry, patients were evaluated with aeroallergen skin tests, a tympanogram, otoscopic examination, and symptom questionnaire. These same evaluations were performed at 4, 8, and 12 weeks.

*Results.* Fifty-nine subjects completed the study. The three treatment groups were not statistically different in any characteristic (age, sex, atopy, family history of allergy, history of tympanostomy tubes, presence of smokers at home, enrollment in day care, antibiotic treatment at entry, history of penicillin sensitivity, or intercurrent illnesses during treatment.) The frequency of atopy in the patient population was 24%. The beclomethasone plus antibiotics group improved in all three measures (tympanometry, otoscopic examination, and symptom scores) more rapidly than the antibiotic alone and placebo nasal spray plus antibiotic groups over the first 8 weeks. At 12 weeks, the differences among groups were no longer significant for tympanometry and otoscopic examination but the difference in symptom scores remained significant comparing antibiotics plus beclomethasone and antibiotics alone ( $P = .015$ ). Over the entire 12 weeks, only the antibiotics plus beclomethasone nasal spray group had significantly improved both right and left mean middle ear pressures (right,  $P = .010$ , left  $P = .004$ ). No difference in response to nasal steroids was observed between atopic and nonatopic subjects.

*Conclusions.* Intranasal beclomethasone may be a useful adjunct to prophylactic antibiotic treatment of chronic middle ear effusion.

*Reviewers' Comments.* From this study it seems that although intranasal steroids may be a useful adjunct to prophylactic antibiotics in the treatment of chronic middle ear effusion, over the long term the differences become less remarkable. Middle ear disease tends to improve with time no matter what the treatment but intranasal steroids should certainly be considered for more stubborn cases. With the current emphasis on using less prophylactic antibiotic, it would be very helpful to see another study using

intranasal steroid without antibiotic in one of the treatment groups.

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### ASSESSMENT OF ADENOIDAL OBSTRUCTION IN CHILDREN: CLINICAL SIGNS VERSUS ROENTGENOGRAPHIC FINDINGS

Paradise JL, Bernard BS, Colborn DK, Janosky JE. *Pediatrics.* 1998;101:979–986

*Purpose of the Study.* To investigate the reliability and correlation of standardized clinical assessments and x-ray assessments of adenoidal obstruction.

*Study Population.* Children were studied as part of a comprehensive, prospective study of the indications for tonsillectomy and adenoidectomy that was carried out at the Children's Hospital of Pittsburgh between 1971 and 1991.

*Methods.* The patient's degree of mouth breathing and speech hyponasality were rated on a 4-point scale and scores were averaged to obtain an overall Nasal Obstruction Index. Lateral x-rays of the nasopharynx were also performed and the adenoid size and degree of nasopharyngeal obstruction were rated. Correlations between clinical assessments and roentgenographic findings were then calculated, as were predictive values for the clinical ratings using the roentgenographic ratings as the gold standard.

*Results.* An assessment of intraobserver agreement with regard to the clinical and x-ray assessments revealed overall excellent agreement between observers. The concordance between the Nasal Obstruction Index and the roentgenographic ratings in a sample of 1033 children revealed a value of 0.51. It was found the concordance was best at the lower and upper extremes of the Nasal Obstruction Index.

*Conclusions.* Standardized clinical ratings of the degree of mouth breathing and speech hyponasality provide reliable and reasonably valid assessments of the presence and degree of adenoidal obstruction of the nasopharyngeal airway. These clinical assessments are particularly valid at the extremes of either marked obstruction or no obstruction.

*Reviewer's Comments.* This is an extremely practical study of a common clinical question. Pediatricians are frequently asked to guess about the importance of adenoid hypertrophy in the assessment of a child's nasal symptoms or recurrent infections and this study helps to guide us in those decisions. As most experienced pediatricians already knew, the two most useful markers of adenoidal obstruction are mouth breathing and the quality of the voice. Dr Paradise and company strike again with another outstanding study in pediatric ear, nose, and throat disease.

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### EFFICACY, PHARMACODYNAMICS, AND PHARMACOKINETICS OF CGP 51901, AN ANTI-IMMUNOGLOBULIN E CHIMERIC MONOCLONAL ANTIBODY, IN PATIENTS WITH SEASONAL ALLERGIC RHINITIS

Racine-Poon A, Botta L, Chang TW, et al. *Clin Pharmacol Ther.* 1997;62:675–690

*Purpose of the Study.* A dose-ranging study was performed to evaluate the safety and efficacy, and pharmaco-

dynamics and pharmacokinetics of CGP 51901, a recombinant monoclonal mouse-human chimeric anti-human immunoglobulin-E (IgE) antibody, in adults with allergic rhinitis. This model was chosen because the cause-effect relationship of antigen exposure and symptoms is well-defined.

**Study Population.** One hundred fifty-five patients (mean ages 38.5–42.8 years), who were relatively symptom-free before the annual mountain cedar allergic rhinitis season and met inclusion criteria, were randomly assigned to one of four treatment groups.

**Methods.** This was a multicenter study performed in randomized, blinded, parallel-group fashion. Subjects received 6 biweekly, intravenous doses of placebo, 15, 30, or 60 mg of CGP 51901 beginning before seasonal allergen exposure during the presymptomatic state. At each study visit serum CGP 51901 and free IgE levels were measured at predose, and one-half and 4 hours postdose. At one center serial blood samples were obtained from predose to 240 hours postdose. Subjects also recorded daily nasal symptoms (sneezing, itchy nose, runny nose, and stuffy nose) on a 0 to 3 scale (0 being no symptoms, 3 being severe symptoms). Pollen counts were measured at each center.

**Results.** One hundred fifty-three subjects completed the trial. All doses were generally well-tolerated; however, 1 subject reported pruritis, generalized urticaria, and chest tightness within 15 minutes of receiving 60 mg of CGP 51901. This episode improved immediately after treatment with epinephrine, nebulized albuterol, and an antihistamine. Subjects categorized as having high ( $\geq 85\%$ ) and moderate (45%–85%) reductions of free IgE demonstrated the greatest suppression of nasal symptoms. Overall, symptoms appeared to follow pollen counts during the treatment period. The greatest decreases of free IgE levels occurred with higher doses; over half the subjects in the 60 mg dose group had  $\geq 85\%$  reduction of free IgE. Data from pharmacodynamic and pharmacokinetic modeling indicate that a serum CGP 51901 concentration of 5200 ng/ml, maintained throughout the dosing interval with the 60 mg dose only, is sufficient to reduce free IgE by 85% in half the samples analyzed.

**Conclusions.** Results of this study strongly suggest that reduction of free IgE levels can result in a substantial reduction of allergic rhinitis symptoms.

**Reviewer's Comments.** Although much too early to anticipate approval of CGP 51901 for the treatment of seasonal allergic rhinitis, this study demonstrates that depletion of circulating free IgE levels can prevent or reduce allergic symptoms.

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## EFFECT OF ENVIRONMENTAL TOBACCO SMOKE ON COUGH IN CHILDREN WITH A HISTORY OF TONSILLECTOMY OR ADENOIDECTOMY

Chen Y, Rennie DC, Lockinger LA, Dosman JA. *Eur Respir J.* 1998;11:1319–1323

**Purpose of the Study.** Although many studies have shown that exposure to environmental tobacco smoke increases the risk of respiratory symptoms in the pediatric population, it is not known how many other factors may increase this risk. The purpose of this study was to determine if children with a history of tonsillectomy or adenoidectomy (T/A) were at an increased risk of developing respiratory symptoms when exposed to environmental tobacco smoke.

**Study Population.** The study was conducted in Humboldt, Saskatchewan, where subjects included all town residents between the ages of 6 and 17 years. Of the 1019 eligible subjects, 892 participated in the study.

**Methods.** The subjects were divided into different groups based on their responses to a questionnaire. Subjects were placed into the history of T/A group if they had ever had either their tonsils or adenoids removed. Exposure to environmental tobacco smoke was based on the number of smokers in the home and the amount the members smoked each day. Subjects who were placed in the "cough" group were further distinguished based on what time of day that the cough occurred, morning, day, or night. The effect of exposure to environmental tobacco smoke was evaluated in the T/A group and compared with the effect in the group with no history of T/A.

**Results.** First, it was shown that the occurrence of current cough increased with increasing number of smokers in the home and with increased cigarette consumption by household smokers. It was also shown that children with a history of T/A had higher occurrences of current cough when compared with the children with no history of T/A when exposed to environmental tobacco smoke. A multiple logistic regression model was used to compare the joint effect of tobacco smoke exposure and history of T/A on current cough before and after adjusting for all the other variables. The adjusted odds ratio was 7.19 for children with a history of T/A if they were living in families who smoked more than 20 cigarettes/day as compared with an adjusted odds ratio of 1.64 among children without a history of T/A.

**Conclusions.** Subjects who lived in smoking families had an increased incidence of developing cough than those subjects who lived in nonsmoking families. T/A increased the influence of tobacco smoke on the development of a cough.

**Reviewers' Comments.** This study clearly demonstrated the influence of tobacco smoke in the home on children's respiratory symptoms. However, it was also apparent that tonsillectomy or adenoidectomy increased this risk to a significant degree. The authors suggested that the tonsil's and adenoid's role in the immune response of the body explain these findings. It may be beneficial to examine other mechanisms of how T/A increases a child's risk for cough in further studies.

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## Asthma

### PATHOPHYSIOLOGY

#### MECHANISM OF RHINOVIRUS-INDUCED CHANGES IN AIRWAY SMOOTH MUSCLE RESPONSIVENESS

Hakonarson H, Maskeri N, Carter C, Hodinka RL, Campbell D, Grunstein MM. *J Clin Invest.* 1998;102:1732–1741

**Purpose of the Study.** Although an important association has been established between specific viral respiratory tract infections and acute exacerbations of asthma, the mechanistic basis of this interplay remains to be elucidated. The aim of this investigation was to address the hypothesis that rhinovirus, the most common viral respi-



ratory pathogen implicated in acute exacerbations of asthma, directly affects airway smooth muscle to produce proasthmatic changes in receptor-coupled airway smooth muscle responsiveness.

**Methods.** Adult New Zealand White rabbits were used as the source for airway smooth muscle cells. Human rhinovirus serotype 16 and adenovirus were cultured using standard techniques and inoculated into the prepared cultures of airway smooth muscle cells. The investigators then proceeded to obtain pharmacodynamic measurements of airway smooth muscle responsiveness and determine cyclic adenosine monophosphate (cAMP) accumulation and Gi protein expression. Moreover, the investigators determined ICAM-1 expression in rabbit airway smooth muscle cells by reverse transcriptase polymerase chain reaction and Southern blot analysis, Western blot analysis, and flow cytometry. ICAM-1 expression was also determined in human airway smooth muscle cells by Northern blot analysis.

**Results.** Isolated rabbit and human airway smooth muscle tissue and cultured airway smooth muscle cells were inoculated with human rhinovirus (serotype 16) or adenovirus, each for 6 or 24 hours. As compared with adenovirus, which had no effect, inoculation of airway smooth muscle tissue with rhinovirus induced heightened airway smooth muscle tissue constrictor responsiveness to acetylcholine and attenuated the dose-dependent relaxation of airway smooth muscle to  $\beta$ -adrenoceptor stimulation with isoproterenol. These changes were largely prevented by pretreating the tissues with pertussis toxin or with a monoclonal blocking antibody to ICAM-1, which is the principal endogenous receptor for most rhinoviruses. The investigators also observed that the rhinovirus-induced changes in airway smooth muscle responsiveness were associated with diminished cAMP accumulation in response to dose-dependent administration of isoproterenol, and this effect was accompanied by upregulated expression of a Gi protein subtype in the airway smooth muscle. Finally, rhinovirus-induced effects on airway smooth muscle responsiveness were accompanied by cell surface expression of ICAM-1.

**Conclusions.** This investigation provides new evidence that by the binding of rhinovirus to its ICAM-1 receptor in airway smooth muscle directly induces proasthmatic phenotypic changes in airway smooth muscle responsiveness and that this binding results in upregulation of ICAM-1 and the enhanced expression and activation of Gi protein in the rhinovirus-infected tissue.

**Reviewer's Comments.** Over the past decade, we have witnessed an explosion of information regarding the role of certain respiratory viruses, particularly rhinoviruses, in the pathogenesis of asthma and airways hyperresponsiveness. This collective body of evidence supports the concept that the airway hyperresponsiveness observed in asthmatic patients during specific viral respiratory infections results from airway inflammation, cytokine release and, in some cases, specific immunoglobulin E production. This current investigation identifies the important role and molecular mechanism by which airway smooth muscle autologously induces its state of altered responsiveness after infection with rhinovirus. Hopefully, this and related data will "pave the way" for the development of rational, clinically useful therapies to reduce the morbidity and mortality experienced by patients with asthma as a direct consequence of certain viral upper respiratory infections.

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## RESPIRATORY TRACT VIRAL INFECTIONS IN INNER-CITY ASTHMATIC ADULTS

Atmar RL, Guy E, Guntupalli KK, et al. *Arch Intern Med.* 1998;158:2453-2459

**Purpose of the Study.** Respiratory tract viral infections (RTVIs) have been identified frequently in association with asthma exacerbations in children, but few studies have shown similar rates of viral infections in adults with asthma. Further studies using newer diagnostic techniques to evaluate the frequency of RTVIs in adults with acute exacerbations of asthma need to be performed.

**Study Population and Methods.** Twenty-nine asthmatic adults were recruited from the pulmonary clinic of an urban county hospital and were followed up in a longitudinal cohort study for signs and symptoms of asthma and RTVI. One hundred twenty-two asthmatic adults presenting to the emergency department (ED) of the same hospital with acute symptoms of asthma underwent evaluation for RTVI in a cross-sectional prevalence study. In both studies, respiratory secretions and paired serum samples were collected from subjects with acute wheezing episodes and evaluated using virus culture, serologic testing, and reverse transcription-polymerase chain reaction (RT-PCR).

**Results.** In the longitudinal cohort study, 138 respiratory illnesses, of which 87 were asthma exacerbations, were evaluated; 41% of all illnesses and 44% of asthma exacerbations were associated with an RTVI. In the ED study, 148 asthma exacerbations were evaluated; 55% were associated with an RTVI. An RTVI was identified in 21 (50%) of 42 of the subjects hospitalized in the ED study. Picornaviruses (rhinoviruses), coronaviruses, and influenza viruses were the most commonly identified causes of RTVI. Forty-six (60%) of the 77 picornavirus infections and 22 (71%) of the 31 coronavirus infections were identified only using RT-PCR.

**Conclusions.** Asthmatic exacerbations in adults are frequently associated with an RTVI. Identification of such infections often requires newer diagnostic methods, such as virus-specific RT-PCR. The high frequency of RTVIs identified in association with asthmatic exacerbations in adults from the inner city suggests that strategies for the prevention of RTVI should be targeted toward this population.

**Reviewer's Comments.** I'm not sure why there are so few studies of RTVI-induced asthma in adults. Those of us caring for adult asthmatics certainly see this association with regularity. At least the grown-ups weren't getting RSV.

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## CHRONIC CHLAMYDIA PNEUMONIAE INFECTION AND ASTHMA EXACERBATIONS IN CHILDREN

Cunningham AF, Johnston SL, Julious SA, Lampe FC, Ward ME. *Eur Respir J.* 1998;11:345-349

**Purpose of the Study.** To investigate the reported association between *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infection and the expression of asthmatic symptoms in susceptible patients.

**Methods.** One hundred eight children with a history of asthma-related symptoms were followed longitudinally for 13 months. Subjects kept a daily diary of symptoms and peak flow rates, and when asthma-related symptoms occurred an investigator was contacted for collection of nasal aspirates. A total of 292 samples were collected during symptomatic episodes and a total of 65 children provided

a sample when asymptomatic. Polymerase chain reaction (PCR) was used to identify the presence of *C pneumoniae* and *M pneumoniae*. The presence of secretory immunoglobulin A (IgA) specific to *C pneumoniae* was also detected.

**Results.** In asymptomatic patients and patients experiencing an acute asthma episode, the rate of *C pneumoniae* detection was similar (28 vs 23%, respectively). Patients who reported multiple episodes tended to remain PCR-positive, which suggested a chronic infection. Subjects who reported four or more exacerbations had secretory-IgA levels more than seven times higher than those patients who had only one symptomatic episode. Throughout the study, PCR detected *M pneumoniae* in just 2 of the 292 symptomatic episodes, and in 2 of the 65 asymptomatic patients.

**Conclusions.** Chronic infection with this very common respiratory pathogen, *C pneumoniae*, as evidenced by persistent positive PCR and elevated secretory-IgA, was associated with recurrent asthma symptoms. This study did not show any connection between *M pneumoniae* and chronic asthma symptoms.

**Reviewers' Comments.** The standard evaluation of patients with chronic asthma can be a lengthy and costly process often without revealing a definitive cause. PCR analysis for *C pneumoniae* is not a routine evaluation in most cases, but this study certainly suggests that this organism could be considered a cause of chronic asthma symptoms in some patients. Further study, including antibiotic therapy in infected patients, is warranted.

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#### OVEREXPRESSION OF LEUKOTRIENE C<sub>4</sub> SYNTHASE IN BRONCHIAL BIOPSIES FROM PATIENTS WITH ASPIRIN-INTOLERANT ASTHMA

Cowburn AS, Sladek K, Soja J, et al. *J Clin Invest.* 1998; 101:834–846

**Purpose of the Study.** To gain a better understanding of why aspirin does not cause bronchoconstriction in all individuals, as it does in patients with aspirin-intolerant asthma (AIA).

**Study Population.** Ten patients with AIA ( $n = 10$ ), 10 patients with aspirin-tolerant asthma (ATA), and 9 nonatopic, normal subjects were included in this investigation. All subjects were nonsmokers and clinically stable at the time of the study.

**Methods.** Bronchial responsiveness to inhaled lys-aspirin was assessed with a dosimeter-controlled nebulizer using a standard protocol. Bronchoscopy and bronchoalveolar lavage (BAL) were carried out according to the American Thoracic Society guidelines. Using the bronchial biopsy specimens, enzymes of the leukotriene and prostanoïd pathways were immunostained; standard BAL fluid mediator assays were also undertaken.

**Results.** Counts of cells expressing the terminal enzyme for cys-LT synthesis, LTC<sub>4</sub> synthase, were fivefold higher in AIA biopsies ( $11.5 \pm 2.2$  cells/mm<sup>2</sup>,  $n = 10$ ) than in ATA biopsies ( $2.2 \pm 0.7$ ,  $n = 10$ ;  $P = 0.0006$ ) and 18-fold higher than in biopsies from normal controls ( $0.6 \pm 0.4$ ,  $n = 9$ ;  $P = 0.0002$ ). Immunostaining for 5-lipoxygenase, its activating protein (FLAP), LTA<sub>4</sub> hydrolase, cyclooxygenase (COX)-1 and COX-2 did not differ. Enhanced baseline cys-LYT<sub>4</sub> synthase+ cells ( $p = 0.83$ ,  $P = .01$ ). Lysine-aspirin challenge released additional cys-LTs into BAL fluid in AIA patients ( $200 \pm 120$  pg/mL,  $n = 8$ ) but not in ATA patients ( $0.7 \pm 5.1$ ,  $n = 5$ ;  $P = .007$ ). Bronchial responsive-

ness to lysine-aspirin correlated exclusively with LTC<sub>4</sub> synthase+ cell counts ( $p = -0.63$ ,  $P = .049$ ,  $n = 10$ ).

**Conclusions.** Aspirin may remove PGE<sub>2</sub>-dependent suppression in all subjects, but only in AIA patients does increased bronchial expression of LTC<sub>4</sub> synthase allow marked overproduction of cys-LTs leading to bronchoconstriction.

**Reviewer's Comments.** Although we now have leukotriene-modifying medications that can be particularly useful in the management of chronic asthma in patients with AIA, a complete mechanistic understanding of this disease has been lacking. This investigation provides novel insights into the pathogenesis of AIA, which may be present in up to 20% of children and adults with asthma. In bronchial biopsy specimens, the investigators reported a dramatic overrepresentation of cells expressing LTC<sub>4</sub> synthase in the AIA patients, as compared with the ATA patients and normal control subjects. This basic difference may provide a basis for the chronic overproduction and for the aspirin-induced increments in cys-LT production in AIA, and for the lack of adverse responses to NSAIDs in ATA and normal individuals. Hopefully, further research in this area will help sort out the clinical heterogeneity that is typical in this group of patients (ie, some AIA patients only reacting to aspirin, while others with AIA may react to aspirin and the whole spectrum of nonsteroidal anti-inflammatory drugs (NSAIDs)).

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#### MODULATION OF AIRWAY INFLAMMATION BY CPG OLIGODEOXYNUCLEOTIDES IN A MURINE MODEL OF ASTHMA

Kline JN, Waldschmidt TJ, Businga TR, et al. *J Immunol.* 1998;160:2555–2559

**Background.** Asthmatics and allergic patients have a surplus of Th-2 T-cells, which are responsible for the production of cytokines that drive the allergic and asthmatic states. Nonallergic, nonasthmatics do not routinely demonstrate a Th-2 profile. Because all children with normal immunity produce Th-1 T-cells, necessary for immune responsiveness to bacterial and viral antigens, it has been speculated that allergic children may somehow be more geared to a Th-2 T-cell pool. If true, the exposure of native infection diminished by immunization and hygiene may make children in industrialized nations more apt to produce Th-2. Bacterial DNA contains generous numbers of unmethylated CpG dinucleotides (CpG ODN) when compared with mammalian cells. These CpG motifs drive a Th-1 response. If allergic children in industrialized nations are not exposed to as many infections, their Th-1 response may be blunted allowing for a Th-2 overproduction.

**Methods.** Mice were sensitized to parasite protein and their allergic response was measured by airway eosinophilia, Th-2 cytokine induction, immunoglobulin E (IgE) production, and bronchial hyperreactivity. In other parasite-sensitized mice the CpG ODN was given at the same time as the parasite. Appropriate controls were included.

**Results.** Mice exposed to parasite protein developed all the characteristics of asthma, including increased IgE, airway hyperreactivity, increased lung IL-4, and lung eosinophilia. In those mice who received parasite and CpG ODN none of the characteristics of asthma developed. The mice who received CpG ODN also produced more interferon-gamma and IL-12, both Th-1 cytokines.

**Conclusions.** This well characterized model for murine asthma could be totally blocked using immunization with a Th-1 inducing agent.

*Reviewer's Comments.* There is emerging a tantalizing story that may partially account for the increase in asthma in industrialized nations. If the immune system of children are not busy with multitudes of indigenous infections, the genetics for inducing a Th-2 response to allergens (eg, mites, pets, food) is less encumbered. These results also point to intriguing strategies for immunization to enhance Th-1 responses, and hopefully slowing down or turning off Th-2 responses.

RUSSELL HOPP, DO  
Omaha, NE

### PERSISTENCE OF SPUTUM EOSINOPHILIA IN CHILDREN WITH CONTROLLED ASTHMA WHEN COMPARED WITH HEALTHY CHILDREN

Cai Y, Carty K, Henry RL, Gibson PG. *Eur Respir J.* 1998;11:848–853

*Purpose of the Study.* To describe induced sputum cell counts in healthy nonasthmatic children, and to compare these with asthmatic children whose asthma was controlled to varying degrees.

*Study Population.* Seventy-two children, ages 8 to 14 years, who were regarded as normal controls and 42 children, ages 6 to 18 years, who were known asthmatics. The 72 normal children were identified via a meticulous screening process. Of the 72 normals, 32 were considered to be atopic on the basis of a positive skin test to one or more common inhalant allergens. The remainder were nonatopic. When considering the 42 asthmatic children, 41 were on inhaled corticosteroids. Their asthma control was categorized as satisfactory (15), symptomatic (16), and asthmatic exacerbations (11).

*Methods.* With appropriate safety measures in place, sputum production was induced in all subjects using inhaled hypertonic saline. If significant drops in forced expiratory volume in one second (FEV<sub>1</sub>) took place, reversal was accomplished with inhaled salbutamol. Sputum samples were analyzed for eosinophils, mast cells, neutrophils, and epithelial cells.

*Results.* In the nonatopic, normal children, the total cell counts were surprisingly higher than the nonasthmatic atopic children, although this latter group did have significantly more eosinophils. In the asthmatic group, eosinophils and epithelial cell numbers were significantly higher than the normals, and this was true regardless of the degree of control. Generally, however, the better the control the fewer eosinophils and epithelial cells noted.

*Conclusions.* Markers of airway inflammation, such as eosinophils, were present in the sputum of normal atopic children to a greater degree than the nonatopic normals, perhaps indicating that given an appropriate insult, wheezing could follow. The same marker of inflammation, the eosinophil, was noted in all asthmatics along with significant epithelial cell shedding. These findings transcended all degrees of control.

*Reviewers' Comments.* The data tend to support the notion that we appear to be making some positive strides with modern pharmacotherapeutic agents in controlling the overt symptoms of asthma, but we still have a ways to go in finally containing the demon of inflammation. In addition, with statistically increased markers of inflammation, as noted in the sputum of normal atopic children, what threshold needs to be crossed before clinically apparent asthma develops? Hypertonic saline inhalations as a sputum generating agent is most certainly safe and effective. With adequate sputum for analysis, we may be better

able to follow and evaluate the atopic and/or asthmatic child in the real world of first-class allergy management.

KAREN DENNY, DO  
THAD H. JOOS, MD  
Detroit, MI

### DIAGNOSIS AND TREATMENT OF GASTROESOPHAGEAL REFLUX IN CHILDREN AND ADOLESCENTS WITH SEVERE ASTHMA

Balson BM, Kravitz EKS, McGeady SJ. *Ann Allergy Asthma Immunol.* 1998;81:159–164

*Purpose.* The relationship of gastroesophageal reflux (GER) disease to asthma is controversial. Recent studies have suggested that reflux to the proximal esophagus may provoke asthma. The prevalence of proximal reflux in children has not been established. Diagnostically, it is not clear what the sensitivity and specificity of noninvasive techniques such as barium swallow and scintiscan are compared with the "gold standard," pH probe, in this population. Furthermore, there is limited information on the effectiveness of combined therapy with H<sub>2</sub> blockers and prokinetic agents in controlling reflux in children. The purpose of this study was threefold: 1) to determine the prevalence of proximal and distal GER in asthmatic children, 2) to determine the value of barium swallow and scintiscan relative to the pH probe in diagnosing GER, and 3) to determine the effectiveness of standard antireflux medical therapy in children.

*Study Population.* Seventy-nine children and adolescents ages 2 to 17 years with "difficult to control" severe asthma requiring residential care were evaluated. None of these patients had symptoms of GER. Asthma medication included the usual inhaled antiinflammatory and bronchodilator medication, in addition to methylxanthines and oral steroids in some cases.

*Methods.* A 24-hour 2-channel pH probe evaluation was carried out on all patients and the prevalence of proximal and distal GER established. In addition, 63 patients had barium swallow and 62 scintiscan with Technetium 99. Using the pH probe data as the "gold standard," sensitivity, specificity, and positive and negative predictive values were calculated. Finally, in 11 subjects a follow-up pH probe was performed after 3 weeks of antireflux therapy with ranitidine and metoclopramide.

*Results.* Reflux into the distal esophagus occurred in 73% (58/79) and reflux into the proximal esophagus occurred in 64.5% (51/79) of the patients. Compared with the pH probe, the barium swallow and scintiscan fared poorly with sensitivity of 46% and 15%, specificity 82% and 73%, positive predictive value of 82% and 50%, and negative predictive values of 51% and 32%, respectively. Of 11 subjects studied by repeat pH probe, 10 had persistent GER.

*Conclusions.* Abnormal reflux into the proximal esophagus occurs in the majority of "difficult to control" asthmatic children. Barium swallow and scintiscan compared poorly with the pH probe in diagnosing reflux, particularly when they are negative. Treatment of gastroesophageal reflux with an H<sub>2</sub> blocker and prokinetic agents had a high failure rate in this population.

*Reviewers' Comments.* This study is important because it suggests that GER, particularly into the proximal esophagus, may be an important contributor to asthma. To make that diagnosis, one needs a pH study. It is interesting to note that none of the 73% of pH positive patients had signs and symptoms of GER. However, the data are somewhat suspect because one doesn't know precisely what the se-



verity of the patients were in terms of the usual criteria, nor whether the drugs they were receiving, ie, methylxanthines, could have contributed to the GER. In addition, there was no attempt to correlate GER with asthma status because the authors felt these children stabilized in the residential setting. Future studies need to not only establish the prevalence of GER in asthmatic children, but attempt to better characterize the type of patients who would be the best candidates for diagnosis and treatment. Finally, the effect of therapy needs to be assessed in terms of both GER and asthma to help establish a cause-and-effect relationship.

RAMA YERRAMSETTI, MD  
STANLEY P. GALANT, MD  
Orange, CA

## DIAGNOSIS AND MANAGEMENT

### POPULATION-BASED STUDY OF RISK FACTORS FOR UNDERDIAGNOSIS OF ASTHMA IN ADOLESCENCE: ODENSE SCHOOLCHILD STUDY

Siersted H, Boldsen J, Hansesn H, Mostgaard G, Hyldebrandt N. *Br Med J*. 1998;316:651-657

*Purpose of the Study.* To describe factors related to the underdiagnosis of asthma in adolescence.

*Study Population.* A total of 495 schoolchildren aged 12 to 15 years were selected from a cohort of 1369 children investigated 3 years earlier. Selection was conducted by randomization ( $n = 292$ ) and by a history indicating allergy or asthma-like symptoms in the subject or family ( $n = 203$ ).

*Methods.* Subjects completed a comprehensive questionnaire and monitored peak expiratory flow bid for 2 weeks. Laboratory examinations included anthropometric measurements, puberty staging, spirometry, treadmill exercise testing, and methacholine challenge. Subjects discontinued bronchodilators but not inhaled steroids before testing. Current asthma symptoms were determined by questionnaire. Physician-diagnosed asthma was identified by asking the subject if they had been diagnosed with asthma, were on asthma medication, or both. Subjects without a previous diagnosis but with asthma-like symptoms by objective evaluation (one or more obstructive airway abnormalities: low ratio of forced expiratory volume in 1 second (FEV<sub>1</sub>) to forced vital capacity, positive response to methacholine or exercise, or peak flow variability) were labeled as undiagnosed asthma.

*Results.* Undiagnosed asthma comprised one third of all identified asthmatics. Underdiagnosis was independently associated with low physical activity, high body mass, family problems, passive smoking, and absence of rhinitis. Girls comprised 69% of undiagnosed patients ( $P = .007$  compared with diagnosed). The major symptom of undiagnosed asthma was cough (58%). Wheezing (35%) or breathing difficulty (50%) were reported less frequently than those with diagnosed asthma. Less than one third of the undiagnosed patients reported symptoms to their physician.

*Conclusions.* Asthma, as defined by symptoms and objective measures, was seriously underdiagnosed among adolescents. The problem was more common in girls and was associated with decreased tendency to report symptoms.

*Reviewers' Comments.* The results from this study suggest that asthma continues to be significantly underdiagnosed in some populations. It is important that histories regarding asthma symptoms be taken during well child

and sick visits, that cough be recognized as a potential manifestation of asthma, and that objective measures of lung function be obtained whenever there is a suspicious history.

WANDA PHIPATANAKUL, MD  
ROBERT A. WOOD, MD  
Baltimore, MD

### MEDICATIONS USED BY CHILDREN WITH ASTHMA LIVING IN THE INNER-CITY

Eggleston PA, Malveaux FJ, Butz AM, et al. *Pediatrics*. 1998;101:349-354

*Purpose of the Study.* It is well recognized that asthma morbidity is disproportionately high in inner-city children. The purpose of the study was to examine medication use of children in an urban environment and to relate this use to other social and medical variables.

*Study Population.* Patients and their families recruited from elementary schools in Baltimore and Washington, DC.

*Methods.* A total of 508 children with asthma were identified by school health records and teacher surveys, and questionnaires were completed by 392 families.

*Results.* In general, children were undermedicated. A total of 78 children (20%) reported no medication or over-the-counter medication use, although 37% reported asthma severe enough to be associated at least 20 days of school missed per year, and 37% had a visit to the emergency room in the past 6 months. Theophylline was the most commonly used daily medication, and only 11% took some form of daily antiinflammatory medication (cromolyn or inhaled corticosteroids). Supervision was also lacking, as more than half of children ages 9 years and older were responsible for their own medication.

*Conclusions.* The authors concluded that poor children with asthma living in urban areas tend to be undermedicated, particularly in terms of antiinflammatory medication.

*Reviewer's Comments.* Although the root cause for the increased amount of asthma in inner-city children remains obscure, this report and previous studies suggest that the increased asthma morbidity in this environment is attributable to problems with health care access and supervision. This suggests that well-targeted public health efforts are likely to make a difference in lives of children with asthma in an urban environment, and the same principles are likely to apply to poor children with asthma in nonurban environments (see McGill KA et al, *Pediatrics* 1998;102:77-83).

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### PARENTAL PERCEPTIONS OF ACCESS TO CARE AND QUALITY OF CARE FOR INNER-CITY CHILDREN WITH ASTHMA

Dinkevich EI, Cunningham SJ, Crain EF. *J Asthma*. 1998; 35:63-71

*Purpose of the Study.* To describe perceptions of asthma care, morbidity, and health service utilization by parents of children with asthma presenting to an inner-city emergency department (ED).

*Study Population.* Parents of children ( $n = 466$ ) receiving asthma treatment in an urban pediatric ED during a consecutive 6-week period in late fall 1995.

**Methods.** Parents completed a 30-item survey including sociodemographic data, source of primary medical care and asthma care for their child, selected measures of access to care, and medications used by their child in the week before the ED visit. Perceived quality of asthma care was measured by six items reported to have been performed by the child's asthma doctor: discussion of home peak flow monitoring, triggers, dogs/cats, smoke, postexacerbation calling instructions, and provision of a written asthma management plan. Functional morbidity was measured by nights of poor sleep, days of cough, and school days missed because of asthma in the previous month.

**Results.** Of the patients surveyed, 325 had previously been diagnosed with asthma. Three hundred eight (97%) reported a source of primary medical care. The primary care provider (PCP) was identified as the child's usual source of asthma care (PCP users) in 126 respondents, while 158 identified the ED as the usual source of asthma care (ED users). The groups did not differ by insurance status, ethnicity, or mean age of the child. Thirty-nine percent of PCP users compared with 15% of ED users had used inhaled steroids or cromolyn in the week before the ED visit ( $P < .0001$ ). PCP users had a higher mean quality score than ED users (3.7 vs 2.8;  $P < .0001$ ), but there was no relationship between source of asthma care and functional morbidity.

**Conclusions.** The ED remains the usual source of asthma care for many inner-city children. Among parents surveyed in the ED, there was a significant relationship between source of usual asthma care and quality of care, but a relationship between usual source of asthma care and functional morbidity could not be identified.

**Reviewer's Comments.** High ED utilizers don't get the message: asthma is a chronic disease requiring 1) daily preventive management including trigger avoidance measures and antiinflammatory therapy, and 2) regular follow-up asthma care at least with the PCP, if not with an asthma specialist. How can we get this message through?

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### ASSOCIATION OF BEING OVERWEIGHT WITH GREATER ASTHMA SYMPTOMS IN INNER-CITY BLACK AND HISPANIC CHILDREN

Luder E, Melnik TA, DiMaio M. *J Pediatr.* 1998;132:699-703

**Purpose of the Study.** The prevalence of both asthma and obesity have been increasing over recent years, and are higher among minorities. The aim of this study was to observe whether the weight status of inner-city minority asthmatic children differed from that of their nonasthmatic peers, and to determine if overweight asthmatic children experienced more severe asthma.

**Study Population.** The study group was composed of 209 black and Hispanic children between the ages of 2 and 18 who carried the single diagnosis of asthma, and who had not received chronic oral steroids or more than 4 short courses of oral steroids within the past year. The control group consisted of 1017 black and Hispanic children enrolled in New York City schools.

**Methods.** Information obtained from the patient record and an interview was used to determine asthma severity. This information included peak expiratory flow (PEF) records, number of medications used, number of emergency visits or hospitalizations, number of school days missed, and ability to participate in play or sports activities. PEF rate was measured at enrollment in patients who

were at least 6 years old and could perform a good effort. Standing height and weight were measured in the patients. Height and weight measurements for the control group were available for comparison. Body mass index (BMI) was calculated and used as the indicator of weight status. Differences in BMI between the asthmatic children and their peers were determined, and the relationship between high BMI and the various measures of asthma severity was examined.

**Results.** The percentile distribution of BMI for the children with asthma was compared with that of the control group as well as the established reference population. The BMI distribution for the asthmatic patients as well as the controls was skewed towards the higher percentiles compared with the reference population, but was skewed to a greater extent for the asthmatics. The asthmatic children had a relative risk of 1.34 of having a BMI at 85th percentile or greater compared with the peer group ( $P = .06$ ). The relative risk for asthmatics of having a BMI at 95th percentile or greater was 1.51 ( $P = .03$ ). The risk of being overweight (based on a BMI of 85th percentile or greater) was found to be significantly associated with days of school missed (30 days or more missed per year), PEF rate of  $\leq 60\%$  predicted, and three or more prescribed asthma medications. The risk of being overweight was not significantly associated with number of hospitalizations, number of emergency visits, or level of sports participation.

**Conclusions.** The prevalence of being overweight was significantly higher in asthmatic children compared with their peers. Being overweight was significantly associated with severity of asthma as measured by PEF rate, days of school missed, and number of asthma medications.

**Reviewers' Comments.** The authors mention that the findings of this study do not allow us to determine whether asthmatic children are more overweight because of a decreased activity level, or if being overweight actually leads to increased severity of asthma. Asthmatic children may be held back from participating in sports by their parents and thus become overweight because of inactivity. Alternatively, overweight children might spend more time indoors, thereby being exposed to greater amounts of indoor allergens, leading to increased asthma. The latter explanation might be more of an issue in inner-city environments.

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MICHAEL S. KAPLAN, MD  
Los Angeles, CA

### RANDOMISED PLACEBO-CONTROLLED CROSSOVER TRIAL ON EFFECT OF INACTIVATED INFLUENZA VACCINE ON PULMONARY FUNCTION IN ASTHMA

Nicholson KG, Nguyen-Van-Tam JS, Ahmed AH, et al. *Lancet.* 1998;351:326-331

**Purpose of the Study.** Influenza virus infection is a cause of major morbidity each year, especially in patients with chronic disease such as asthma. Although current recommendations are to administer influenza vaccine to children and adults with asthma, compliance is suboptimal because of various reasons including fear that the vaccine itself may trigger an asthma exacerbation. The purpose of this study was to assess the safety of influenza vaccine in patients with asthma.

**Study Population.** Two hundred sixty-two patients (114 males and 148 females) ages 18 to 75 years with a history of asthma, defined as recurrent episodes of airway obstruction

tion that resolved on treatment, and whose diagnosis had been made by a clinical specialist.

**Methods.** Participants were randomly assigned to receive in a double-blind, crossover design, either the vaccine or placebo separated by 2 weeks. The primary clinical outcome measure was an asthma exacerbation within 72 hours of injection, defined by a decline in early-AM peak expiratory flow (PEF) of more than 20% compared with the lowest of the best three early morning PEF values during the 3 days before the injection. Secondary outcome measures were: changes in upper/lower respiratory symptoms, systemic symptoms, and inhaled  $\beta_2$ -agonist use 72 hours before and after injection; antibiotic and oral steroid therapy use 7 days after injection; and unscheduled medical consultations and hospital admissions for an exacerbation within 7 days of each injection.

**Results.** Among the 255 participants with complete paired data, a total of 11 (4.3%) participants had an asthma exacerbation (with a decrease in PEF of at least 20%) after vaccine compared with 3 (1.2%) after placebo ( $P = .06$ ). Five of these 11 participants were determined to have a cold by the nature of their upper respiratory symptoms. When the data from these 5 participants was excluded, 6 (2.4%) had a decrease in PEF of at least 20% after vaccine compared with 3 (1.2%) after placebo ( $P = .51$ ). However, 5 (2.0% overall) of these 6 patients had a drop in PEF of >30% after vaccine compared with none (0%) after placebo ( $P = .06$ ). This approached statistical significance. The mean decrease in PEF for the 6 subjects was 17.6%. There was no significant difference in all the secondary parameters except in systemic symptoms after the vaccine compared with placebo. Lastly, 5 out of 6 reactions with the vaccine, compared with 1 out of 3 with placebo, were among the 97 first-time vaccine recipients.

**Conclusions.** Although pulmonary function changes can certainly occur as a complication of the influenza vaccine in patients with asthma, the risk is very small and outweighed by the benefits of vaccination.

**Reviewers' Comments.** Approximately 15% of patients with asthma are infected with influenza virus each year. From previous studies it is estimated that 75% of asthmatic children with serologically proven influenza infection had a decrease in forced expiratory volume in 1 second (FEV<sub>1</sub>) of 20% or more. Influenza vaccine prevents about 75% of influenza infections. Therefore, given this data, and the complication rates with vaccine from this study, it is clear that the vaccine prevents far more exacerbations of asthma than it causes.

NARESH J. PATEL, DO  
ROBERT F. LEMANSKE, JR, MD  
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## 20-YEAR TRENDS IN THE PREVALENCE OF ASTHMA AND CHRONIC AIRFLOW OBSTRUCTION IN AN HMO

Vollmer WM, Osborne ML, Buist AS. *Am J Respir Crit Care Med.* 1998;157:1079–1084

**Purpose of the Study.** To present data on age- and sex-specific patterns of change in an analysis of a 20-year trend in treated prevalence of asthma among members of a large health maintenance organization (HMO).

**Study Population.** Data were derived primarily from the abstracted medical records of a random sample of Kaiser Permanente (KP), Northwest Division, members and from an eligibility file that tracks health plan eligibility for members included in the outpatient utilization sample.

**Methods.** Data are presented for each of six age and sex categories, and include both the treated prevalence of the broader category of chronic airflow obstruction (CAO), defined as asthma, chronic bronchitis, or emphysema. The three age groups were: 0 to 14-year-olds, 15- to 64-year-olds, and 65+ years.

**Results.** Three main findings emerged from this study. First, for the 20-year period from 1966–1987 the treated prevalence of asthma increased steadily and significantly in this population in both males and females and in all age ranges except males over 65 years of age. Second, these increases parallel increases in the broader category of CAO and therefore are not likely merely to reflect diagnostic shift from chronic bronchitis/emphysema toward asthma in the midst of an otherwise stable pattern of chronic airways disease. Third, these results also demonstrate the dangers of extrapolating trends in one type of asthma health care utilization outcome, for example hospitalizations, to other types of health care utilization outcomes.

**Conclusions.** These findings support other evidence of a real increase in asthma prevalence.

**Reviewer's Comments.** Epidemiologic studies similar to this report are extremely important in assessing changes in prevalence as well as the changing nature of health care outcomes. A comprehensive evaluation of hospitalizations, emergency department visits, days lost from school or work, medication requirements, etc will be important in understanding the impact of our environment as well as the success or failure of our treatment strategies.

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## IMPACT OF CHRONIC COUGH ON QUALITY OF LIFE

French CL, Irwin RS, Curley FJ, Krikorian CJ. *Arch Intern Med.* 1998;158:1657–1661

**Purpose of the Study.** Cough is the most common complaint for which adult patients seek medical care in the United States; however, the reason(s) for this is unknown. The purpose of this study was to determine whether chronic cough was associated with adverse psychosocial or physical effects on the quality of life and whether the elimination of chronic cough with specific therapy improved these adverse effects.

**Study Population and Methods.** The study design was a prospective before-and-after intervention trial with patients serving as their own controls. Study subjects were a sample of 39 consecutive and unselected adult patients referred for evaluation and management of a chronic, persistently troublesome cough. Baseline data were available for 39 patients and follow-up for 28 patients (22 women and 6 men). At baseline, demographic, Adverse Cough Outcome Survey (ACOS), and Sickness Impact Profile (SIP) data were collected and patients were managed according to a validated, systematic protocol. Following specific therapy for cough, ACOS, and SIP instruments were readministered.

**Results.** The ages, sex, duration, and spectra and frequencies of the causes of cough were similar to multiple other studies. At baseline, patients reported a mean SD of  $8.6 \pm 4.8$  types of adverse occurrences related to cough. There were significant correlations between multiple ACOS items and total, physical, and psychosocial SIP scores. Psychosocial score correlated with total number of symptoms ( $P < .02$ ). After cough disappeared with treatment, ACOS complaints decreased to a mean  $\pm$  SD of  $1.9 \pm 3.2$  ( $P < .0001$ ) as did total (mean  $\pm$  SD,  $4.8 \pm 4.5$  to  $1.8 \pm 2.2$ ) ( $P = .004$ ),



psychosocial (mean  $\pm$  SD,  $4.2 \pm 6.8$  to  $0.8 \pm 2.3$ ) ( $P = .004$ ), and physical (mean  $\pm$  SD,  $2.2 \pm 2.9$  to  $0.9 \pm 1.8$ ) ( $P = .05$ ) SIP scores. Multiple linear regression analysis showed that 54% of variability of the psychosocial SIP score was explained by 4 ACOS items while none of the physical score was explained.

**Conclusions.** Chronic cough was associated with deterioration in patients' quality of life. The health-related dysfunction was most likely psychosocial. The ACOS and SIP appear to be valid tools in assessing the impact of chronic cough.

*Reviewer's Comments.* I had always suspected that people who were wrenching their guts out coughing over a period of time were kind of unhappy with things. Perhaps studies like this will help to remind us all to be more sensitive to the fact that chronic respiratory diseases adversely affect patients' lives.

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Denver, CO

### COMPLIANCE WITH NATIONAL ASTHMA MANAGEMENT GUIDELINES AND SPECIALTY CARE: A HEALTH MAINTENANCE ORGANIZATION EXPERIENCE

Legorreta AP, Christian-Herman J, O'Connor RD, Hasan MM, Evans R, Leung KM. *Arch Intern Med.* 1998;158:457-464

**Purpose of the Study.** To improve asthma disease management, the National Asthma Education Program (NAEP) Expert Panel published *Guidelines for the Diagnosis and Management of Asthma* in 1991. To compare the current status of asthma disease management among patients in a large health maintenance organization (HMO) with the NAEP guidelines and to identify the factors that may be associated with medical care (eg, emergency department visits and hospital admissions) and adherence to the guidelines.

**Study Population.** Analyses of 1996 survey data from 5580 members with asthma (age range, 14 to 65 years) covered by a major HMO in California (Health Net).

**Results.** In general, adherence to NAEP guidelines was poor. Seventy-two percent of respondents with severe asthma reported having a steroid inhaler, and of those, only 54% used it daily. Only 26% of respondents reported having a peak flowmeter, and of those, only 16% used it daily. Age (older), duration of asthma (longer), increasing current severity of disease, and treatment by an asthma specialist correlated with daily use of inhaled steroids. Ethnicity (African-American and Hispanic) correlated negatively with inhaled steroid use but positively with emergency department visits and hospital admissions for asthma. Increasing age and treatment by an asthma specialist were also identified as common factors significantly related to the daily use of a peak flowmeter and, interestingly, to overuse of  $\beta_2$ -agonist metered-dose inhalers.

**Conclusions.** Although the NAEP guidelines were published 7 years ago, compliance with the guidelines was low. It was especially poor for use of preventive medication and routine peak-flow measurement. Furthermore, the results showed that asthma specialists provided more thorough care than did primary care physicians in treating patients with asthma. Combining the results of the regression analyses revealed that some of the variation in rates of emergency department visits and hospitalizations among some subpopulations can be explained by the underuse of preventive medication. This study serves the goal of documenting the quality of care and services currently pro-

vided to patients with asthma through a large HMO and provides baseline information that can be used to design and assess effective population-based asthma disease management intervention programs.

*Reviewer's Comments.* Most HMOs claim to be interested in programs such as population-based asthma disease management intervention programs. Unfortunately, most are not willing to pay for it. Primary care physicians are given incentives not to refer to specialists. Capitated specialists are generally not provided with compensation that would allow the time and attention these patients need. Until payers of health care demand changes (and show a willingness to pay for them), it seems to me that asthma will remain an undertreated disease.

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### RELATIONSHIP BETWEEN EXHALED NITRIC OXIDE IN CHILDHOOD ASTHMA

Frank TL, Adishesha A, Pickering AC, et al. *Am J Respir Crit Care Med.* 1998;158:1032-1036

**Purpose.** Nitric oxide (NO) can be derived from constitutive nitric oxide synthase (NOS), which is involved in physiologic regulation of airway function, or from inducible nitric oxide synthase (iNOS), which is involved in inflammatory disease of the airways and in host defense against infection. It is iNOS that is active in asthmatic airways. The purpose of this study was to determine if exhaled nitric oxide (eNO) levels in children varied according to their asthmatic and atopic states.

**Methods.** Between 1993 and 1995, questionnaires were sent to parents or guardians of 3290 children in the Wythen-shawe Community Asthma Project (WYCAP) regarding respiratory symptoms and asthma-related conditions. The parents of 2434 children completed the questionnaire. A stratified weighted random sample of respondents attending one of the general practices was personally invited to participate in the study. Children were not excluded if they had a previous diagnosis of asthma or were receiving treatment for asthma. The clinical assessment included a full medical history and physical examination, an exercise challenge, spirometry with reversibility to a  $\beta_2$ -agent, 1-week electronic peak flow daily record, and skin prick testing to house dust mite, grass pollen, cockroach, dog, and cat. Both the eNO and nasal nitric oxide (nNO) levels were measured. Three independent consultant pediatricians were supplied with all the information from the clinical assessment except for the NO findings. After reviewing the results, the pediatricians were asked to rate the subjects into four categories that reflected the probability that each child had asthma: >90% (probable asthma), 50% to 90% (possible asthma), 10% to 50% (asthma unlikely), or <10% (nonasthmatic).

**Results.** Atopic, probable asthmatic children had higher geometric mean eNO (12.5 ppb) than did nonatopic probable asthmatics (3.2 ppb), the atopic nonasthmatics (3.8 ppb), and the nonatopic nonasthmatics (3.4 ppb) ( $P < .05$ ). Atopic children with positive exercise test results had higher geometric mean eNO levels than the other groups.

**Conclusions.** Elevated levels of eNO were observed in atopic asthmatic children compared with nonatopic asthmatic children. Nonatopic asthmatics had levels of eNO similar to those of nonasthmatics whether atopic or not. A positive exercise test result also showed a higher eNO level compared with those with negative exercise test results, but the important co-factor was the atopic status with the highest values being observed in atopic asthmatics.

*Reviewers' Comments.* This is an interesting observation that has tremendous potential as a noninvasive marker of inflammation in childhood asthma. The results suggest that asthma and atopy as co-factors determine the magnitude of eNO production. What is missing here is knowing more about the clinical status of the patient and what medications they may have received, to determine the relationship of airway inflammation to eNO. It is not clear why atopy makes such a big difference in the asthmatic group. Further studies are needed comparing atopic and nonatopic asthmatics with a similar degree of asthma severity.

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STANLEY P. GALANT, MD  
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### A COST-SAVING ALGORITHM FOR CHILDREN HOSPITALIZED FOR STATUS ASTHMATICUS

McDowell KM, Chatburn RL, Myers TR, O'Riordan MA, Kerckmar CM. *Arch Pediatr Adolesc Med.* 1998;152:977-984

*Purpose of the Study.* The purpose of this study was to show that the use of an "Assessment-driven protocol" for those children admitted to the hospital for status asthmaticus will result in improved health care outcomes at reduced costs.

*Study Population.* Children 1 to 18 years of age were admitted to a ward where an asthma care algorithm (ACA) was used. Control subjects were admitted to different wards and were managed according to orders of the admitting physician. There were no ACA forms or protocols followed in the control group. The study was nonrandomized. Patients were in either the control or protocol group based on bed availability at the time of admission.

*Methods.* The algorithm was established after an extensive review of the literature and reflects the state of the art for the hospitalized child with asthma. The protocol involved a multidisciplinary team of physicians, nurses, and respiratory technicians using an intense regimen of standard therapy. Assessments of the patient's condition were used to make treatment decisions and to determine the frequency of treatment. The algorithm provided specific criteria for changes in treatment, for transfer to the intensive care unit, and for discharge. All patients in the ACA were educated regarding symptom recognition, trigger avoidance, and the proper use of medications. Primary outcome measures for the study included the length of stay, hospital costs, and the need for readmission. A secondary outcome was the number of variances or changes from the protocol that occurred.

*Results.* There were 104 children in the ACA (treatment) group and 97 in the control group. The two groups were comparable except for age, race, cromolyn use, and oxygen saturation at the time of admission. The ACA group was older, had lower oxygen saturation, had more white children, and had less use of cromolyn at the time of admission. The ACA group had a significantly shorter length of stay (1.99 vs 2.73 days,  $P < .001$ ). The significance remained after adjustments for age, race, and sex. When the patients were stratified according to disease severity, there was a significant decrease in the length of stay for the mild and severe patients. In regard to medical treatment, there were fewer aerosol treatments given to the ACA group and there was no difference in the dosage of albuterol or corticosteroids between the groups. The cost-savings using the ACA was approximately \$700 per patient. Three children in the

ACA group and 1 in the control group had a relapse. There were only 8 variances from the protocol with a potential 150 opportunities for variance.

*Conclusions.* The use of an intensive, assessment-driven algorithm for pediatric status asthmaticus resulted in decreased length of hospital stay and decreased cost without any increase in morbidity. The length of stay was shortened by almost a full day. This algorithm used frequent assessments of the patients and provided specific criteria for changes in the management program. The algorithm allowed for more rapid reductions in level of support even in the most severe patients.

*Reviewer's Comments.* The results of this study are in distinct contrast to the article reviewed last year for the "Synopsis Book." The work by Kwan-Gett (*Arch Pediatr Adolesc Med.* 1997;151:684-689) showed no differences in outcome measures after 1 year of using an asthma clinical pathway. The current study addressed one of the shortcomings of the earlier work in that this study was prospective. The work of McDowell et al also described and adhered to very specific criteria for treatment advancement and for discharge. Baseline "lengths of stay" also differed between the two studies and it was pointed out that it may be very hard to decrease the average asthma length of stay to <2 days. A major point of the article is the need for frequent assessment and monitoring of the patient to initiate change as soon as possible.

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### ASTHMA IN US OLYMPIC ATHLETES WHO PARTICIPATED IN THE 1996 SUMMER GAMES

Weiler JM, Layton T, Hunt M. *J Allergy Clin Immunol.* 1998;102:722-726

*Purpose of the Study.* The purpose of the study was to determine how many US Olympic athletes who were chosen to participate in the 1996 summer games had a past history of asthma or symptoms that suggested asthma.

*Study Population.* All athletes who represented the United States in the 1996 summer Olympic Games in Atlanta were required to complete a medical history questionnaire that was designed by the US Olympics Committee. All US athletes completed and signed the questionnaire. There were 60 questions, most allowing for a yes or no response. Sixteen of the 60 questions asked were about allergic and respiratory disease and were similar to questions asked of athletes who participated in the 1984 summer Olympic games. All medical history questionnaires were sent to the US Olympic Training Center in Colorado Springs, Colorado, where the information related to allergic and respiratory disease was transcribed onto SymptomScoreCardII diary cards.

*Results.* Of the 699 athletes who completed the questionnaires, 107 or 15% had a previous diagnosis of asthma and an additional 97 recorded use of an asthma medication at some time in the past. One hundred seventeen (16.7%) reported use of an asthma medication, the diagnosis of asthma, or both which was the basis for the diagnosis of asthma. A total of 10.4% of the athletes were currently taking an asthma medication at the time they were processed in Atlanta or noted that they took asthma medications on a permanent or semipermanent basis and were considered to have active asthma. Frequency of active asthma varied from 45% of cyclists and mountain bikers to none of the divers and weight lifters. Only about 11% of the athletes who participated in the 1984 summer Olympic games had a diagnosis of asthma.

*Conclusions.* Asthma appeared to have been more prevalent in athletes who participated in the 1996 summer games than in the general population or in those who participated in the 1984 summer games.

*Reviewer's Comments.* This is a very cogent article that highlights the issue of exercise-induced asthma. It is common knowledge that many famous US Olympic athletes and professional sports participants have asthma. However, this article tries to get at the heart of the prevalence of this condition in participants in the US Olympic Games. There is a very nice discussion about the difference in the prevalence of asthma in different sports. Also there is a discussion on the medications that were being used by the athletes. It was fascinating that approximately one third of them were using inhaled corticosteroids on a regular basis, demonstrating the extent of the underlying asthma.

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### EXERCISE-INDUCED ASTHMA IN CHILDREN—A COMPARATIVE STUDY OF FREE AND TREADMILL RUNNING

Garcia DelaRubia S, Pajarone-Fernandez MJ, Sanchez-Solis M, et al. *Ann Allergy Asthma Immunol.* 1996;80: 232-237

*Objective.* Because exercise is one of the most common triggering factors for asthma in children, the purpose of this study was to determine if there are any differences in postexercise spirometry after treadmill and free running provocation tests.

*Methods.* The results of a treadmill test performed by 30 children with asthma and 30 children without asthma were compared with those of a free running test in similar environmental conditions of temperature, humidity, and exercise intensity, assessed by heart rate as well as airway status at the time of the test.

*Results.* Seventy-three percent of the patients had a positive treadmill test and 63% had a positive running test. For the spirometric parameters that were used, there were no significant differences in the percent decrease post-exercise after either of the provocation tests. For the forced expiratory volume in 1 second (FEV<sub>1</sub>), which is the most highly regarded and sensitive diagnostic parameter, the sensitivity was 53% for the treadmill test and 67% for the free-running test and the specificity was 100% for both tests. Peak flow sensitivity was 43% for treadmill and only 27% for free-running with a specificity of 94% and 97%, respectively.

*Conclusions.* Maintaining the same environmental conditions and exercise intensity, the treadmill and free-running tests can be used interchangeably for the evaluation of exercise-induced asthma.

*Reviewer's Comments.* This is a useful study that demonstrates that treadmill and free-running tests are overall equivalent in the assessment of exercise-induced asthma. This study supports the usefulness of a free-running test for screening purposes, as it appears to be as sensitive as a treadmill, provided spirometry is used as the index, and environmental conditions and exercise intensity are controlled. A free-running test offers the further advantages of familiarity, simplicity of use, and inexpensive status, although it is more difficult to control for cardiopulmonary measurements.

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### HIGH PREVALENCE OF BRONCHIAL HYPERRESPONSIVENESS AND ASTHMA IN ICE HOCKEY PLAYERS

Leuppi JD, Kuhn M, Comminot C, Reinhart WH. *Eur Respir J.* 1998;12:13-16

*Purpose of the Study.* To determine if ice hockey players are at increased risk for asthma or exercise-induced asthma because they exercise or play intensively in cold air.

*Study Population.* Twenty-six ice hockey players and 24 floor ball players were invited to participate in the study.

*Methods.* All subjects were instructed to avoid any medications, including antiasthma drugs, for at least 48 hours before the study. All players were asked to complete a 22-item questionnaire, on their personal history of allergy and smoking habits to identify subjects with a history of asthma or atopic diseases. Spirometry was obtained and bronchial hyperresponsiveness was assessed with a methacholine challenge test. An exercise challenge was done using an 8-minute standardized free-running or free-skating test. Asthma was defined as bronchial hyperresponsiveness plus positive answers to the two cardinal questions of the questionnaire—"Have you ever had asthma?" and "Was this confirmed by your doctor?"

*Results.* No significant difference in prevalence of atopy was measured by the questionnaire. No significant differences were observed in spirometry between the 2 groups. Ice hockey players had an increased bronchial hyperresponsiveness compared with the floor ball players and the general Swiss population (data derived from the SAPALDIA study), and 34.6% (9 of 26) of ice hockey players and 20.8% (5 of 24) of floor ball players showed a positive methacholine challenge test ( $P < .05$ ). Asthma, as defined by the study criteria, tended to be more prevalent in ice hockey players than in floor ball players (absolute values: 5/26 and 1/24, not significant; relative values: 19.2% and 4.1%,  $P < .05$ ). A positive exercise challenge occurred in 3/26 and 1/24, respectively.

*Conclusions.* Bronchial hyperresponsiveness, asthma, and exercise-induced asthma occur more frequently in ice hockey players than in floor ball players.

*Reviewers' Comments.* The signs and symptoms attributable to asthma are often subtle and tend to be mistaken for being "out of shape." Coaches, trainers, and the athletes themselves need to be made aware of the wide variability in symptomatology so the athlete may receive appropriate therapy which should enhance their sports participation. In some instances, asthma may not become evident under game conditions because actual playing time consists of frequent short periods of heavy exertion. On the other hand, during or after a prolonged practice session, all too often wheezing is observed. The rink or gym are excellent places to monitor lung function with a peak flow meter and take appropriate steps in the management of bronchospasm. My personal experience in exercise-induced asthma observed in athletes has made me a firm believer in the handy-dandy peak flow meter.

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### ENVIRONMENTAL ALLERGENS

#### A PLACEBO-CONTROLLED TRIAL OF A HEPA AIR CLEANER IN THE TREATMENT OF CAT ALLERGY

Wood RA, Johnson EF, Van Natta ML, Hua Chen P, Eggleston PA. *Am J Respir Crit Care Med.* 1998;158: 115-120



*Purpose of the Study.* Air cleaners and air filtration devices have enjoyed considerable popularity as a form of environmental control to remedy allergic problems. There are, however, many unanswered questions in regard to their efficacy. This study attempts to address the question of efficacy of the high-efficiency particulate arrester (HEPA) cleaners in reducing allergen levels and disease activity in the homes of cat-allergic patients who continue to live with the triggering allergen (cat).

*Study Population.* This study involved adults who had asthma and/or allergic rhinitis. They all had a history of allergic symptoms with cat exposure to the extent they required daily medications. They also had at least one cat in the home.

*Methods.* A 1-month baseline period helped to determine the minimum amount of medication needed to control asthma and/or allergic rhinitis symptoms. Daily diaries were kept regarding medication use, peak flow, nasal and chest symptom scores, and sleep difficulty. At a home visit, the number of cats and the presence of carpeting was noted. Baseline air and dust samples were collected in the patient's bedroom. Pillows and mattresses were then covered and bedding was washed weekly. Patients were instructed to keep the cat(s) out of the bedroom. A second home visit was conducted to ensure compliance with the environmental control measures. For the next 3 months, a Honeywell Enviricare HEPA filter was placed in the bedroom. This unit provided 15 air changes/hour in a 12- × 15-foot room. In the control group the filter was removed. Home visits occurred every month to sample the air and dust. A timer on the air filter units monitored compliance. Cat antigen, Fel d 1, was measured by enzyme-linked immunosorbent assay (ELISA). Other variables that were evaluated included spirometry, methacholine sensitivity, and radioallergosorbent test (RAST).

*Results.* There were 35 patients in the study; 17 served as the control group. All study patients had cat-induced rhinitis and 28 had cat-induced asthma. Thirteen study patients had one cat and 18 had two. All but 1 patient had carpeting in the bedroom. There were no significant differences between the treatment and control groups in medication use or demographics. There was no change in the level of airborne Fel d 1 in either group during the baseline period when the cat was kept out of the bedroom and covers were in place. When the HEPA filter was added, there was a modest decrease over 3 months in the level of airborne Fel d 1 in the group with the active air filter. The geometric mean level decreased from 3.0 ng/m<sup>3</sup> at baseline to 1.7 ng/m<sup>3</sup> at 3 months. There was no difference in cat allergen levels in settled dust samples at any point during the study. There was a trend toward decreased nighttime nasal symptoms in the treatment group; however, this did not reach statistical significance. No significant differences were observed in chest symptoms, peak flow measures, sleep, medication use, spirometry, methacholine challenges, or RAST results.

*Conclusions.* The HEPA filter did provide for a significant decrease in Fel d 1 levels in the air. However, those using a HEPA filter did not experience any significant difference in any measure of disease activity for both rhinitis and asthma.

*Reviewer's Comments.* It must be noted that this paper does not deal with children at all; however, it does deal with a common problem that affects children. Parents see these forms of allergy treatment advertised and may ask their pediatricians about their efficacy. There are numerous options available for environmental control, many of which have not been studied in any rigorous way. This article points out a number of key concepts using this form of environmental control measure. Airborne levels do de-

crease, but the new level achieved was not associated with significant differences in disease control. The study emphasizes the importance of avoidance and the lack of efficacy of the HEPA units in this model of allergy.

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#### THE MELBOURNE HOUSE DUST MITE STUDY: LONG-TERM EFFICACY OF HOUSE DUST MITE REDUCTION STRATEGIES

Sporik R, Hill D, Thompson P, et al. *J Allergy Clin Immunol.* 1998;101:451-456

*Purpose of the Study.* The investigators evaluated the effectiveness of dust mite control measures in bedrooms of mite-allergic children with asthma.

*Study Population.* Eighty-five children with moderate asthma requiring chronic inhaled medication were selected. All were skin test-positive to the dust mite *Dermatophagoides pteronyssinus*.

*Methods.* Samples of house dust were obtained on 10 visits over a 16-month period. Locations sampled included child's and parents' bedroom floors and child's mattress or mattress encasement. Any existing encasements were removed on visit 1. During visit 3, investigators encased all mattresses and began interventional measures, which were repeated at each subsequent visit. Encasements were wiped down, and carpets and floors were washed: uncarpeted floors with "anti-mite" shampoo, and carpets with either "anti-mite" or placebo shampoo. Subjects washed bed linens weekly, and were told not to vacuum 1 week before each visit. Samples with <10 g dust were not analyzed.

*Results.* Although not insignificant, dust mite antigen from uncarpeted floors remained low throughout the study. Neither shampoo diminished levels of Der p 1 in carpeting; levels were similar in untreated parents' bedrooms, and were >10 µg Der p 1/g dust, the proposed threshold for provoking symptoms in sensitized individuals. The use of encasements substantially lowered concentrations of Der p 1 recovered from mattresses after one visit (28.4 to 4.2 µg/g). Of all samples from mattress encasements, 96% had <10 µg Der p 1/g dust. In fact, many samples from uncarpeted floors and mattress encasements had insufficient dust to examine.

*Conclusions.* Mattress encasements and absence of carpeting were associated with low concentrations of dust mite antigen.

*Reviewers' Comments.* Investigators only measured one dust mite associated protein. Nonetheless, the levels found after implementing these measures were generally below the threshold for provoking asthma, although not low enough to prevent allergic sensitization. Controlling indoor humidity may reduce levels further. The authors in this study did not correct for air conditioning by measuring indoor humidity; this may explain the lack of correlation between mite allergen levels and seasonal variation in humidity. Parents must implement effective measures and not waste time and money on air cleaners, excessive vacuuming, and housecleaning which provide little, if any, benefit in reducing dust mite antigen exposure. Strict examination of data from controlled studies help us discern fact from fiction and help us guide parents around often a wealth of misinformation presented by well-meaning friends and family or, in some cases, those with proprietary interests.

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## ASSOCIATION BETWEEN DER P 1 CONCENTRATION AND PEAK EXPIRATORY FLOW RATE IN CHILDREN WITH WHEEZE: A LONGITUDINAL ANALYSIS

Jalaludin B, Xuan W, Mahmic A, Peat J, Tovey E, Leeder S. *J Allergy Clin Immunol.* 1998;102:382–386

**Purpose of the Study.** To investigate the association between *Der p 1* allergen in bedding and lung function in children with wheezing.

**Study Population.** Thirty children with history of wheezing, age 8 to 12 years, followed for 12 months in Sydney, Australia.

**Methods.** The levels of house dust mite (HDM) were measured at the beginning of the study in March 1994, and at 6, 8, 10, and 12 months into the study. Fifteen children with the lowest (mean, 5.5  $\mu\text{g/g}$ ) and 15 children with the highest (mean, 148.8  $\mu\text{g/g}$ ) *Der p 1* levels in their bedding were included in the study. The children were skin-tested for HDM and underwent bronchial histamine challenge. The children kept an asthma diary twice a day, after waking up in the morning and in the evening before going to bed. The asthma diary included information about peak expiratory flow rate (PEFR), asthma symptoms, and medications used.

**Results.** There were 16 boys and 14 girls with a mean age of 9.6 years. Seventeen children (57%) had a positive skin test to HDM, 15 children (50%) had airway hyperreactivity on histamine challenge, and 25 children (83%) had received a diagnosis of asthma from a doctor. There was no difference in the minimum PEFR between the 2 groups at baseline. Minimum PEFR improved over the study period in both groups. At baseline, compared with children without HDM sensitivity, children with HDM sensitivity had a greater proportion of days with morning wheeze, use of salbutamol in the morning, and use of inhaled steroids. *Der p 1* concentrations were lowest in December but not significantly different from other times. For children with HDM atopy there was a moderate negative correlation between the log *Der p 1* level and the minimum PEFR on each of the 5 occasions (correlation coefficient range:  $-0.35$ – $-0.61$ ). The correlation coefficients were statistically significant except for March and December. The association between PEFR and the log *Der p 1* concentration was significant ( $\beta$ -coefficient =  $-14.17$ ,  $P = .024$ ) in children with HDM atopy but not in children without HDM atopy.

**Conclusions.** This study supports the hypothesis that HDM allergens have an adverse effect on the lung function of children with wheezing.

**Reviewers' Comments.** This study has demonstrated that natural changes in HDM levels can lead to reductions in PEFR in children who are allergic to HDM. These findings highlight the importance of maintaining low HDM levels throughout the year in the home environment of children sensitized to HDM. Unfortunately, this study did not analyze other potential confounders such as animal allergens, pollens, molds, viral infections, and air pollution.

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## RELATIONSHIP OF INDOOR ALLERGEN EXPOSURE TO SKIN TEST SENSITIVITY IN INNER-CITY CHILDREN WITH ASTHMA

Eggleston PA, Rosenstreich D, Lynn H, et al. *J Allergy Clin Immunol.* 1998;102:563–569

**Purpose of the Study.** To determine whether there was a dose response between exposure to dust mite, cockroach and cat and sensitization to these allergens in inner-city children.

**Study Population.** Five hundred children participating in the National Cooperative Inner City Asthma Study.

**Methods.** Children were prick skin-tested with a Multi Test device. Samples of home dust were collected from the floor and furniture in the kitchen, bedroom and living room, and the levels of major allergens for dust mite (*Der p 1*, *Der f 1*), cockroach (*Bla g 1*) and cat (*Fel d 1*) were measured by an enzyme-linked immunosorbent assay (ELISA) method.

**Results.** Levels of each allergen correlated significantly between rooms in individual homes. Mite and cat allergen levels were frequently below the detection limit of the assay. Cockroach allergen (*Bla g 1*) concentrations in the bedroom were related to the prevalence of positive skin test responses to cockroach extract among the children, with an odds ratio for sensitization of 1.45 (1.11–1.92). Positive skin test responses to cockroach allergen were seen in 15% of children whose bedroom allergen levels were below the level of detection, compared with a rate of 32% in bedrooms with *Bla g 1* levels of 1.2 U/g and 40 to 44% among those in bedrooms with levels of 4 U/g or greater. The relationship between exposure and positive skin test responses was stronger among atopic children with a greater number of positive skin responses.

**Conclusions.** Despite widespread exposure to household allergens, the strongest relationship between exposure and sensitization was observed in the bedroom. The dose response between exposure to cockroach allergen and sensitization suggested that exposure to low doses, 2 U/g or less, was a risk factor and that the risk plateaus above 4 U/g. Atopy modified the relationship of exposure to sensitization.

**Reviewers' Comments.** It is important to understand the relationship between environmental allergen exposure and the risk of atopic individuals becoming sensitized to that allergen. This knowledge is essential for development of environmental strategies aimed at reducing the amount of allergen in the environment. This study showed that higher levels of exposure clearly increase the risk of sensitization to cockroach allergen. The study also showed that atopic children are at higher risk of becoming sensitized at low levels of exposure to allergen. The strongest relationship of sensitization to cockroach allergen is in the bedroom, although the highest *Bla g 1* levels are found in the kitchen. This has important implications for the strategies of effective allergen control and indicates that allergen removal in the bedroom may be particularly important.

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## B-ADRENERGIC AGONIST THERAPY

### ADDITION OF SALMETEROL VERSUS DOUBLING THE DOSE OF BECLOMETHASONE IN CHILDREN WITH ASTHMA

Verberne A, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF. *Am J Respir Crit Care Med.* 1998;158:213–219

**Purpose of the Study.** In studies involving adults, the addition of salmeterol to moderate doses of inhaled corticosteroids (ICS) led to better control of asthma symptoms, increased peak flow, and decreased diurnal variation in peak flow values. This study sought to compare the effects

of 1 year of treatment with a moderate dose of an inhaled steroid, the same dose of the steroid with added salmeterol, and a doubling dose of an inhaled steroid in children with moderate asthma.

**Study Population.** There were 177 children enrolled in the study. The children were 6 to 16 years old and all had moderate to severe asthma. The initial forced expiratory volume in 1 second (FEV<sub>1</sub>) was between 55% to 90% of predicted and increased at least 10% after the use of inhaled albuterol. All participants also had a positive methacholine challenge, stable asthma, and were on 200 to 800 µg of an ICS for at least 3 months before study entry.

**Methods.** The study was double-blinded and randomized. After a 6-week run-in period, there were 54 weeks of active treatment and a follow-up observation 2 weeks later. All patients were given beclomethasone dipropionate (BDP) 200 µg twice a day. Patients were randomized to receive either salmeterol 50 mcg, BDP 200 µg, or a placebo twice a day. At each clinic visit the children had their height and weight checked. Pulmonary functions were monitored at each visit. Compliance was checked by counting the number of blisters remaining on the medication cards. Diaries were kept with records of symptoms, rescue medication use, and peak flow values.

**Results.** The baseline characteristics of all three treatment groups were similar with regard to sex, age, height, duration of asthma, allergic status, ICS use, and initial FEV<sub>1</sub>. Compliance was slightly better in the BDP + salmeterol group—94% of doses were taken. At the end of the 54-week treatment period, there was no significant difference found between the treatment groups for the FEV<sub>1</sub>. There was still no difference found when the results were analyzed according to presenting dose of ICS, duration of use, baseline FEV<sub>1</sub>, methacholine sensitivity, and symptom scores. When airway responsiveness to methacholine was evaluated, it was found that all treatment groups had improved; however, the type of treatment made no difference. All treatment groups had improved peak flow values, but there was a more significant change observed in the BDP + salmeterol group during the first few months of the study. There was no difference between the treatment groups in day to day peak flow variability. Symptom control was better in all but there was no difference between the treatment groups. Growth was significantly slower in the BDP-800 µg/day group at 3.6 cm over the study period (BDP 400 group-4.5 cm and BDP + salmeterol group-5.1 cm).

**Conclusions.** The addition of salmeterol to BDP or the doubling of the BDP dose in children with moderate asthma resulted in no difference in airway caliber, airway responsiveness, symptom scores, or exacerbation rates of asthma when compared with BDP 200 µg bid alone in children over the year of the study. The authors also conclude that rigorous monitoring and frequent visits help with medication compliance and subsequent improvement in disease activity. They also warn of the need to balance the antiinflammatory effect of higher doses of ICS against the effects on growth in children.

**Reviewer's Comments.** The adult literature would have us believe that salmeterol may offer significant improvement in children who have moderate asthma. This study has shown that salmeterol does not offer any significant degree of improvement and more importantly it also shows that increased ICS doses also do not provide any significant differences either. Could it be that in this type of asthma clinical outcomes are optimized not so much by the doses and mixtures of therapies, but more by monitoring,

frequent evaluations, and making sure that the children adhere to the treatment program?

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## EFFICACY OF SALMETEROL XINAFOATE POWDER IN CHILDREN WITH CHRONIC PERSISTENT ASTHMA

Weinstein SF, Pearlman DS, Bronsky EA, et al. *Ann Allergy Asthma Immunol.* 1998;81:51-58

**Purpose.** Salmeterol xinafoate is a long-acting, highly selective β<sub>2</sub>-adrenergic agonist providing bronchodilation for a median duration of 12 hours and protecting against a variety of bronchoconstrictory stimuli for a similar time interval. Salmeterol is available as an aerosol and a dry powder inhaler approved down to the age of 4 years. Because younger children have difficulty in properly using a metered dose inhaler, a powder inhaler, which is breath-activated, would be an advantage particularly in this population. The purpose of this study was to evaluate the efficacy and safety of salmeterol powder versus placebo in children 4 to 11 years of age with chronic, persistent asthma.

**Population.** Male and female patients ages 4 to 11 years with asthma as defined by American Thoracic Society (ATS) criteria who required daily maintenance therapy for at least 6 months were eligible. In addition entry criteria included either peak expiratory flow (PEF) (in younger children) or forced expiratory volume in 1 second (FEV<sub>1</sub>) between 50% to 80% of predicted and 15% reversibility with albuterol. Treatment with antiinflammatory agents (ie, disodium cromolyn, nedocromil, or inhaled corticosteroids) was permitted throughout the study if the medication had been taken for at least 3 months before the study.

**Methods.** This was a multicenter, double-blind, placebo-controlled study. During a 1- to 2-week run-in period the patients received their usual medications and a placebo powder twice a day and rescue albuterol as needed, while keeping a diary of signs and symptoms, PEF, and medication use. Patients qualified for randomization on the basis of albuterol need, symptoms, and daily compliance. At randomization, the patient received either salmeterol powder in a nonpressurized breath activated delivery device or placebo. Patients were evaluated by signs and symptoms of asthma, PEF, and albuterol use by diary card as well as 12-hour pulmonary function tests after study medication in the research center over a period of 12 weeks. The primary efficacy variable was PEF or FEV<sub>1</sub> measured over 12 hours. Safety variables included vital signs, electrocardiogram, 12-hour Holter monitoring, and incidence of patient withdrawal from the study.

**Results.** Two hundred seven patients, 102 on salmeterol and 105 on placebo, were randomized. On day 1 and week 12, both the PEF and FEV<sub>1</sub> were significantly ( $P < .01$ ) higher on drug than placebo over the 12-hour post-dosing period. In addition, overall reduction in rescue albuterol and mean asthma score were also significantly greater ( $P < .01$ ) in the salmeterol group compared with placebo. The frequency of adverse events was similar in both groups.

**Conclusions.** Salmeterol powder (50 µg bid) is effective and safe in producing bronchodilation and reducing signs and symptoms in children with chronic persistent asthma. Over a 12-week period there was no evidence of tachyphylaxis.

**Reviewers' Comments.** This is a useful study since delivery of inhaled medication, particularly in very young



children, can be problematic. Current modalities in this population include metered dose inhalers, which are difficult to coordinate and require a spacer, and nebulizers, which are expensive and time-consuming for chronic usage. Compliance with the dry powder inhaler mechanism in this study appears to be very good with the children easily learning the technique. In addition, the study found efficacy and no evidence of tachyphylaxis for bronchodilation over a 12-week period, which is similar to findings with older children and adults. The issue of tachyphylaxis to the protection from bronchoconstrictory stimuli, particularly exercise, was not addressed here, but continues to be an important issue. The major question with salmeterol, however, is not the delivery system, but where it best fits in the current guidelines for asthma therapy. Its optimal use appears to be not as monotherapy, but rather as an addition to antiinflammatory therapy when the latter has not provided optimal therapy.

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### EFFECTS OF TREATMENT WITH FORMOTEROL ON BRONCHOPROTECTION AGAINST METHACHOLINE

Lipworth B, Tan S, Devlin M, Aiken T, Baker R, Hendrick D. *Am J Med.* 1998;104:431–438

*Purpose of the Study.* In addition to their bronchodilatory effects,  $\beta_2$ -agonists protect against bronchoconstriction, such as that caused by methacholine challenge. However, tachyphylaxis to this beneficial effect develops after chronic use of  $\beta_2$ -agonists. They studied whether the frequency or dose of treatment with a long-acting  $\beta_2$ -agonist (formoterol) effects the degree of bronchoprotection afforded against methacholine challenge and to compare this with the effects of a short-acting  $\beta_2$ -agonist (terbutaline).

*Study Population and Methods.* In a randomized, parallel group, double-blind study at two centers, patients with stable asthma of mild to moderate severity who were treated with inhaled corticosteroids were treated with formoterol 6  $\mu\text{g}$  twice daily, 24  $\mu\text{g}$  twice daily, 12  $\mu\text{g}$  once daily; terbutaline 500  $\mu\text{g}$  four times daily; or placebo. Treatments were given by dry powder inhaler for a period of 2 weeks. Of the 72 patients who were enrolled, 67 completed the study. Methacholine challenge was performed to calculate the provocative dose that caused a 20% decrease in forced expiratory volume in 1 second at baseline (unprotected) after an initial 1-week run-in without  $\beta_2$ -agonists, 1 hour after the first dose of study treatment, and again 1 hour after 7 and 14 days of study treatment.

*Results.* Each of the four active treatments exhibited significant tachyphylaxis ( $P < .05$ ) to protection against methacholine challenge when comparing first/last dose (as geometric mean protection ratio versus baseline): formoterol 24  $\mu\text{g}$  twice daily (9.6-fold/1.6-fold), 12  $\mu\text{g}$  once daily (7.1-fold/2.2-fold), 6  $\mu\text{g}$  twice daily (6.2-fold/2.3-fold), and terbutaline 500  $\mu\text{g}$  four times daily (2.9-fold/2.0-fold). There were no significant differences among treatments after 2 weeks in bronchoprotection against methacholine challenge. For all formoterol regimens, the bronchodilator response 1-hour after inhalation was maintained over the 2-week treatment period. Diurnal control of morning and evening peak flow was significantly better with formoterol 24  $\mu\text{g}$  twice daily than with terbutaline.

*Conclusions.* Tachyphylaxis to bronchoprotection against methacholine challenge develops after 2 weeks of therapy with formoterol, a long-acting  $\beta_2$ -agonist, at all

three dosage regimens that were tested. In contrast, the bronchodilator effects of formoterol were maintained during the 2 weeks of treatment.

*Reviewer's Comments.* I always have a tough time knowing if there is clinical importance to these kinds of studies, especially regarding long-term usage. Based on clinical observation, it would not appear (at least to me) that patients using these medications develop greater bronchial reactivity over time. Nevertheless, other long-acting inhaled bronchodilators (eg, salmeterol) can show this kind of tachyphylaxis to bronchoprotection against methacholine and exercise, while maintaining their bronchodilator effects. This article was accompanied by a related editorial (Abishenganden *J. Am J Med.* 1998;104:494–497).

ALLEN D. ADINOFF, MD  
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### RAPID REVERSIBILITY OF THE ALLERGEN-INDUCED PULMONARY LATE-PHASE REACTION BY AN INTRAVENOUS $\beta_2$ -AGONIST

Peebles R Jr, Permutt S, Togias A. *J Appl Physiol.* 1998;84:1500–1505

*Purpose of the Study.* To determine the degree to which  $\beta_2$ -adrenergic receptor agonists can reverse the allergen-induced late reduction in lung function.

*Study Population.* Seven allergic subjects with mild asthma.

*Methods.* In phase I of the study, terbutaline was administered as an initial bolus followed by continuous intravenous infusion over 45 minutes to determine the maximal attainable bronchodilation at baseline. In phase II, the subjects underwent an allergen inhalation (ragweed) challenge until forced expiratory volume in 1 second (FEV<sub>1</sub>) declined by at least 20%. Seven hours later, subjects were randomized and crossed over to receive terbutaline or a vehicle intravenous infusion identical to the phase I infusion protocol. Forced expiratory spirometry was performed at baseline and every hour after allergen-inhalation challenge. Spirometry was performed before and every 5 minutes through terbutaline (phase II and I) and placebo infusion (phase II) as well.

*Results.* At baseline, there was no significant difference in FEV<sub>1</sub> or forced vital capacity (FVC) between phase I and phase II. In phase I, terbutaline infusion led to significant improvement in FEV<sub>1</sub> compared with preinfusion value ( $P < .03$ ). After ragweed bronchoprovocation FEV<sub>1</sub> decreased <85% at any single timepoint between hour 4 and 7 postallergen inhalation. On the day placebo was infused 7 hours after allergen inhalation, FEV<sub>1</sub> values did not change significantly compared with the preinfusion value ( $P > .2$ ). In contrast, on the day terbutaline was infused, FEV<sub>1</sub> was significantly higher than preinfusion ( $P < .02$ ). The overall pattern of FVC was the same as for FEV<sub>1</sub>. The kinetic curves for bronchodilator response to terbutaline infusion in phase I and in phase II were superimposable, indicating that the terbutaline induced bronchodilation was driven by the same pharmacologic mechanism.

*Conclusions.* The late reduction in lung function caused by allergen inhalation challenge in asthmatic subjects is rapidly and almost completely reversible by an intravenous  $\beta_2$ -adrenoreceptor agonist.

*Reviewers' Comments.* Most previous studies have demonstrated that inhaled  $\beta_2$ -adrenoreceptor agonists are only partially effective in reversing allergen-inhaled late phase airway obstruction. Interestingly, the ability to reverse this type of airway obstruction appears to be signifi-

icantly enhanced using an intravenous route for drug administration. These observations challenge the current dogma that the airway obstruction observed 4 to 8 hours after allergen challenge is mostly related to airway edema, inflammation, and mucus secretion as opposed to bronchial smooth muscle spasm. A third arm of the study in which equivalent doses of  $\beta$ -agonist were given by aerosol would have been helpful in determining what role drug delivery may have contributed to the observed results.

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### THE USE OF ALBUTEROL IN HOSPITALIZED INFANTS WITH BRONCHIOLITIS

Dobson JV, Stephens-Groff SM, McMahon SR, Stemmler MM, Brallier SL, Bay C. *Pediatrics*. 1998;101:361-368

**Objective.** To determine whether the utilization of albuterol by nebulization improves the physiologic or clinical outcome in hospitalized infants with moderate bronchiolitis.

**Design.** A prospective, double-blind, placebo controlled, randomized clinical trial performed from December 1995, to March 1996. The population included 52 patients <24 months of age with a diagnosis of moderately severe, acute viral bronchiolitis, who were randomized to receive nebulized albuterol or saline placebo for 72 hours. There was a standardized protocol with primary outcome measures including improvement in oxygen saturation, as well as the time required to achieve discharge criteria, including appropriate oxygen saturation, reduction in accessory muscle use, and wheezing. An additional secondary outcome was the actual length of hospital stay. Adverse outcomes were also compared between treatment groups.

**Results.** There was no significant difference in oxygen saturation between the albuterol- and placebo-treated patients at any time during the hospitalization, nor was there a difference in time to reach discharge criteria, length of hospital stay, or frequency of adverse outcomes.

**Conclusions.** Nebulized albuterol therapy does not appear to improve the recovery or reduce the severity of acute, moderate bronchiolitis in hospitalized infants.

**Reviewer's Comments.** These results are consistent with previous studies, however, no attempt was made to separate children on the basis of family history of atopy or immunoglobulin E (IgE), so as to determine if there was a selective effect of albuterol in those with a higher probability of reactive airway disease or asthma. Furthermore, no attempt was made to add supplemental therapy, ie, steroids, to determine if the combination might enhance the response to albuterol, particularly in the subset of patients who may have a family history of atopy or a high IgE. Nonetheless, the reviewer's conclusion stands that the routine use of albuterol as a means for reducing hospital days or the severity of illness in bronchiolitis is not supported by this study.

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### COMPARISON OF TWO DOSAGE REGIMENS OF ALBUTEROL IN ACUTE ASTHMA

McFadden ER Jr, Strauss L, Hejal R, Galan G, Dixon L. *Am J Med*. 1998;105:12-17

**Purpose of the Study.** The standard therapy for acute episodes of asthma in the United States consists of three 2.5-mg doses of aerosolized albuterol given every 20 minutes. Whether this approach represents optimum therapy has never been tested.

**Study Population and Methods.** This study used a prospective, sequential design in which the effects of two doses of 5.0 mg of aerosolized albuterol administered during 40 minutes (high-dose) were contrasted with the standard dose (three 2.5-mg doses) in adults with acute attacks of asthma. Improvements in pulmonary function, clinical resolution of the asthma attacks, and admission rates were used as primary endpoints. Both regimens were part of an overall care plan that involved objective, pretested decision algorithms.

**Results.** In an emergency department, 160 patients who presented with acute exacerbations of asthma received either standard ( $n = 80$ ) or high-dose ( $n = 80$ ) albuterol treatment. There were no significant baseline differences in gender, racial composition, clinical signs and symptoms, medication use, or peak expiratory flow (PEF) between the groups. Both treatment schedules were effective, but the high-dose regimen increased lung function more rapidly and to a greater extent than standard-dose therapy. It also resulted in lower charges to third-party payers. More subjects attained the discharge criteria quicker and left the emergency department with PEFs closer to normal. Fewer patients in the high-dose group were admitted, but this trend did not quite reach statistical significance.

**Conclusions.** Two 5.0-mg treatments of aerosolized albuterol at a 40-minute interval provide effective therapy for acute exacerbations of asthma. This combination of dose and frequency promotes maximum bronchodilation, increases efficiency, and reduces the risks of undertreatment.

**Reviewer's Comments.** McFadden still seems to find a new twist in the acute asthma treatment scenario. This group, in general, is very aggressive in the treatment of acute asthma, and this study would extend that trend. The "high-dose" group did complain more of side effects. Could this be the reason they left the emergency department quicker than the low-dose group?

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### CONTINUOUS INTRAVENOUS TERBUTALINE FOR PEDIATRIC STATUS ASTHMATICUS

Stephanopoulos DE, Monge R, Schell KH, et al. *Crit Care Med*. 1998;26:1744-1748

**Purpose.** To determine the effects of intravenous terbutaline in the treatment of status asthmaticus.

**Population.** Eighteen children (2 to 17 years) with status asthmaticus failing therapy with inhaled  $\beta$ -agonist, intravenous corticosteroid, and ipratropium bromide.

**Results.** Patients were treated with aerosolized ipratropium bromide and intravenous corticosteroid concurrently with intravenous terbutaline infusion. The dose of terbutaline ranged from 0.05 to 10.0  $\mu\text{g}/\text{kg}/\text{minute}$ . Patients receiving doses of 0.4 to 2.0  $\mu\text{g}/\text{kg}/\text{minute}$  required intravenous epinephrine to counteract a drop in diastolic blood pressure (mean, 27 mm Hg; range 10-50). When the terbutaline dose was  $>2 \mu\text{g}/\text{kg}/\text{min}$ , there was no longer need for epinephrine. There were no significant arrhythmias noted but 3 patients who were also receiving epinephrine had transient ST segment depression. The creatinine phosphokinase-myocardial band (CPK-MB) levels

elevated but not in relation to the terbutaline dose. Ten of the 18 patients required mechanical ventilation. There were no deaths in the group.

*Reviewer's Comments.* This study was conducted without a loading dose of terbutaline as reported in other papers. The patients demonstrated safety at these dosing ranges but >50% of the patients required mechanical ventilation.

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## STEROID THERAPY

### DOSE-RELATED EFFICACY OF BUDESONIDE ADMINISTERED VIA A DRY POWDER INHALER IN THE TREATMENT OF CHILDREN WITH MODERATE TO SEVERE PERSISTENT ASTHMA

Shapiro G. *J Pediatr.* 1998;132:976-982

*Purpose of the Study.* To evaluate the efficacy and safety of dry powder inhaled budesonide in the treatment of children with moderate to severe persistent asthma.

*Study Population.* Four hundred four children (6 to 18 years old) with forced expiratory volume in 1 second (FEV<sub>1</sub>) between 50% and 80%, using at least two asthma medications and with a minimum 6-month history of inhaled glucocorticosteroid-dependent asthma were enrolled in a randomized, double-blind, placebo-controlled, parallel group, multicenter study.

*Methods.* The patients received either 100, 200, 400  $\mu$ g of budesonide or placebo twice daily for 12 weeks. Pulmonary function tests were performed in the early morning of each clinic visit that were scheduled at 2 week intervals during the study. Peak expiratory flow (PEF) was measured by the patients in the morning. The patients recorded daytime and nighttime asthma symptom scores. Adverse effects were also recorded. Early morning basal cortisol levels and stimulated plasma cortisol levels were measured before randomization and at the end of the study period. The patients received physical examinations, electrocardiograms, and chest-radiographs at baseline and at the end of the study period.

*Results.* Three hundred five of the 404 patients completed the double-blind period. The dropout rates were 49% for the placebo-treated group and 15% to 18% for the active treatment groups. Morning PEF decreased by 3.9% in the placebo-treated group, whereas there were mean increases of 4.4%, 5.6%, and 6.7% in the groups receiving 100, 200, 400  $\mu$ g of budesonide twice daily, respectively ( $P < .001$ ). FEV<sub>1</sub> had a mean decrease of 4.6% in the placebo-treated group. There was a dose-dependent improvement ( $P = .015$ ) in FEV<sub>1</sub> with mean increases of 3.1%, 7.7%, and 7.3% in the groups treated with 100, 200, 400  $\mu$ g of budesonide twice daily, respectively. Daytime and nighttime symptom scores improved ( $P = .001$ ) in the active treatment groups. There was a 26% increase in inhaled bronchodilator use in the placebo-treated group and a decrease of 24%, 30%, and 40% in the groups receiving 100, 200, 400  $\mu$ g of budesonide twice daily, respectively ( $P = .001$ ). A dose-dependent relationship was also noted ( $P = .036$ ). There was no significant change from baseline in cortisol levels. No significant adverse effects were noted between the four groups.

*Conclusions.* Dry powder inhaled budesonide provided a dose-dependent improvement in pulmonary function and clinical symptoms and was well-tolerated in children with moderate to severe persistent asthma.

*Reviewers' Comments.* The dry powder inhaler is an efficient and well-tolerated system for medication delivery that is less technique dependent than conventional metered dose inhalers. This study does not compare the efficacy of budesonide with other inhaled glucocorticosteroids or maintenance antiinflammatory medications. Also, no suppression of the hypothalamic-pituitary-adrenal axis was noted during the 12-week study period.

### EFFICACY AND SAFETY OF BUDESONIDE INHALATION SUSPENSION (PULMICORT RESPULES) IN YOUNG CHILDREN WITH INHALED STEROID-DEPENDENT, PERSISTENT ASTHMA

Shapiro G, Mendelson L, Kraemer M, et al. *J Allergy Clin Immunol.* 1998;102:789-796

*Purpose of the Study.* The purpose of the study was to evaluate the efficacy and safety of three different twice-daily doses of budesonide inhalation suspension in inhaled steroid-dependent asthmatic children.

*Study Population.* There was a placebo group of 44 children, average age 80 months; the three dosing schedules for the budesonide included 0.25 mg bid, 47 children with an average age of 78 months; 0.50 mg bid, 42 children, average age 82 months; and 1.0 mg bid, 45 children, average age 81 months. The study was performed in 17 centers in the United States and represented administration of either placebo or specified dose of budesonide via jet nebulizer. The patients were required to have a forced expiratory volume in 1 second (FEV<sub>1</sub>) with an at least 50% of predicted normal value and a reversibility of at least 15% after a standard dose of inhaled bronchodilator. The study design was a randomized, double-blind, placebo-controlled parallel group study. The study lasted for 14 weeks.

*Results.* Baseline demographics, symptom scores, and pulmonary function data were similar across the four treatment groups. All doses of budesonide inhalation suspension were superior to placebo in improving nighttime and daytime asthma symptom scores, reducing the use of breakthrough medication, and improving morning peak flow. The number of dropouts because of worsening asthma was also significantly fewer in the budesonide groups. There were no differences between doses of budesonide. Adverse events and basal and adrenocorticotrophic hormone stimulated cortisol responses were not different between the budesonide and placebo groups.

*Conclusions.* Budesonide inhalation suspension at any of the three doses was an effective and safe treatment for young children with inhaled steroid-dependent persistent asthma.

*Reviewer's Comments.* This article allows for the discussion of several controversial points. One is the efficacy of inhaled corticosteroids as delivered by jet nebulizer versus by metered-dose inhaler with a device such as an aero-chamber with mask. Although comparative trials are still lacking, there is literature to suggest that inhaled steroids, both budesonide and fluticasone, can be delivered in a clinically effective manner by using a metered-dose inhaler with an aero-chamber and mask. Issue two is the ongoing discussion regarding the relative efficacy of different concentrations of inhaled corticosteroids. This study had a very interesting finding that the positive outcomes did not appear to be significantly different between groups treated with budesonide regardless of the concentration. This too echoes previous papers that suggested that often the in-



crease in dose of an inhaled corticosteroid does not result in a marked improvement in function. This becomes extremely important when one considers the potential side effects of these medications. The third interesting facet of this study is the fact that there appeared to be no change in baseline adrenal function, or the ability to respond to stimulation. This is encouraging in this ongoing discussion of the relative safety of these compounds. The study, performed for only 14 weeks, does not allow for any conclusions concerning the potential inhibition of growth at any of the tested concentration. This represents a very well conducted study that adds to the literature on how these various medications can be delivered, the clinical significance of different concentrations, and their relative safety.

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### THE EFFECT OF FLUTICASONE PROPIONATE ON FUNCTIONAL STATUS AND SLEEP IN CHILDREN WITH ASTHMA AND ON THE QUALITY OF LIFE OF THEIR PARENTS

Mahajan P, Pearlman D, Okamoto L. *J Allergy Clin Immunol.* 1998;102:19–23

*Purpose of the Study.* The purpose of the study was to assess the effect of treatment with fluticasone propionate (FP) on functional status and sleep disturbances in children and to evaluate possible changes in the quality of life of the parents of these children.

*Study Population.* There was a placebo group of 106 children, average age 8.5 years; a group treated with 50  $\mu\text{g}$  of FP bid numbering 111, average age 8.5 years; and a third group treated with 100  $\mu\text{g}$  of FP, 108 patients, mean age of 8.2 years.

*Study Methods.* Questionnaires were completed by parents and caregivers at baseline and at weeks 24 and 52, including the functional status II-R (FS II), the sleep scale for children (SLP-C), and the quality of life of parents of asthmatic children (QOL-PAC). Change from baseline to weeks 24 and 52 within each treatment group was analyzed by using paired *t* tests and differences between treatment groups were analyzed using analysis of covariance.

*Results.* Mean FSII and SLP-C scores improved significantly over baseline values with either of the two FP dosing schedules. They were significantly better than those in the placebo group. The FSII scores at week 52 and SLP-C scores at weeks 24 and 52 decreased significantly in the placebo group. QOL-PAC results revealed that scores in the burden scale were significantly improved in both FP groups at 24 and 52 weeks. Subjective norms in social scales improved significantly only in the 100  $\mu\text{g}$  FP group at week 52.

*Conclusions.* The authors claim that the results of this study demonstrate that either dose of FP was associated with significant improvements in functional status and decreased sleep disturbances in children with asthma. In addition, treatment with children with FP was associated with a decreased burden on the parents of these children with asthma. The authors state that the patients selected had mild to moderate daily asthma and that in general because of the patients increased quality of life, the quality of life of the caregivers also improved.

*Reviewer's Comments.* The findings of this study are not particularly surprising. One would expect that with meaningful doses of inhaled corticosteroids, regardless of which product, that a patient with mild to moderate persistent asthma would have decreased symptoms and improved quality of life. It is also not surprising that the perception of

the caregiver of their quality of life would be markedly improved. The fact that the patients felt less tired with less interference of sleep and therefore less interference of the parents' sleep would all be expected in any patient and their family in which better asthma control has been achieved. Perhaps the most significant aspect of this article is the relatively low dose of inhaled corticosteroids that were used. It has become abundantly clear that the different inhaled corticosteroid products have different potencies. Reviewing the National Institutes of Health (NIH) guidelines produced in 1997 of the common products available in the United States, FP appears to be the most potent. Preliminary long-term studies would suggest that with a dose of 50  $\mu\text{g}$  bid over a period of 6 months there is no inhibition of growth and that there is only minimal and probably not significant inhibition of growth at 100  $\mu\text{g}$  bid. Furthermore, preliminary Canadian data suggests that this relatively long-acting inhaled corticosteroid could be used on a qd basis. This would make this medication convenient and less expensive, complementing the obvious effectiveness demonstrated in this and other studies. This is not to suggest that this product is necessarily better than the other inhaled corticosteroids but that it may be more convenient because of its potency and duration of action.

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### EFFECTIVENESS AND SAFETY OF INHALED CORTICOSTEROIDS IN CONTROLLING ACUTE ASTHMA ATTACKS IN CHILDREN WHO WERE TREATED IN THE EMERGENCY DEPARTMENT: A CONTROLLED COMPARATIVE STUDY WITH ORAL PREDNISOLONE

Volovitz B, Bentur L, Finkelstein Y, et al. *J Allergy Clin Immunol.* 1998;102:605–609

*Purpose of the Study.* The purpose of the study was to prospectively investigate the efficacy and safety of inhaled corticosteroids in controlling moderately severe acute asthma attacks in children.

*Study Population.* The study population included children 6 to 16 years of age with diagnosed asthma who were treated in the emergency department with a moderately severe acute asthma attack, defined as a peak expiratory flow rate (PEFR) of 35 to 75% of predictive values and a pulmonary index score of 8 to 13 with a maximum score of 15.

*Methods.* Children were treated in the emergency department with moderately severe asthma attacks with inhaled terbutaline. Children were then allocated to receive a dose of either 1600  $\mu\text{g}$  of budesonide by turbobalmer or 2 mg/kg of prednisolone. The pulmonary index score and PEFR were measured hourly for the first 4 hours. After discharge the children were treated with the same initial dose divided four times daily followed by a 25% reduction in dose every second day for 1 week. The parents recorded asthma symptoms and the frequency of the use of  $\beta$ -agonists on a daily diary card. Serum cortisol concentrations were measured at the end of weeks 1 and 3.

*Results.* Twenty-two children, 11 in each group, with similar baseline parameters completed the study. There was a similar improvement in pulmonary index score and PEFR in the two groups. Children treated with budesonide showed an earlier clinical response than those given prednisolone. Those treated with prednisolone also showed a decrease in serum cortisol concentration.

*Conclusions.* Children with moderately severe asthma attacks who were treated in the emergency room with

inhaled budesonide starting at 1600  $\mu\text{g}$  appeared to be as effective as oral prednisolone without suppressing serum cortisol concentrations.

*Reviewer's Comments.* This is an extremely interesting study that echoes observations made in Canada concerning the use of high-dose inhaled corticosteroids for acute exacerbations of asthma. This question really becomes a practical one with the introduction high-dose inhaled corticosteroids whose onset of action is relatively quick; namely, budesonide and fluticasone. In patients who have a significant decrease in pulmonary function but are not demonstrating life-threatening deterioration, it may be a reasonable approach to use high-dose inhaled corticosteroids, especially the faster acting agents. Even if there is an effect on the HPA axis with the high-dose inhaled corticosteroids, it is very unlikely that one would see as much adrenal suppression as one would with 60 mg of prednisone a day. It will be interesting to see if the observations made in Canada and in this study are confirmed in studies with larger numbers of patients.

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### DIFFICULT-TO-CONTROL ASTHMA: CLINICAL CHARACTERISTICS OF STEROID-INSENSITIVE ASTHMA

Chan MTS, Leung DYM, Szeffler SJ, Spahn JD. *J Allergy Clin Immunol.* 1998;101:594–601

*Purpose of the Study.* To better define patterns of response to oral glucocorticoids (GC) in adolescent asthmatics, to evaluate their clinical characteristics, and to determine the prevalence of steroid-insensitive asthma in this population.

*Study Population.* A total of 164 adolescent patients, admitted to National Jewish Medical and Research Center between July 1993 and February 1997 for difficult-to-control asthma.

*Methods.* This was a retrospective study of adolescents with asthma. Data collected included medical history, pulmonary function testing (PFT), methacholine challenge results, AM cortisol levels, serum immunoglobulin E (IgE), total eosinophil counts (TEC), serum eosinophilic cationic protein (ECP), and soluble IL-2 receptor (IL-2R). Patients were first divided into two groups: those who required an oral GC burst (40 mg/day prednisone for at least 7 days) during their hospitalization and those who did not require an oral GC burst. Patients were further divided based on their response to GC therapy. Steroid-sensitive (SS) patients were defined as those whose AM forced expiratory volume in 1 second ( $\text{FEV}_1$ ) improved  $>15\%$  after GC therapy. Steroid-insensitive (SI) patients were defined as those with  $<15\%$  improvement in their AM  $\text{FEV}_1$  after GC therapy. The SI group was further evaluated based on PFT patterns, with patients demonstrating a "chaotic" ( $>30\%$  variability in lung function) versus "nonchaotic" ( $<30\%$  variability) pattern.

*Results.* The mean age of patients was 14 years. Most (90%) were receiving high-dose inhaled GC, and  $>50\%$  were receiving maintenance oral GC. Of the 164 patients reviewed, 87 (53%) required an oral GC burst during hospitalization. Based on their response to GC therapy, 21 (24%) patients were defined as SI and 61 (76%) patients as SS. Patients with SI asthma required oral GC therapy at a younger age, required larger oral maintenance GC dosing, and were more likely to be African-American, compared to those with SS asthma. The SI asthmatics were defined by their PFT pattern as "chaotic" ( $n = 12$ ) and "nonchaotic"

( $n = 9$ ), with the "nonchaotic" group being distinguished by later diagnosis of asthma, treatment with oral GC at a later age, and African-American ethnicity. No difference in inflammatory markers (eg, ECP, TEC, IL-2R levels) were detected among any of the groups compared.

*Conclusions.* The authors conclude that SI asthma is common (24%) in their referral population. The overrepresentation of African-Americans in the SI group indicates the need for further study of the prevalence of SI asthma and the impact of early asthma intervention on this form of asthma.

*Reviewer's Comments.* This is the first study to describe patterns of response to oral GC in adolescent asthmatics. Although a retrospective analysis from a tertiary referral center, the numbers of patients involved and the data collection performed in this population certainly provides a framework to begin to address the difficult problem of SI asthma. Of significance, 24% of patients were found to be SI. This prevalence is higher than expected, possibly attributable to the referral population base, yet analysis of these patients allows the authors to provide clinical characteristics of SI asthma that have previously been undefined. The increased incidence African-Americans in the SI group and the finding of two spirometric profiles of SI patients ("chaotic" and "nonchaotic") indicate the need for further study of this important group of SI patients. The current trends in asthma morbidity and mortality further support the analysis of this subset of asthmatics.

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### PERCEPTION OF THE ROLE AND POTENTIAL SIDE EFFECTS OF INHALED CORTICOSTEROIDS AMONG ASTHMATIC PATIENTS

Boutlet LP. *Chest.* 1998;113:587–592

*Purpose of the Study.* Misunderstanding of the role of asthma medication and fear of untoward side effects may reduce compliance to therapy. The objective of this study was to survey asthmatic patients to determine their perception of the role and potential side effects of inhaled corticosteroids (ICS) and what effect these perceptions had on compliance.

*Study Population.* A national telephone survey was conducted on 603 asthmatic patients over 16 years of age.

*Methods.* Interviews were conducted from mid-to-late September 1995, in Canada. A pretested questionnaire was developed and continuous monitoring of each interviewer in the study was performed. The questionnaire included questions about various aspects of corticosteroid therapy, particularly relating to perceived modes of action and side effects of those agents. A profile was assessed in regards to years diagnosed with asthma, medication usage and dosing, a physician managing the asthma, severity of disease, and frequency of emergency room (ER) visits.

*Results.* Thirty-nine percent had used regular or intermittent inhaled corticosteroids in the past 12 months. A large proportion of asthmatic patients did not understand the role of their medications and had misconceptions and fears in regard to ICS, therefore reducing their willingness to use them. Forty-three percent believed that ICS opened airways and relieved constriction and only 22% mentioned that they reduced inflammation or swelling of airways. Fifty-three percent of patients were very or somewhat concerned about using ICS with 59% expressing fear of side effects. Thirty-nine percent knew that side effects were minor if used as prescribed. The most common fears were in regard to body image, bone density, and reduction in

efficacy over time. Two thirds of patients had not discussed their concerns with their physicians. Thirty-one percent indicated they were not aware that ICS existed for asthma treatment. Finally, a large number of the patients were not adequately controlled according to recent asthma consensus guidelines.

**Conclusions.** These observations stress the importance for those involved in asthma care to question their patients about their understanding of the role of asthma medications along with fears, misconceptions, what is considered adequate asthma control, and to provide adequate education.

**Reviewers' Comments.** This is a nice survey of a large population in regard to fears and misconceptions of ICS in the treatment of asthma. Adherence to maintenance therapy is vital in control of asthma, but if patients are not appropriately educated, compliance is likely to be a greater problem. As physicians, we must take time to inform our parents of the importance of adequate control of disease and discuss issues of maintenance medications, including their mode of action, proper usage, and potential side effects. With proper education and counseling, hopefully compliance will be optimized to reduce the negative consequences of the disease.

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#### SHORT-TERM GROWTH IN ASTHMATIC CHILDREN USING FLUTICASONE PROPIONATE

Visser M, Van Aalderen W, Elliott B, Odink R, Brand P. *Chest*. 1998;113:584–586

**Purpose of Study.** Inhaled corticosteroids may reduce short-term growth velocity in children. The purpose of this study was to compare lower leg growth velocity by knemometry in asthmatic children receiving inhaled fluticasone propionate (FP), 100 µg twice daily.

**Study Population.** Twenty-one asthmatic children (13 boys and 8 girls, aged 6–10 years, prepubertal) from a university hospital outpatient clinic in pediatric pulmonology.

**Methods.** The baseline trial was a 6-week period with patients using 100 µg of inhaled FP bid with a dry-powder inhaler. There was then a 2-week washout period during which no inhaled corticosteroids or other anti-inflammatory medications were used. Before the study period, all patients were using inhaled corticosteroids (100–400 µg/day). Treatment was not blinded and treatment order was fixed. During the trial and washout period, patients were seen every 2 weeks. Inhaler technique and compliance were checked. Knemometry was performed at a fixed time of day.

**Results.** There was no significant differences between lower leg growth velocities in each of the four 2-week periods ( $P = .33$ ).

**Conclusions.** No significant suppression of lower leg growth velocity was found in prepubertal asthmatic children using FP, 100 µg by dry powder inhaler bid for 6 weeks.

**Reviewers' Comments.** This is yet another study assessing the effects of inhaled steroids on growth. However, this study only observed very short term growth and doesn't answer the more important question of long-term growth suppression. Because knemometry does not necessarily predict long-term growth further study will be needed.

WANDA PHIPATANAKUL, MD  
ROBERT A. WOOD, MD  
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#### NEUROPSYCHOLOGICAL AND BEHAVIORAL CHANGES IN ASTHMATIC CHILDREN TREATED WITH BECLOMETHASONE DIPROPIONATE VERSUS THEOPHYLLINE

Bender BG, Ikle DN, DuHamel T, Tinkleman D. *Pediatrics*. 1998;101:355–360

**Objective.** The objective of study was to determine the psychological side effects of theophylline and beclomethasone in asthmatic children.

**Design.** Multicenter, randomized, double-blind, parallel-group study in which 102 asthmatic children were assigned to one of two treatments, beclomethasone three times daily, or theophylline twice daily. At baseline, 1 month, and 1 year, parents completed standardized behavioral questionnaires while children received psychometric testing of attention, concentration, memory, learning, and problem-solving.

**Results.** There was no consistent difference in treatment effects between the two drugs. There were two significant treatment-by-period results that were discordant; one suggested slightly improved attention in the theophylline group, while the other indicated slight advantage in attention scores in the beclomethasone group. There were numerous significant period results indicating that behavior and cognitive test performance improved over a 1-year period regardless of the treatment.

**Conclusions.** Neither theophylline or beclomethasone should be removed from consideration because of concern for significant psychological side effects. Although there is a possibility that a subset of asthmatic children, particularly preschoolers, may be at risk for medication induced changes, there are no controlled studies to prove this. Parental misconceptions of medication side effects often occur because of temporary effects that occur at the initiation of treatment or because they erroneously associate the effects of the chronic illness, asthma, with the medications.

**Reviewer's Comments.** This study was conducted in children 6 to 17 years of age and thus cannot speak to the effects in preschoolers; however, it is refreshing to note that the behavioral side effects of theophylline and beclomethasone were *not* significant and that behavioral side effects were more likely to be associated with the asthma. These results would suggest that treatment of asthma resolved the apparent behavioral effects of asthma, rather than creating behavioral side effects. This is further support for effective treatment of asthma, from a behavioral standpoint, and verifies the safety of theophylline and beclomethasone as medications for asthma therapy with regard to learning and behavior.

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Waterbury, CT

#### GROWTH IN ASTHMATIC CHILDREN TREATED WITH FLUTICASONE PROPIONATE

David BA, Edwin AB, Craig FL, Robert AN, David GT, Mark LV, Peter K, and the Fluticasone Propionate Asthma Study Group. *J Pediatr*. 1998;132:472–477

**Purpose of the Study.** To determine whether inhaled fluticasone propionate (FP) has long-term effects on growth in children with persistent asthma.

**Study Population.** Three hundred twenty-five prepubescent children 4 to 11 years of age with persistent asthma and in the recent past normal growth rates.

**Methods.** The patients were divided into three groups; 106 patients received placebo, 111 patients received FP 50



$\mu\text{g}$  bid, and 108 patients received FP 100  $\mu\text{g}$  bid via a diskhaler. Of 325 patients, 57 showed signs of puberty during the study (19 from the placebo group, 26 from the FP 50  $\mu\text{g}$  group, 12 from the FP 100  $\mu\text{g}$  group) and were excluded from the study. Of the remaining 268 patients, 23% of the patients withdrew from the placebo group and 2% and 4% withdrew from the FP 50  $\mu\text{g}$  and 100  $\mu\text{g}$ , respectively, because of lack of efficacy. The patients were evaluated initially for a 2-week run-in period to confirm their asthma stability, obtain baseline data, and assess the compliance with the diskhaler. The patients were then followed after the first, second, and fourth weeks of treatment and then every 4 weeks throughout the 52-week treatment period. Growth was measured monthly. Radiographic determination of bone age of the left hand and wrist was performed at baseline and at 24 and 52 weeks and the compliance was assessed by counting number of package blisters used.

**Results.** There were no statistically significant differences in mean height, growth velocity, or mean skeletal age between any of the treatment groups at any time. Over a period of 1 year, mean height ( $\pm$  SE) increased 6.15  $\pm$  0.17 cm in the placebo group, 5.94  $\pm$  0.16 cm in the FP 50  $\mu\text{g}$  group, and 5.73  $\pm$  0.13 cm in the FP 100  $\mu\text{g}$  group ( $P = .308$ , overall). At the end of treatment corresponding mean changes in growth velocity from baseline were  $-0.11 \pm 0.15$ ,  $-0.40 \pm 0.20$ ,  $-0.46 \pm 0.15$  cm/year, respectively. These changes in height were comparable to normal growth rates for patients of a similar age.

**Conclusions.** FP in doses of 50  $\mu\text{g}$  bid and 100  $\mu\text{g}$  bid administered for 1 year via a diskhaler did not have any significant effect on growth velocity or bone age.

**Reviewers' Comments.** Although prolonged treatment with inhaled corticosteroids is generally well-tolerated, some concern remains about the potential for an adverse influence on growth in children. Resolving this issue is complicated by the potential for asthma to delay growth and influence bone age, especially if the disease is not well-controlled. This study provides useful data on the subject. This is a prospective, randomized, double-blind study with proper accounting for the patients entering the study. The target enrollment size of 90 patients per treatment group was chosen to provide 80% power of detecting a 1.0 cm per year difference in height velocity. Given the satisfactory safety profile, as noted by the authors, using up to 200  $\mu\text{g}$  of FP per day for 1 year, and the low dropout rate in the treated groups, primary care physicians may well be more inclined to institute such medications in the comprehensive treatment of an asthmatic child.

KANWALJEET K. CHOPRA, MD  
THAD H. JOOS, MD  
Detroit, MI

#### DURATION OF GROWTH SUPPRESSIVE EFFECTS OF REGULAR INHALED CORTICOSTEROIDS

Doull IJ, Campbell MJ, Holgate ST. *Arch Dis Child*. 1998; 78:172-173

**Purpose of the Study.** To investigate the growth suppressive effects of inhaled corticosteroids in children with asthma.

**Study Population.** Fifty children receiving beclomethasone 200  $\mu\text{g}$  bid.

**Methods.** Height was measured by a single observer every 4 weeks for 30 weeks. Growth rate on treatment was compared with pretreatment growth rate.

**Results.** During the first 6 weeks of therapy with inhaled corticosteroids the children's average growth slowed

from 0.140 mm/week to 0.073 mm/week ( $P = .011$ ). However, by weeks 25 to 30, growth velocity had recovered to baseline, 0.120 mm/week ( $P = .607$ ), despite continued therapy.

**Conclusions.** The growth suppressive effect of inhaled corticosteroids may be relatively short-lived, with the most pronounced effect during the first 6 weeks.

**Reviewer's Comments.** Inhaled corticosteroids are an important part of our treatment of asthma in children. Yet we continue to be presented with evidence that they may have some real but subtle effects on growth. We should minimize the dose of these agents and use alternatives, such as nedocromil, when effective. However, the benefit of inhaled steroids to maintain good asthma control still far outweighs the risk to growth in the vast majority of patients. This study is actually reassuring, suggesting that the potential impact of inhaled corticosteroids on growth may lessen over time, even with their continued use.

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#### BONE MINERAL DENSITY IN CHILDREN WITH ASTHMA RECEIVING LONG-TERM TREATMENT WITH INHALED BUDESONIDE

Agertoft L, Pedersen S. *Am J Respir Crit Care Med*. 1998; 157:178-198

**Purpose of the Study.** To assess the effects of long-term treatment with inhaled budesonide (BUD) on total body bone mineral density (BMD), total body bone mineral capacity (BMC), total body calcium (TBC), and body composition in children with asthma.

**Study Population.** One hundred fifty-seven asthmatic children treated with inhaled BUD at a mean daily dose of 504  $\mu\text{g}$  (range, 189-1322  $\mu\text{g}$ ) for 3 to 6 years (mean, 4.5 years).

**Methods.** Dual energy x-ray absorptiometry (DEXA Scan) was performed and measurements compared with those of 111 age-matched children also suffering from asthma but who had never been treated with exogenous corticosteroids for more than 14 days (control group).

**Results.** There were no statistically significant differences between the two groups in BMD (BUD = 0.915 g/cm<sup>2</sup>, controls = 0.917 g/cm<sup>2</sup>), BMC (BUD = 1378 g, controls = 1367 g), TBC (BUD = 524 g, controls = 519 g), or body composition (lean body weight = 27 600 g [BUD] and 26 923 g [control], % body fat = 20.1% [BUD] and 20.3% [control]). There was no correlation between any of these parameters and duration of treatment, accumulated or current dose of budesonide.

**Conclusions.** Three to 6 years of treatment with inhaled BUD at an average daily dose of 504  $\mu\text{g}$  has no adverse effect on total BMD, total BMC, TBC, or body composition in children with chronic asthma.

**Reviewer's Comments.** This study is reassuring in providing much needed information on relatively safe doses of an inhaled steroid, in this case budesonide. The investigators conducted this study under open-label conditions in a nonrandomized manner. They took several steps to monitor adherence to the treatment program and compared their results with a suitable control group. Similar information is needed for the other inhaled steroids and their respective delivery devices, especially those recommended in the treatment of asthmatic children.

STANLEY J. SZEFLER, MD  
Denver, CO

## COLLAGEN METABOLISM AND GROWTH IN PREPUBERTAL CHILDREN WITH ASTHMA TREATED WITH INHALED STEROIDS

Crowley S, Trivedi P, Risteli L, Risteli J, Hindmarsh PC, Brook CG. *J Pediatr*. 1998;132:409–413

*Purpose of the Study.* To investigate growth and markers of collagen and bone metabolism in prepubertal children with asthma who were treated with inhaled or oral corticosteroids.

*Study Population.* Fifty-six prepubertal children (mean age: 8.32 years; SD: 2.06 years) with stable asthma were divided into four groups for the investigation: inhaled budesonide ( $n = 19$ ), inhaled beclomethasone dipropionate ( $n = 20$ ), inhaled steroid and prednisolone ( $n = 4$ ), and nonsteroid treatment ( $n = 13$ ).

*Methods.* The investigators measured growth velocity over the 12-month study period and, on a single occasion, determined markers of collagen types I and II synthesis (PINP: aminoterminal propeptides of type I procollagen, PICP: carboxyterminal propeptide of type I procollagen, and PIIINP: animoterminal propeptide of type III procollagen); collagen type I degradation (ICTP: carboxyterminal telopeptide of type I collagen); and bone metabolism (bone-specific alkaline phosphatase and osteocalcin).

*Results.* Children treated with inhaled steroids had reduced collagen synthesis (PINP, PIIINP) compared with the control subjects ( $P = .038$ ;  $P = .045$ ); however, PICP was increased ( $P = .05$ ). Carboxyterminal telopeptide of type I collagen was reduced in patients treated with inhaled steroids ( $P < .0005$ ) as compared with nonsteroid-treated patients. Serum osteocalcin, but not bone-specific alkaline phosphatase, was significantly reduced in children treated with inhaled steroids ( $P < .02$ ). Finally, significant correlation was observed between PIIINP and ICTP and growth velocity.

*Conclusions.* Collagen turnover is reduced in children with asthma receiving long-term inhaled steroid treatment. Markers of collagen synthesis (eg, PINP, PIIINP) may provide a more accurate reflection of growth disturbance than osteocalcin and bone-specific alkaline phosphatase.

*Reviewer's Comments.* Unless you have been residing on a remote desert island, it would be almost impossible to have missed the US Food and Drug Administration's decision in the fall of 1998 requiring manufacturers of inhaled and intranasal corticosteroids to include in product labels a notice that these drugs may reduce the rate of growth in some children. This timely article by Crowley et al contributes useful data to the longstanding debate about the potential for inhaled corticosteroids to reduce growth rate in some children with asthma. With similar lung function in all study groups, the investigators attributed the impaired growth velocity to side effects from corticosteroids. Hopefully, regular (every 3 to 6 months) and reliable growth velocity measurements, as well as markers of collagen synthesis, will be documented in the long-term natural history investigations currently examining the role of inhaled corticosteroids in the management of children with asthma, even those with mild persistent disease. Although corticosteroids are the most effective antiinflammatory medication for asthma, we must seriously consider the benefit/risk ratio of these medications, especially when multiple routes of administration (ie, inhaled, intranasal, and oral) may exist in the same patient.

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## EFFECTS OF BUDESONIDE AND FLUTICASONE ON 24-HOUR PLASMA CORTISOL. A DOSE-RESPONSE STUDY

Donnelly R, Williams KM, Baker AB, Badcock C-A, Day RO, Seale JP. *Am J Respir Crit Care Med*. 1997;156:1746–1751

*Purpose of the Study.* To characterize dose-response relationships for the effects of fluticasone propionate (FP) and budesonide (BUD) on diurnal cortisol production, and thereby obtain a quantitative estimate of the dose-potency ratio (FP:BUD) for adrenal suppression.

*Study Population.* Twenty-eight normal male volunteers.

*Methods.* The effects of 5 days of treatment with BUD (800, 1600, and 3200  $\mu\text{g}/\text{day}$  via pMD1 [pressurized metered dose inhaler]) and FP (750, 1500, and 2000  $\mu\text{g}/\text{day}$  via pMD1) on integrated area under the curve of 24-hour plasma cortisol profiles ( $\text{AUC}_{24\text{h}}$ ) were compared in a randomized, placebo-controlled, seven-period crossover study. Plasma cortisol concentrations were measured during the last 24 hours of each treatment period.

*Results.* Each treatment (except BUD 800  $\mu\text{g}$ ) produced significant dose-dependent reductions in  $\text{AUC}_{24\text{h}}$  compared with placebo; eg, percent reductions in  $\text{AUC}_{24\text{h}}$  were 23%, 41%, and 69% for the three doses of BUD, and, correspondingly, 46%, 85%, and 93% for the three doses of FP. Model-derived measurements of dose potency ratios showed that FP was 2.9 times more potent than BUD in reducing AUC (95% CI, 2.5–3.5).

*Conclusions.* On a  $\mu\text{g}$ -for- $\mu\text{g}$  dose basis, the systemic effects of a given dose of FP on  $\text{AUC}_{24\text{h}}$  cortisol were equivalent to the effects of three times the dose of BUD.

*Reviewer's Comments.* This is a very nice study that attempts to develop an objective assessment of the dose-response relationship of two commonly used inhaled steroids on a measure of systemic effect. The one limitation in the study is the use of a pMD1 delivery device for BUD. This method of administration is not available in the United States. The Turbuhaler device is the one approved here. At least one study shows that the systemic effect of BUD Turbuhaler is approximately twice that of a pMD1. Therefore, it appears that the systemic effects of FP pMD1 and BUD Turbuhaler are approximately the same. Similar studies are needed to characterize all of the available inhaled steroids in their respective delivery devices. In addition, a similar system is need to characterize efficacy.

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## POSTERIOR SUBCAPSULAR CATARACTS, BRUISES AND HOARSENESS IN CHILDREN WITH ASTHMA RECEIVING LONG-TERM TREATMENT WITH INHALED BUDESONIDE

Agertoft L, Larsen FE, Pedersen S. *Eur Respir J*. 1998;12:130–135

*Purpose of the Study.* To assess the effect of long-term treatment with inhaled budesonide on the occurrence of posterior subcapsular cataracts (PSC), bruises, and hoarseness in children with asthma.

*Study Population.* One hundred fifty-seven asthmatic children, aged 5 to 16 years, on long-term inhaled budesonide and a control group of 111 age-matched asthmatic children who had never received exogenous steroids.

*Methods.* Both groups were assessed every 6 months. Slit lamp examination was performed on all the patients by

the same ophthalmologist. Opacities were classified as PSC or non-PSC, which are not related to corticosteroid therapy. Both groups were examined for bruising on one forearm and one lower leg on the dominant side and the number and size were recorded. Families were asked to rate bruising tendency on scale of 1 to 10. The level of the activity was recorded on scale of 1 to 10. Also families were asked if their child had experienced hoarseness or change of voice. All of the above data recorded with no knowledge of the treatment received by the patients. Patients were excluded from the study if they received systemic steroids >2 weeks for both groups and from the control group if they received inhaled steroids for >2 weeks.

**Results.** The two groups were comparable with respect to age, height and weight. The mean duration of asthma was longer and forced expiratory volume in 1 second (FEV<sub>1</sub>) was higher in the budesonide group. The mean compliance with budesonide was assessed to be 78%. The mean total accumulated dose of budesonide was 813.1 mg (249–2800), and the mean treatment duration was 4.4 years, giving a mean average daily dose of 504 µg (189–1322 µg). One patient in the budesonide group had PSC in one eye that was diagnosed 2 years before initiation of budesonide treatment. This fact was not known to the examining ophthalmologist. No other incidents of PSC were found in both groups. Three children were diagnosed with non-PSC opacities: two children in the budesonide group had congenital unilateral cataracts and 1 child in the control group had a congenital bilateral cataract. Fisher's exact test did not find an increased risk in the budesonide group ( $p = .46$ ). There were no significant differences in the number of bruises, area on arm and leg covered with bruises, or and in the tendency to bruise between the two groups ( $p = .70, 0.97, 0.98$ , respectively). There was no significant difference between the two groups in the occurrence of hoarseness or any voice changes (BUD = 20%, control = 21%).

**Conclusions.** Three to 6 years of treatment of children with inhaled budesonide at an average daily dose of 504 µg is not associated with increased occurrence of PSC, bruises, tendency to bruise, hoarseness, or noticeable voice changes in children with chronic asthma.

**Reviewers' Comments.** This is a well-designed and well-controlled study with a good sample size in both the budesonide and the control group. The excellent safety profile of budesonide is clearly demonstrated. This study will help to alleviate the anxiety of parents and health care providers regarding the use of inhaled corticosteroids in the management of childhood asthma. Most of the anxieties have arisen from extrapolating side effects of systemically administered corticosteroids, or steroid use in adult populations to the inhaled forms. And the question is how many more of these studies are needed to convince people that inhaled corticosteroids are effective and safe in the treatment of childhood asthma?

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## LEUKOTRIENE ANTAGONIST THERAPY

### MONTELUKAST, A ONCE-DAILY LEUKOTRIENE RECEPTOR ANTAGONIST, IN THE TREATMENT OF CHRONIC ASTHMA: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND TRIAL

Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB. *Arch Intern Med.* 1998;158:1213–1220

**Purpose of the Study.** To determine the clinical effect of oral montelukast sodium, a leukotriene receptor antagonist, in asthmatic patients aged 15 years or more.

**Study Population.** Fifty clinical centers randomly allocated 681 patients with chronic, stable asthma to receive placebo or montelukast after demonstrating a forced expiratory volume in 1 second (FEV<sub>1</sub>) 50% to 85% of the predicted value, at least a 15% improvement FEV<sub>1</sub> (absolute value) after inhaled β-agonist administration, a minimal predefined level of daytime asthma symptoms, and inhaled β-agonist use. Twenty-three percent of the patients used concomitant inhaled corticosteroids.

**Methods.** Randomized, multicenter, double-blind, placebo-controlled, parallel-group study. A 2-week, single-blind, placebo run-in period was followed by a 12-week, double-blind treatment period (montelukast sodium, 10 mg, or matching placebo, once daily at bedtime) and a 3-week, double-blind, washout period. FEV<sub>1</sub> and daytime asthma symptoms were the primary endpoint measures.

**Results.** Montelukast improved airway obstruction (FEV<sub>1</sub>, morning and evening peak expiratory flow rate) and patient-reported endpoints (daytime asthma symptoms, "as-needed" β-agonist use, nocturnal awakenings) ( $P < .001$  compared with placebo). Montelukast provided near-maximal effect in these endpoints within the first day of treatment. Tolerance and rebound worsening of asthma did not occur. Montelukast improved outcome endpoints, including asthma exacerbations, asthma control days ( $P < .001$  compared with placebo), and decreased peripheral blood eosinophil counts ( $P < .001$  compared with placebo). The incidence of adverse events and discontinuations from therapy were similar in the montelukast and placebo groups.

**Conclusions.** Montelukast, compared with placebo, significantly improved asthma control during a 12-week treatment period. Montelukast was generally well-tolerated, with an adverse event profile comparable with that of placebo.

**Reviewer's Comments.** This study appears to be a variation on a theme of previous studies with similar results. Montelukast (Singulair) and zafirlukast (Accolate) seem to be very useful medications for at least mild persistent asthma, particularly in patients who have grown weary of inhaled preparations. Montelukast has advantages over zafirlukast of once daily dosing without regard to food intake, and a pediatric approved chewable preparation. Montelukast has been shown helpful in exercise-induced bronchospasm (Kemp, *J Allergy Clin Immunol.* 1997;99:S321), aspirin-intolerant asthma (Kuna, *Am J Respir Crit Care Med.* 1997;155:A975), and in reducing the dose of inhaled corticosteroids (Leff, *Am J Respir Crit Care Med.* 1997;155:A976). Recent concerns regarding Churg-Strauss vasculitis may dampen some of the enthusiasm.

### MONTELUKAST, A LEUKOTRIENE-RECEPTOR ANTAGONIST, FOR THE TREATMENT OF MILD ASTHMA AND EXERCISE-INDUCED BRONCHOCONSTRICTION

Leff JA, Busse WW, Pearlman D, et al. *N Engl J Med.* 1998;339:147–152

**Purpose.** To evaluate the effect of 12 weeks of therapy with montelukast 10 mg (Singulair) on exercise-induced asthma.



**Population.** One hundred ten patients (15–45 years) were randomly assigned to montelukast 10 mg or placebo once daily for 12 weeks followed by a 2-week washout period.

**Study Design.** Exercise challenges were performed at baseline and weeks 4, 8, 12, and 14. The data was analyzed with regard to the persistence of change in forced expiratory volume in 1 second (FEV<sub>1</sub>) over baseline for 60 minutes (area under the curve) and how quickly the FEV<sub>1</sub> returned to within 5% of baseline. Methacholine challenges were performed at baseline and 12 weeks.

**Results.** The average exercise-induced drop in FEV<sub>1</sub> before randomization was 36 ± 12% for both groups with resting FEV<sub>1</sub> 83 ± 11%. The treatment group demonstrated a 47% reduction in area under the curve after exercise. The FEV<sub>1</sub> dropped 22% in the treatment group compared with 32% drop in placebo group. The mean time required to return FEV<sub>1</sub> to within 5% of the baseline was 44.3 minutes for the treatment group compared with 60.6 minutes in the placebo group. Approximately 25% of the montelukast patients had no protection with exercise challenge. There were no significant side effects and an equal number of patients from each group withdrew from the study.

**Reviewer's Comments.** Although exercise asthma was attenuated, the group mean change in FEV<sub>1</sub> (22%) in the treated group was still consistent with a positive exercise challenge. Also, 25% of the patients had no protective effect in the exercise challenge. The efficacy of this class of drugs in mild to moderate asthma continues to be defined. Careful assessment of response as measured by symptom control and peak flow monitoring is necessary to assure the desired response has occurred.

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## A RANDOMIZED CONTROLLED TRIAL COMPARING ZILEUTON WITH THEOPHYLLINE IN MODERATE ASTHMA

Schwartz HJ, Petty T, Dube LM, Swanson LJ, Lancaster JF. *Arch Intern Med.* 1998;158:141–148

**Purpose of the Study.** Zileuton, a leukotriene pathway inhibitor, was compared with slowly absorbed theophylline in a randomized, double-blind study of patients with chronic asthma. The primary efficacy measure was improvement in forced expiratory volume in 1 second (FEV<sub>1</sub>).

**Study Population.** Eligibility criteria included FEV<sub>1</sub> of 40% to 80% of predicted, documented reversibility of airway disease, and age 18 to 60 years.

**Methods.** Initially, the theophylline dosage was titrated to achieve trough concentrations of 8 to 15 µg/mL. After washout and 1-week placebo lead-in, patients were randomly assigned to 13 weeks of the appropriate theophylline dose or zileuton, 400 or 600 mg 4 times daily. The FEV<sub>1</sub> was measured before the morning dose at 2-week intervals and serially after the dose on days 36 and 92. Patients kept daily diaries of asthma symptoms, β-agonist usage, and peak expiratory flow rate; on days 36 and 92, they completed quality-of-life questionnaires.

**Results.** Of 471 eligible patients at 38 centers, 377 were randomly assigned to the study; 313 completed the study. On first-dose administration, all groups showed 11% to 13% improvement in FEV<sub>1</sub> within 30 minutes. Patients who received zileuton, 400 mg, had significantly greater improvement at several points than did theophylline-treated patients. The range of long-term maximum improvement in FEV<sub>1</sub> in the groups was 30% to 34% (*P* = .40 for zileuton 600 mg; *P* = .90 for zileuton 400 mg vs theophylline).

Initially, the theophylline group improved significantly more in symptom scores, β-agonist usage, and peak expiratory flow rate, but at maximal effect there was no significant difference. All groups showed significant improvement in quality of life. No overall differences were observed between the zileuton dosage groups. Adverse events were comparable in all groups.

**Conclusions.** Zileuton appears as effective and safe as theophylline in patients with chronic asthma.

**Reviewer's Comments.** The use of zileuton in treating asthma presents a few practical problems, including the need (at least initially) of four times daily dosing, and monitoring of liver enzymes. Other leukotriene modifiers currently available have much more convenient dosing schedules and better safety profiles. It remains to be seen where zileuton will fit in the many choices available for treating asthma.

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## A DRUG INTERACTION BETWEEN ZAFIRLUKAST AND THEOPHYLLINE

Katial RK, Stelzle RC, Bonner MW, Marino M, Cantilena LR, Smith LJ. *Arch Intern Med.* 1998;158:1713–1715

**Purpose of the Study.** The apparent low adverse effect profile of the new drug zafirlukast has made it an attractive choice in the treatment of asthma. This study describes the first case of a potentially serious drug-drug interaction between zafirlukast and theophylline.

**Study Population, Methods, and Results.** A 15-year-old white girl with asthma had been taking theophylline (Slobid, Rhone-Poulenc Rorer Pharmaceuticals Inc, Collegeville, PA) (300 mg twice daily), with drug levels of approximately 61 micromol/L (11.0 µg/mL) for several years. Recently, her serum theophylline levels had increased to the toxic range (133.2 µL/L [24 µg/mL]) shortly after the addition of zafirlukast (Accolate, Zeneca Pharmaceuticals, Wilmington, Del) to her regimen. Attempts were made to stop and then restart the theophylline therapy at progressively lower doses; however, with each attempt, the patient's reaction to the drug became more toxic, with serum theophylline levels ranging between 99.9 and 149.9 µg/L (18 and 27 µg/mL). So this potential drug-drug interaction could be investigated, the patient stopped taking both drugs for 1 week. Then, she again started taking theophylline (75 mg twice daily), and over 2 days reached a steady state serum theophylline level of 12.8 to 14.4 µL/L (2.3–2.6 µg/mL). On the third day, zafirlukast (20 mg twice daily) was reintroduced to the regimen, and the theophylline therapy was continued. By the fifth day, a dramatic sevenfold increase was seen in the serum theophylline level (101.6 micromol/L [18.3 µg/mL]). The areas under the curve for theophylline alone and theophylline with zafirlukast were 29.3 and 197 (mg × h)/L, respectively.

**Conclusions.** One explanation for the noted increase in the theophylline level is that metabolism occurs mainly by cytochrome P450 (CYP 1A2), an enzyme that is known to be inhibited with high concentrations of zafirlukast. Although the current metabolism of the two drugs in combination is poorly understood, the potential for serious interactions seems to exist in the rapidly growing population of persons with asthma, for whom they may be prescribed. The noted increase in the theophylline level after zafirlukast administration is in contrast to the original reports by the manufacturer. Therefore, we recommend that physicians evaluate serum theophylline levels closely when prescribing the two drugs in combination.

*Reviewer's Comments.* The initial report I read suggested that theophylline *decreased* serum concentrations of zafirlukast (*Medical Letter*. 1996;38:111) Zafirlukast also inhibits CYP3A4, which catalyzed the metabolism of corticosteroids. Zileuton is also metabolized by cytochrome P450, and can markedly increase serum concentrations of theophylline. Montelukast has fewer drug interactions than either zafirlukast or zileuton. In vitro studies indicate that montelukast does not inhibit CYP-450 enzymes. Clinical studies indicate that the drug does not interact with theophylline (Malmstrom, *Am J Ther*. 1998;5:189) or prednisone.

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## OTHER THERAPIES

### RANDOMIZED CONTROLLED TRIAL OF IPRATROPIUM BROMIDE AND FREQUENT LOW DOSES OF SALBUTAMOL IN THE MANAGEMENT OF MILD AND MODERATE ACUTE PEDIATRIC ASTHMA

Ducharme FM, Davis GM. *J Pediatr*. 1998;133:479–485

*Purpose of the Study.* Previous studies have demonstrated the benefit of inhaled ipratropium as an adjunct to inhaled  $\beta_2$  bronchodilators in the treatment of acute severe asthma in children. The purpose of this study was to observe children with mild to moderate exacerbations of asthma, comparing the efficacy, safety, and possible synergy of inhaled salbutamol with or without inhaled ipratropium.

*Study Population.* Two hundred ninety-eight events in 275 patients were analyzed. The children were 3 to 17 years of age and presented to a single emergency room facility with mild to moderate exacerbations of asthma over a 2½-year period of time. To qualify they also had to be able to reproducibly perform forced oscillometry (a noneffort dependent, quiet breathing/tidal volume measurement of airway resistance) and they required more than one salbutamol treatment.

*Methods.* The study was blinded, randomized, and placebo-controlled for the ipratropium. Patients were excluded if they had a severe asthma exacerbation, or significant comorbidity such as heart disease or cystic fibrosis. Eligible patients were randomized to one of four treatment groups: high-dose salbutamol (0.15 mg/kg q 60 minutes; maximum dose 5 mg) with or without 250  $\mu$ g ipratropium; frequent low-dose salbutamol (0.075 mg/kg q 30 minutes) with or without ipratropium. Ipratropium or placebo were given only once 30 minutes after the first salbutamol treatment. The primary endpoint was the change from baseline in respiratory resistance as measured by forced oscillometry. Values were ascertained at the time of the peak effect of both drugs; 30 minutes after salbutamol and 60 minutes after ipratropium. Secondary endpoints were oxygen saturation, the need for oral corticosteroids as a discharge medication, hospital admission, and relapse within 10 days. Prior home treatment and maintenance medications were cofactored into the analysis.

*Results.* The use of forced oscillometry allowed 69% of the children to participate who would have otherwise been excluded by the inability to reproducibly perform standard spirometry. All treatment groups improved significantly from baseline to 90 minutes ( $P < .001$ ). There were no differences in the acute management at home nor the physician assessment of severity among the four treatment groups. No group differences were observed in the mag-

nitude of improvement or in the number of patients who required an additional hour of treatment. In a subgroup of children in whom cough and rhonchi were prominent features, the anticholinergic effects of ipratropium did not provide additional benefit beyond salbutamol alone. There were no group differences in the need for corticosteroids, oxygen saturation, hospitalization rates, or relapse rates. The frequent, low-dose regimen of salbutamol was associated with a greater incidence of vomiting than hourly, high-dose salbutamol. There were no group differences in the incidence of other side effects.

*Conclusions.* In children with a mild to moderate exacerbation of asthma neither frequent low-dose salbutamol nor the addition of inhaled ipratropium provided additional beneficial effect compared with hourly high-dose salbutamol alone.

*Reviewer's Comments.* This is the largest study of its kind and unique in its ability to objectively evaluate changes in lung function in young children who represent a significant population of pediatric asthma patients presenting for acute care for mild to moderate exacerbations. Previous studies have demonstrated the benefit of frequent low-dose albuterol and the synergistic effect of inhaled ipratropium in children with severe exacerbations. This study suggests that these intense strategies may not be necessary for children with mild to moderate exacerbations, economizing on provider time and materials without sacrificing patient outcomes. However, it is possible that higher or more frequent doses of ipratropium may have shown a greater improvement in lung function as suggested in recent studies (Querishi FA, et al. *Ann Emerg Med*. 1997;29:205–211 and Schuh S, et al. *J Pediatr*. 1995;126:639–645).

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### EFFECT OF NEBULIZED IPRATROPIUM ON THE HOSPITALIZATION RATES OF CHILDREN WITH ASTHMA

Qureshi F, Pestian J, Davis P, et al. *N Engl J Med*. 1998; 339:1030–1035

*Purpose.*  $\beta$ -agonists have been identified as primary therapy for acute asthma and adjunctive therapy with anticholinergic agents has yielded variable results. This study evaluates the addition of ipratropium to  $\beta$ -agonist in the treatment of acute asthma.

*Study Population.* A double-blind study of 434 children (2–18 years) with acute asthma.

*Methods.* All patients received a weight appropriate dose of inhaled albuterol (2.5 to 5.0 mg) every 20 minutes. At the second dose 2 mg/kg of prednisolone was administered. The treatment group was administered 500  $\mu$ g ipratropium bromide with doses number 2 and 3 and the control group was given placebo.

*Results.* Overall, the hospitalization rate was lower in the group given ipratropium. This was particularly evident in the patients where the initial PEFr was  $<50\%$  and the asthma symptom score was elevated. The addition of ipratropium resulted in a hospitalization rate that decreased from 52% to 38% in the most severely affected patients.

*Comments.* In a study published in the *Journal of Pediatrics* in the same month, no effect was discerned with the addition of ipratropium 250  $\mu$ g to two dosing ranges of albuterol. There appears to be an inconsistent additive effect when ipratropium is added to albuterol. Patients who have more severe airway obstruction and who do not

respond to initial  $\beta$ -agonist therapy are more likely to respond to combined therapy.

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### NEBULIZED MAGNESIUM SULFATE VERSUS NEBULIZED SALBUTAMOL IN ACUTE BRONCHIAL ASTHMA: A CLINICAL TRIAL

Mangat HS, D'Souza GA, Jacob MS. *Eur Respir J*. 1998; 12:341-344

*Purpose of the Study.* This study investigated the efficacy of nebulized magnesium sulfate as a bronchodilator in acute asthma as compared with nebulized salbutamol.

*Study Population.* A total of 33 patients, 12-60 years of age, with a known history of asthma participated in the study.

*Methods.* This was a randomized, double-blind, placebo-controlled trial. All subjects received 100 mg of intravenous hydrocortisone and were then randomized to receive 2.5 mg of salbutamol every 20 minutes for four consecutive doses, or 95 mg of 3.2% solution of magnesium sulfate also 20 minutes apart for four doses. The outcome measures included improvements in the peak expiratory flow (PEF), admission rates, and use of the Fischl index. This index takes into account the subjects' use of accessory muscles, wheezing, dyspnea, heart rate >120, respiratory rate >18, pulsus paradoxus >18, and a PEF <120. The presence of each of these signs scores 1 point and a total of more than 4 points implies severe asthma. Patients were also monitored for common adverse effects frequently associated with the use of magnesium sulfate.

*Results.* Of the 16 subjects in the magnesium sulfate group, 14 showed an improvement in their Fischl index decreasing from a mean score of 4.31 pretreatment to 0.43 posttreatment. The remaining 2 subjects required supplemental therapy. One of these subjects improved and was discharged, while the other was admitted. In the control group 15 of the 17 subjects showed an improvement in their Fischl index going from a mean of 4.29 pretreatment to 0.76 posttreatment. Of the 2 subjects whose symptoms were refractory to this treatment, both required admission despite supplemental therapy. Improvement in the Fischl index pretreatment and posttreatment was statistically significant for the salbutamol and magnesium sulfate groups. There was no statistical significance in the treatment effect between groups. Comparisons of the PEF of the groups also showed an improvement, increasing 35% in the experimental group and 42% in the control group. The mean final PEF was not significantly different between the two groups. Subjects in the experimental group did not exhibit an increased incidence of the adverse effects commonly associated with magnesium sulfate.

*Conclusions.* Nebulized magnesium sulfate was found to have a clinically and statistically significant bronchodilator effect, and may well play a role as an adjunct to  $\beta_2$ -agonists in acute asthma. The optimum dose response relationship needs to be addressed in future studies.

*Reviewers' Comments.* Asthma continues to be a source of significant morbidity and mortality. This study is the first controlled clinical trial addressing the efficacy of nebulized magnesium sulfate in acute asthma, and is an important step toward identifying additional agents that can be used as adjunctive therapy. It will be important to establish the strength of the treatment effect in a larger study population and perhaps delineate the characteristics

of patients most likely to benefit from the use of magnesium sulfate.

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### A COMPARISON OF ACTIVE AND SIMULATED CHIROPRACTIC MANIPULATION AS ADJUNCTIVE TREATMENT FOR CHILDHOOD ASTHMA

Balon J, Aker PD, Crowther ER, et al. *N Engl J Med*. 1998;339:1013-1020

*Purpose.* To determine the effect of active spinal manipulation on lung function and symptom control in childhood asthma.

*Study Population.* Eighty children (7 to 16 years) with stable asthma for 6 weeks were randomized to either active spinal manipulation (38) or control massage therapy (42) for 20 to 36 sessions over a 4-month period.

*Methods.* After randomization, patients were followed for a 4-month period. Baseline and 4-month spirometry and methacholine challenge were performed. Patients recorded daily peak expiratory flow rates (PEFR) and daily symptom scores.

*Results.* In both groups peak flows increased while asthma symptoms and  $\beta$ -agonist use decreased. There were no statistically or clinically relevant significant differences in the two groups. There were no significant differences in spirometry or methacholine challenge over the 4-month study.

*Reviewer's Comments.* Alternative interventions for the control of chronic diseases are frequently used by patients. It is important that objective information be available to patients regarding treatment options. This carefully controlled study provides strong evidence that chiropractic manipulation has nothing to offer for the treatment of childhood asthma.

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### PROSPECTIVE, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY ON THE EFFECT OF HIGH-DOSE, INTRAVENOUS IMMUNOGLOBULIN IN CHILDREN AND ADOLESCENTS WITH SEVERE BRONCHIAL ASTHMA

Niggemann B, Leupold W, Schuster A, et al. *Clin Exp Allergy*. 1998;28:205-210

*Purpose of the Study.* To study the effect of high-dose intravenous gammaglobulin (IVIg) in severe childhood asthma.

*Study Population.* Thirty-one children (15 girls, 16 boys), 9 to 22 years of age (median, 14 years), with long-term severe asthma (forced expiratory volume in 1 second [FEV<sub>1</sub>] <70%), requiring more than 2 months of inhaled steroid (>800  $\mu$ g/day of budesonide or beclomethasone) and at least 10 days of a systemic glucocorticoid in connection with an asthma exacerbation in the previous year, were included in the study.

*Methods.* The study was performed as a prospective, double-blind, placebo-controlled, multicenter study in Germany. They were randomized into 2 groups, one received 1 g/kg of IVIg and the other received an identical dose of intravenous albumin. Baseline twice daily symptom scores and peak-flow measurements and monthly



lung function and bronchial hyperresponsiveness (BHR) to histamine measurements were made over a 2-month stabilization period and then repeated monthly during the 3-month treatment period and during a 1-month follow-up period.

**Results.** There were no statistically significant differences between the two groups at baseline. Sixteen of the children (10 in active group, 6 in control group) were atopic by skin testing. The IVIG treated group had fewer days of upper respiratory infections versus the control group. There was a trend toward fewer symptoms in the treatment versus the control group, but this did not reach statistical significance. There was no statistical significance between the IVIG treated and control groups for BHR to histamine, lung function, peak expiratory flow rates including variability, blood eosinophil counts, total immunoglobulin E (IgE) level or inhaled steroid doses.

**Discussion.** These results are quite different from the results reported by Landwehr et al (see below) who observed significant improvement with IVIG treatment in the 11 steroid dependent asthmatics that they studied. There are several differences between these studies. The group in this study was not steroid-dependent and was a less severe group compared with the Landwehr study. The Landwehr study evaluated 5 children and 6 adults (all treated with IVIG, no placebo-control) and this study looked included 31 children (16 on IVIG). This study did not address the steroid-sparing effect of IVIG, which was the primary focus of the Landwehr study. The dose of IVIG used in the Landwehr study was twice the dose of this study. Neither study found a change in BHR with IVIG treatment although histamine was used in this study and methacholine in the other.

**Reviewer's Comments.** This study further supports the need for more extensive placebo-controlled studies of IVIG treatment in severe asthma, including possible dose-response studies. From a cost-effective standpoint, it seems most reasonable to study this treatment in a more severely affected group (ie, oral steroid-dependent asthmatics).

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## BENEFITS OF HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN IN PATIENTS WITH SEVERE STEROID-DEPENDENT ASTHMA

Landwehr LP, Jeppson JD, Katlan MG, et al. *Chest*. 1998; 114:1349-1356

**Purpose of the Study.** To determine the efficacy of intravenous gammaglobulin (IVIG) in severe asthma to reduce steroid requirements.

**Study Population.** Eleven severe steroid-dependent asthmatics (5 adolescents, mean age 14 years; 6 adults, mean age 38.5 years) were studied at National Jewish Medical Center in Denver, Colorado. Subjects were excluded if they had cystic fibrosis, chronic bronchitis, acute sinusitis, immunodeficiency, or other chronic diseases besides asthma.

**Methods.** Steroid dependency was defined as requiring  $\geq 0.25$  mg/kg/day for a minimum of 2 months before entry into the study and subjects must have had at least one exacerbation of their asthma during the previous 3 months requiring an additional short course of high-dose oral steroids. All subjects had been taking daily or alternate day oral steroids for several years. All subjects received optimal asthma therapy including high-dose inhaled steroids and short- and long-acting  $\beta$ -agonists. Subjects underwent a 2-month observation period before starting IVIG

during which aggressive attempts were made to wean their steroids. The subjects then underwent a 6-month treatment period during which they received in addition to optimal asthma treatment, 2 g/kg/28 days of IVIG. They were then followed for an additional 30 days until the study end. Pre- and postbronchodilator pulmonary function testing and bone densitometry was performed the month before the treatment period and at the end of the study. Twice daily peak expiratory flow rates (PEFRs) were obtained and diurnal variability was calculated. Symptom score diaries were kept twice daily by subjects or family members and medication usage was monitored throughout. Bronchial hyperresponsiveness was determined by methacholine challenge at baseline, at midpoint of the treatment phase, and at the study end.

**Results.** Monthly treatment with high-dose IVIG resulted in a substantial decrease in oral steroid requirements in all subjects with an average pre-IVIG treatment daily steroid dose of  $31.6 \pm 5.1$  mg to an average daily dose of  $5.5 \pm 0.2$  mg at the end of the 6-month treatment, an 82% overall mean reduction in oral steroid dose. There was no significant difference in the dosage difference between adolescent and adult subjects, although the initial taper was more rapid in the adolescents. All parameters of pulmonary function showed overall improvement, including 3 adolescents who had forced expiratory volume in 1 second (FEV<sub>1</sub>) levels in normal range ( $>80\%$  of predicted) at study completion. There was, however, no difference in methacholine reactivity despite improvements in overall clinical improvement, pulmonary function, PEFR measurements, and symptom scores. Bone mineral density improved in 9 of 10 subjects studied.

**Discussion.** A significant steroid-sparing effect of high-dose IVIG was found in both groups, without an adverse effect on pulmonary function. Previous studies have shown symptom reemergence upon IVIG cessation, although this study only reported follow-up for 1 month posttreatment. The authors suggest that the lack of change in methacholine hyperresponsiveness may indicate that IVIG reduces inflammation and symptoms without affecting airway smooth muscle responsiveness, but further studies are needed to investigate this possibility. The mechanism of action of IVIG in asthma is unknown, but possible mechanisms include effects on cytokine production, improved host defense, and other immunomodulatory effects.

**Reviewer's Comments.** Given the significant side effects of long-term oral steroid use, alternative antiinflammatory agents for the treatment of severe asthma have been sought for years with disappointing results (eg, methotrexate, gold, troleandomycin). The results of this study as well as a similar study by the same group in younger children (Mazer, *J Allergy Clin Immunol*. 1991) are encouraging. However, a large scale longer term placebo-controlled study is needed to truly determine the efficacy of this product in severe steroid-dependent asthmatics. In addition, cost-benefit and risk-benefit analysis needs to be determined, given the high cost of such treatment and the fact that previous viral contaminations have occurred.

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## THE USE OF CYCLOSPORIN IN CORTICOSTEROID-DEPENDENT ASTHMA

Coren ME, Rosenthal M, Bush A. *Arch Dis Child*. 1997; 77:522-523

**Purpose of the Study.** To describe the authors' experience in using cyclosporin in 5 children with steroid-dependent asthma.

**Study Population.** Five children 8 to 15 years of age with poorly controlled asthma despite high-dose inhaled steroids and at least 10 mg of oral prednisone daily. All had been skin-tested with appropriate environmental controls instituted. In addition, all had normal immunoglobulin levels, sweat tests, and pH probes, ruling out complicating or alternative diagnoses.

**Methods.** Open trial of cyclosporin 5 mg/kg daily.

**Results.** Case 1, 8-year-old girl: no better after 6 months, no side effects.

Case 2, 15-year-old girl: monthly prednisone decreased from 900 mg to 200 mg, stopped because of severe hirsutism.

Case 3, 8-year-old girl: monthly prednisone initially decreased from 800 mg to 200 mg but relapsed while still on cyclosporin, mild hirsutism.

Case 4, 9-year-old boy: monthly prednisone decreased from 750 mg to 0, decreased glomerular filtration rate but no increase in creatinine or blood pressure, major improvement in height and weight.

Case 5, 10-year-old girl: monthly prednisone decreased from 300 mg to 0, mild hirsutism, major improvement in height and weight.

**Conclusions.** Cyclosporin may be useful in refractory childhood asthma. A prospective study is required to confirm this.

**Reviewer's Comments.** With current asthma therapy including high-dose inhaled corticosteroids, very few patients require regular oral corticosteroids. In those few who are steroid-dependent, cyclosporin, which inhibits helper T cell function, may be an effective alternative. Cyclosporin is not without potential side effects (hirsutism, paraesthesia, headache, hypertension, renal toxicity) and loses its effectiveness if stopped. Risks and benefits must be weighed against those of oral steroids.

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## COMBINATION DRUG THERAPY FOR THE PREVENTION OF EXERCISE-INDUCED BRONCHOCONSTRICTION IN CHILDREN

Benedictus F, Gianluca T, Pazzelli P, Solinas L, Niccoli A, Parente C. *Ann Allergy Asthma Immunol.* 1998;80:352-356

**Purpose of the Study.** To evaluate the effectiveness of a new precombined aerosol combination of salbutamol and nedocromil in preventing exercise-induced bronchoconstriction compared with salbutamol alone.

**Study Population.** Twelve subjects (9 boys and 3 girls) 7 to 13 years of age were recruited from the Paediatric Asthma Clinic at Perugia General Hospital. All had asthma as defined by the American Thoracic Society.

**Methods.** The study was a double-blind, double dummy, randomized, crossover, placebo-controlled study. Before study entry, a screening exercise test was performed. Those with a drop of 15% or more in forced expiratory volume in 1 second (FEV<sub>1</sub>) after the screening test entered the blinded part of the study. In random, cross-over, blinded order, each patient was tested on 3 separate days with different treatments given by metered dose inhaler before exercise: salbutamol 200 µg, salbutamol (200 µg)/nedocromil (4 mg), or placebo. Pulmonary function tests and heart rate were measured preexercise and at 1, 5, 10, 15, and 30 minutes postexercise. Complete protection was considered if the percentage drop in FEV<sub>1</sub>

was <10% while clinical protection was considered if the percentage decrease after receiving the drug was half or less the percentage fall in the screening challenge.

**Results.** No significant difference was noted in the maximum percentage decrease in FEV<sub>1</sub> on screening versus placebo days. Both active drugs were significantly more protective than placebo for percentage decrease in FEV<sub>1</sub> (salbutamol: *P* < .001; salbutamol/nedocromil: *P* < .005), but there was no difference between the two medication formulations. Complete protection was obtained in 12/12 (100%), 10/12 (83%), and 1/12 (8%) of subjects for the salbutamol/nedocromil combination, salbutamol alone, and placebo, respectively. Clinical protection was obtained in 12/12 (100%), 11/12 (92%), and 2/12 (16%) of children by salbutamol/nedocromil, salbutamol alone, and placebo, respectively. *P* values were <.01 for salbutamol versus placebo and salbutamol/nedocromil versus placebo in both complete and clinical protection. *P* values were not significant for salbutamol versus salbutamol/nedocromil in both protection parameters.

**Conclusions.** Although inhaled β-agonists alone are highly efficacious in preventing exercise-induced bronchoconstriction, in a minority of patients a combined treatment with salbutamol and nedocromil may be advantageous. This group may represent a subgroup of subjects who release more, or different, mediators in response to exercise.

**Reviewers' Comments.** In theory it seems reasonable that combined medications such as salbutamol/nedocromil may be of more benefit to selected patients with exercise-induced asthma and may help with compliance by decreasing the number of inhalers. Overall, however, the vast majority of patients appear adequately protected with salbutamol alone.

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## Immunology

### IMMUNODEFICIENCY DISEASES

#### IMPAIRMENT OF MYCOBACTERIAL IMMUNITY IN HUMAN INTERLEUKIN-12 RECEPTOR DEFICIENCY

Altare F, Durandy A, Lammas D, et al. *Science.* 1998;280:1432-1435

#### SEVERE MYCOBACTERIAL AND SALMONELLA INFECTIONS IN INTERLEUKIN-12 RECEPTOR-DEFICIENT PATIENTS

de Jong R, Altare F, Haagen I-A, et al. *Science.* 1998;280:1435-1438

**Purpose of the Studies.** Bacille Calmette-Guérin (BCG) and nontuberculous mycobacteria (NTM) are poorly virulent mycobacteria that sometimes cause disseminated disease in children. It was recently discovered that complete interferon gamma (IFN-γ) receptor deficiency causes a predisposition for this type of infection, and lack of mature granulomas; partial deficiency leads to a milder course of infection with mature granuloma formation. Some patients with disseminated NTM infections, however, do not have this defect. Because interleukin-12 (IL-12) is a potent inducer of IFN-γ, this study evaluated the possibility that

IL-12 receptor abnormalities were responsible for disseminated BCG or NTM in the patients without any other immunodeficiency or defect in the IFN- $\gamma$  receptor.

**Study Population.** A total of 7 unrelated patients were reported (4 in the first, 3 in the second paper). All experienced disseminated NTM infections and 5/7 had also experienced disseminated Salmonella infections. There were no other significant infections (viral, bacterial, fungal). None had a recognizable immunodeficiency (primary or secondary) and all had normal numbers of T, B, and NK cells.

**Methods.** A variety of molecular biologic and immunologic techniques were used to define the role of IL-12 receptor deficiency in this immunodeficiency phenotype.

**Results.** DNA sequence and immunologic analyses excluded defects in IFN- $\gamma$  receptor and IL-12. Specific mutations in genes encoding the IL-12 receptor  $\beta$ 1 chain were identified (distinct mutations for each patient including missense, nonsense, and frameshift). Addition of recombinant IL-12 in NK cytotoxicity assays did not result in increased activity in patients versus controls. Affected patient's T cells had reduced IFN- $\gamma$  production after stimulation with a variety of mitogens and antigens but cells did have normal surface expression of IFN- $\gamma$  receptor expression and normal expression of IL-12. There was no detectable surface expression of IL-12 receptor  $\beta$ 1. Adding exogenous IL-12 did not increase IFN- $\gamma$  production by T cells nor did adding antibody to IL-12 cause a decrease in the low constitutive expression of IFN- $\gamma$ . Tuberculin-specific, delayed type hypersensitivity reactions were normal. Like patients with partial deficiency of the IFN- $\gamma$  receptor, these patients had well-circumscribed granuloma formation in affected organs.

**Conclusions.** The lack of IL-12 receptor  $\beta$ 1 results in human immunodeficiency characterized by unusual susceptibility to mycobacterial and Salmonella infections. IL-12 dependent IFN- $\gamma$  secretion is the unifying pathophysiologic cause for this immunodeficiency that is phenotypically identical to partial IFN- $\gamma$  receptor deficiency. Although more patients must be evaluated, it appears that this pathway is essential for immune responses to these intracellular organisms but is dispensable (redundant pathways exist) for other infectious organisms.

**Reviewer's Comments.** It is very exciting that the molecular mechanisms responsible for the primary immunodeficiencies are being unraveled at a remarkable pace. As evidenced by this work, unusual manifestations of immunodeficiency are being elucidated and provide fundamental insights into immune system mechanisms. These findings already provide clues to better therapies (1 patient was treated successfully with recombinant IFN- $\gamma$ ) and because IL-12 receptor signaling is involved in other conditions such as cancer, there are many diagnostic and therapeutic ramifications from these studies.

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#### TUMOR NECROSIS FACTOR (TNF) AND LYMPHOTOXIN-A POLYMORPHISMS ASSOCIATED WITH COMMON VARIABLE IMMUNODEFICIENCY: ROLE IN THE PATHOGENESIS OF GRANULOMATOUS DISEASE

Mullighan CG, Fanning GC, Chapel HM, Welsh KI. *J Immunol.* 1997;159:6236–6241

**Purpose of the Study.** Common variable immunodeficiency is a polygenic disorder of uncertain cause, which is often associated with autoimmune disease. There appear

to be several distinct subtypes of common variable immunodeficiency and one subtype includes patients with granulomatous splenomegaly, decreased numbers of circulating CD4 T cells, and lymphadenopathy. This study investigated whether inherited polymorphisms in the MHC class III region (which includes tumor necrosis factor [TNF]- $\alpha$  and lymphotoxin- $\alpha$ ) contributed to the development of this subtype of common variable immunodeficiency.

**Study Population.** Ninety patients with common variable immunodeficiency were studied. Twenty of those 90 patients had granulomas and were felt to belong to a distinct subgroup.

**Methods.** Eight HLA class I and class II loci were typed using standard polymerase chain reaction (PCR) methods. Three biallelic TNF- $\alpha$  polymorphisms were genotyped and three lymphotoxin- $\alpha$  polymorphisms were genotyped using allele-specific PCR. Peripheral blood phenotyping was performed using standard flow cytometry techniques.

**Results.** The presence of granulomas correlated strongly with decreased numbers of total T cells, decreased numbers of total B cells, and depletion of naive T cells. This subpopulation of patients with granulomas also had an overrepresentation of the haplotype: A\*01–Cw\*0701–B\*0801–DRB1\*0301–DQB1\*0201 which contains the TNF-308A polymorphism. In addition, an association between granulomas and the TNF+488A allele was demonstrated.

**Conclusions.** This important study confirms that there is a clinically distinct subset of patients with common variable immunodeficiency and granulomatous disease. This subset appears to have a distinct genetic cause and characteristic derangements of peripheral blood lymphocyte subsets.

**Reviewer's Comments.** TNF is essential for the formation of granulomas and this study hypothesized that inherited differences in TNF production might predispose patients to the granulomatous complications of common variable immunodeficiency. In whites, the TNF-308A polymorphism is in linkage disequilibrium with the haplotype cited above, which makes it difficult to prove whether the TNF polymorphism itself is responsible for the granulomatous complications. Despite this limitation, this study makes a compelling case that overproduction of TNF is implicated in the granulomatous complications of common variable immunodeficiency.

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#### FUNCTIONAL ANALYSIS OF PERIPHERAL BLOOD B CELLS IN PATIENTS WITH X-LINKED AGAMMAGLOBULINEMIA

Nonoyama S, Tsukada S, Yamadori T, et al. *J Immunol.* 1998;161:3925–3929

**Purpose of the Study.** X-linked agammaglobulinemia (XLA) is classically described as a pure humoral immunodeficiency in which boys fail to produce mature B cells and as a consequence, make no immunoglobulin. With the advent of genetic testing for this disorder, it has become clear that there are boys with XLA who have small numbers of peripheral blood B cells and small amounts of antibody. This study evaluated the function of the peripheral blood B cells in boys with XLA.

**Study Population.** Five of 9 patients with XLA had detectable peripheral blood B cells. Four of the 5 patients had missense mutations of Btk identified. In the fifth patient, absence of Btk protein was demonstrated by Western blot.



**Methods.** B cell function was evaluated using CD40 crosslinking and interleukin (IL)-4 stimulation. Proliferation, immunoglobulin E (IgE) production, and upregulation of CD23 were measured. In addition, patients were immunized to  $\phi$ X174.

**Results.** Proliferation, CD23 expression, and IgE production were all normal in the B cell cultures from XLA patients. Although antibody titers after immunization were not normal, XLA patients were capable of responding to the immunization and demonstrated an enhanced response after a secondary immunization suggesting immunologic memory is intact. Significantly, the patients did not undergo isotype switching to IgG on secondary immunization.

**Conclusions.** CD40-mediated B cell function in XLA patients appears to be relatively normal. The authors suggest that this bypass strategy could be used as a potential therapy for XLA.

**Reviewer's Comments.** The function of Btk is incompletely understood. Analysis has been complicated by the fact that murine models of XLA exhibit significant differences from the human disease. This study demonstrates that B cells from patients with Btk mutations are not intrinsically dysfunctional. This implies that Btk may be important in B cell maturation but is dispensable for some functions after maturation. This study also implies that there is a Btk bypass pathway that allows some B cells to mature. Using a Btk bypass therapeutic strategy would have significant theoretical risks but is certainly an approach worth consideration.

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#### MONOCYTES FROM WISKOTT-ALDRICH PATIENTS DISPLAY REDUCED CHEMOTAXIS AND LACK OF CELL POLARIZATION IN RESPONSE TO MONOCYTE CHEMOATTRACTANT PROTEIN-1 AND FORMYL-METHIONYL-LEUCYL-PHENYLALANINE

**Badolato R, Sozzani S, Malacarne F, et al. *J Immunol.* 1998;161:1026-1033**

**Purpose of the Study.** Several previous studies have documented a subtle abnormality of neutrophil and macrophage function in patients with Wiskott-Aldrich syndrome. This study was designed to investigate the cause of phagocyte dysfunction in Wiskott-Aldrich syndrome. Monocyte/macrophage dysfunction could contribute to the recurrent infections seen in this syndrome.

**Study Population.** Four patients with Wiskott-Aldrich syndrome were studied.

**Methods.** Morphologic changes after stimulation were defined by light microscopy and immunofluorescence for actin. Chemotaxis was measured in a microchamber and superoxide production was defined using a cytochrome c reduction technique.

**Results.** Monocyte chemotaxis responses to macrophage inflammatory protein 1 $\alpha$  (MIP1 $\alpha$ ), monocyte chemoattractant protein-1 (MCP-1), and formyl-methionyl-leucyl-phenylalanine (FMLP) were abnormal. Similarly, actin polarization and morphologic polarization were defective in the stimulated monocytes from patients with Wiskott-Aldrich syndrome. Conversely, respiratory burst and upregulation of adhesion molecules was intact after stimulation.

**Conclusions.** Monocyte activities requiring chemotaxis or polarization are defective in patients with Wiskott-Aldrich syndrome. Aberrant leukocyte recruitment to ar-

reas of inflammation could contribute to the recurrent infections in this syndrome.

**Reviewer's Comments.** A previous report demonstrated that actin polarization after stimulation of T cells is aberrant in this disorder; therefore, this report is consistent with a global abnormality affecting transduction of cell surface signals to the cytoskeleton. This was also expected based on the molecular characterization of the WASp protein, which is defective in Wiskott-Aldrich syndrome. The WASp protein acts as a docking site for signaling molecules and GTPases implicated in actin polymerization. The implications of these findings is that treatment of patients with biological agents such as cytokines may be beneficial as modulators in particular clinical settings but is unlikely to overcome the defect in this syndrome because it is cell-intrinsic.

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#### THE OUTCOME OF PATIENTS WITH HYPOGAMMAGLOBULINEMIA IN INFANCY AND EARLY CHILDHOOD

**Dalal I, Reid R, Nisbet-Brown E, Roifman CM. *J Pediatr.* 1998;133:144-146**

**Purpose of the Study.** The investigation was a prospective study to determine the long-term antibody levels of children initially diagnosed with hypogammaglobulinemia.

**Study Population.** Thirty-five children, <4 years of age, who presented with immunoglobulin G (IgG) levels 2 standard deviations below the mean on 2 or more occasions and who had no clinical or laboratory evidence of cellular or other immunodeficiency states. There were 24 males and the mean age at presentation was 19.6 months.

**Methods.** Evaluation consisted of an assessment of overall health status and a panel of laboratory tests, including immunoglobulins, IgG subclasses, antibodies to polio virus (Normal  $\geq$ 1:8) and tetanus (Normal  $>$ 0.05 IU/mL), isohemagglutinin titers (Normal anti-A  $>$ 1:16, anti B  $>$ 1:8), and antipneumococcal antibodies, with the use of standard techniques. The children were followed for up to 120 months with many of the initial laboratory examinations being repeated at subsequent visits. Immunoglobulin was administered to 9 children for appropriate indications.

**Results.** There were 3 distinct groups identified. 1) 29 children with full recovery and who never had any type of invasive infections. 2) 3 children continued to have low IgG levels and poor antibody titers to one or more immunization. 3) children whose IgG levels became normal but they were unable to mount an adequate response to antigenic challenge, eg, tetanus and/or pneumococcal vaccines.

**Conclusions.** The condition may well not be as benign as was thought and careful long-term follow-up is most certainly in order. Invasive infections and low antibody levels at presentation may well be the signals that indicate a permanent antibody deficiency state.

**Reviewer's Comments.** An excellent long-term follow-up of this not too uncommon immunological problem carried out at one of the North America's premier children's institutions. I'd recommend reading the full article either electronically or on paper.

THAD JOOS, MI  
Detroit, MI

**BIPHASIC KINETICS OF PERIPHERAL BLOOD T CELLS AFTER TRIPLE COMBINATION THERAPY IN HIV-1 INFECTION: A COMPOSITE OF REDISTRIBUTION AND PROLIFERATION**

**Pakker NG, Notermans DW, Boer RJD, et al. *Nature Med.* 1998;4:208–214**

*Purpose of the Study.* To evaluate the kinetics of immune reconstitution after triple combination therapy for human immunodeficiency virus (HIV)-infected patients.

*Study Population.* 33 HIV-infected adults with CD4+ T lymphocyte counts  $\geq 50$  cells/ $\mu$ L, plasma HIV RNA level  $\geq 30\,000$  copies/mL, and no previous antiretroviral treatment.

*Methods.* Subjects received triple antiretroviral therapy (ritonavir, zidovudine, lamivudine). Peripheral blood CD4, CD8, CD19, CD45RA, CD45RO, and CD62L cell analyses were performed at multiple time points over 36 weeks of treatment. Mathematical modeling for CD4+ and CD8+ T cell recovery was performed.

*Results.* Both CD4+ and CD8+ T cell recovery during antiretroviral therapy showed a biphasic pattern. Rapid recovery occurred during the first 3 weeks for CD4+ T cells, and first 6 weeks for CD8+ T cells; most of them were “memory/effector” T cells (CD45RO+ or CD45RA+CD62L–). The early recovery of memory CD4+ and CD8+ T cells was followed by a slow recovery period of CD4+ and CD8+ T cells that were largely “naïve” (CD45RA+CD62L+), with virtually no further recovery of memory T cells.

*Conclusions.* Based on mathematical modeling analyses, the initial rapid increase in memory CD4+ and CD8+ T cells after the triple antiviral therapy result from redistribution, but not T cell proliferation. A gradual repopulation of the T cell compartment then follows with newly produced naïve T cells.

*Reviewers’ Comments.* Ideally, the ultimate goal of HIV therapy is not only to stop viral replication and eradicate the virus, but also to restore immune function in the compromised host. In contrast to previous studies, this article provides a deeper understanding of the nature of T cell compartment reconstitution after triple antiretroviral therapy. Evidence that there is a gradual repopulation of the T cell compartment with newly generated naïve T cells is indeed encouraging. An accompanying article by Gorachov (reviewed below), and a brief editorial entitled “Getting to the HAART of T cell dynamics” by Roederer in the same issue of *Nature* provide further relevant insights.

AKALUCK THATAYATIKOM, MD  
ANDREW H. LIU, MD  
Denver, CO

**PERTURBATION OF CD4+ AND CD8+ T-CELL REPERTOIRES DURING PROGRESSION TO AIDS AND REGULATION OF THE CD4+ REPERTOIRE DURING ANTIVIRAL THERAPY**

**Gorochov G, Neumann AU, Kereveur A, et al. *Nature Med.* 1998;4:215–221**

*Purpose of the Study.* To study the diversity of the T lymphocyte repertoire during the course of human immunodeficiency virus (HIV)-1 infection and after combination antiretroviral therapy.

*Study Population.* Eleven HIV-infected adults undergoing triple antiviral therapy were compared with 7 untreated HIV-infected adults and 5 noninfected controls.

*Methods.* Assessment of T-cell antigen receptor (TCR) repertoire in CD4+ and CD8+ T cells by TCR sequence analysis.

*Results.* In nontreated HIV-infected subjects, CD8+ T cell TCR repertoire showed drastic alteration at all stages that were independent of clinical status, CD4+ or CD8+ T cell counts, or viral load. The severity of alteration of the CD4+ T cell repertoire was associated with viremia or CD4+ cell counts: patients with high CD4+ cell counts and low viremia had normal CD4+ T cell repertoire diversity; in contrast, higher viremia or lower CD4+ cell counts in patients with progressive disease were associated with reduction in CD4+ repertoire diversity. In patients with successful triple therapy, after 3 to 6 months of the treatment, CD4+ T cell repertoire normalized to match seronegative controls.

*Conclusions.* CD4+ T cell TCR repertoire is restored within the first 6 months of successful triple therapy, in contrast to persistent restriction of CD8+ TCR repertoire.

*Reviewers’ Comments.* One important measure of the integrity of the T lymphocyte arm of the immune system is to determine TCR repertoire diversity, which provides insight to the variety of antigens that T cells can recognize. The encouraging finding of this study is that the restricted CD4+ TCR repertoire in HIV-infected patients can be normalized after the triple antiretroviral therapy. The normalized T cell repertoires, combined with results of Pakker’s study showing increased naïve T cells after 4 to 6 months of treatment, suggest that the CD4+ T cell compartment of successfully treated HIV patients might be restored in quality as well as quantity (ie, CD4+ T cell counts) with triple therapy. A brief editorial entitled “Getting to the HAART of T cell dynamics” by Roederer on pages 145 to 146 of the same issue of *Nature* is an insightful summary of these articles.

AKALUCK THATAYATIKOM, MD  
ANDREW H. LIU, MD  
Denver, CO

**“BUFFALO HUMP” IN MEN WITH HIV-1 INFECTION**

**Lo JC, Mulligan K, Tai VW, Algren H, Schambelan M. *Lancet.* 1998;351:867–870**

**VISCERAL ABDOMINAL-FAT ACCUMULATION ASSOCIATED WITH USE OF INDINAVIR**

**Miller KD, Jones E, Yanoski JA, Shankar R, Feuerstein I, Falloon J. *Lancet.* 1998;351:871–875**

*Purpose of the Studies.* Protease inhibitors represent a major advance in the treatment of human immunodeficiency virus (HIV) infection, and constitute the cornerstone of highly active antiretroviral therapy for many patients. Unfortunately, the widespread use of this compound has resulted in unique patterns of abnormal fat accumulation that have been recently described and studied.

*Methods.* In these two studies a total of 18 HIV-infected adults were identified and studied. The 8 patients with a “buffalo hump” were on various antiretroviral regimens, four of which included a protease inhibitor. These patients were studied for evidence of Cushing’s syndrome. The 10 individuals in the second paper were evaluated with abdominal computer tomography to measure total adipose

tissue and visceral adipose tissue. These 10 individuals had developed clinical evidence of abdominal fat accumulation and were being treated with highly active antiretroviral therapy including the protease inhibitor Indinavir.

**Results.** The 8 patients with "buffalo hump" did not have Cushing's syndrome as determined by the effective suppression of plasma cortisol values with low-dose dexamethasone administration. Further, these individuals had no other clinical evidence of Cushing's syndrome other than the appearance of a "buffalo hump," the accumulation of adipose tissue in the dorsocervical region. The individuals treated with Indinavir were demonstrated to have intraabdominal fat accumulation. Additionally, serum triglyceride values were increased in these patients after starting Indinavir and correlated with the degree of abdominal fat accumulation.

**Conclusions.** The encouraging clinical responses of HIV-infected patients to new treatment regimens is tempered with the understanding that complications are likely to occur and likely to be related to the intense pharmacologic regimens required to control HIV. Abnormal fat accumulation in patients with HIV is one of these complications.

**Reviewer's Comments.** The abnormal fat accumulation observed in patients treated with highly active antiretroviral regimens may be the visual manifestation of a more global abnormality in lipid metabolism. This process has been termed the "lipodystrophy syndrome" and is associated with changes in body shape, hyperlipidemia, and insulin resistance. The clinical picture appears to be consistent with Cushing's syndrome, but this diagnosis cannot be confirmed in a majority of patients. The abnormal fat distribution is not merely a cosmetic issue. Patients appear to be at increased risk for cardiovascular complications and diabetes. The long-term impact of the abnormal lipid metabolism observed in patients effectively treated with anti-HIV drugs will be watched carefully. Finally, it must be emphasized that as patients live longer on intense therapy for their HIV, newer problems are likely to arise that will require rapid and intense study.

JOSEPH A. CHURCH, MD  
Los Angeles, CA

#### PREDICTIVE VALUE OF QUANTITATIVE PLASMA HIV RNA AND CD4+ LYMPHOCYTE COUNT IN HIV-INFECTED INFANTS AND CHILDREN

Palumbo PE, Raskino C, Fiscus S, et al. *JAMA*. 1998;279:756-761

**Purpose of the Study.** Pediatric human immunodeficiency virus (HIV) infection may have unique pathogenic features that preclude routine extrapolation of laboratory monitoring results from adult studies. This present study was designed to evaluate the prognostic value of plasma HIV RNA and CD4+ T lymphocyte count for HIV disease progression in infants and children.

**Methods.** Data from a "cohort" of 566 infants and children were analyzed. Assays were performed with standard techniques. Clinical trial endpoints consisted of time to first HIV disease progression or death.

**Results.** Baseline plasma RNA levels were high relative to adult levels, and both baseline RNA and CD4+ T-cell counts were independently predictive of subsequent clinical course. For each log<sub>10</sub> reduction in baseline RNA with treatment was associated with a risk reduction of approximately 50%. Disease progression predictive power was enhanced by the combined use of plasma HIV RNA and CD4+ T-cell counts. Plasma RNA <10 000 copies/mL, or

CD4+ T-cell counts >500/μL (for children <6.5 years of age) or greater >200/μL (for children >6.5 years of age) were associated with a 2-year disease progression rate of >5%.

**Conclusions.** Two key laboratory markers, plasma HIV RNA and CD4+ T-cell counts, are independent predictors of clinical course among HIV-infected pediatric patients. The linear, age-independent relationship between plasma RNA and relative risk of disease progression strongly supports therapeutic efforts to achieve plasma virus levels as low as possible, and to maintain these levels as long as possible.

**Reviewer's Comments.** For some time it has been assumed from adult data that low T-cell numbers and high virus levels were bad for HIV-infected patients. This paper quantitatively assesses the impact of these two predictive markers and clearly indicates that they are independent predictors of clinical course. Increasingly, these "surrogate" markers of disease progression are being used as primary endpoints in clinical trials because of the type of data presented in this paper. The impact of this method of analysis is that results of clinical trials will be available more quickly with more rapid availability of novel treatment regimens being made available.

JOSEPH A. CHURCH, MD  
Los Angeles, CA

#### ABBREVIATED REGIMENS OF ZIDOVUDINE PROPHYLAXIS AND PERINATAL TRANSMISSION OF THE HUMAN IMMUNODEFICIENCY VIRUS

Wade NA, Birkhead GS, Warren BL, et al. *N Engl J Med*. 1998;339:1409-1414

**Purpose of the Study.** Pediatrics AIDS Clinical Trials Group Protocol 076 (ACTG 076) documented a reduction in the rate of perinatal transmission of human immunodeficiency virus (HIV) from >25% to 8.3% with a regimen of zidovudine ("AZT") given antepartum, intrapartum, and to the newborn. The purpose of this study was to examine the effects of abbreviated AZT regimens on HIV transmission.

**Methods.** Data was obtained from the HIV polymerase chain reaction (PCR) Testing Service of the New York State Department of Health. Pregnant women who received abbreviated regimens rather than the recommended regimen did so because of limited prenatal care, or by choice. The requisition form used by the PCR Testing Service included information on the demographic characteristics of the infants and the timing of any perinatal treatment with AZT.

**Results.** Specimens from 939 HIV-exposed infants were submitted for PCR testing. When treatment was begun in the prenatal period, the rate of HIV transmission was 6.1%; when begun intrapartum, the rate was 10.0%; when begun within the first 48 hours of the infant's life, the rate was 9.3%; and when begun on day 3 of life or later, the rate was 18.4%; in the absence of zidovudine prophylaxis the rate of HIV transmission was 26.6%.

**Conclusions.** These results confirm the efficacy of AZT prophylaxis and strongly suggests that there are reductions in the rate of perinatal transmission of HIV even with abbreviated regimens that are begun intrapartum, or in the first 48 hours of life.

**Reviewer's Comments.** In the United States, perinatal transmission of HIV is becoming a rare event in situations where effective antiretroviral therapy is initiated in the perinatal time frame. For most of the developing world; however, the intense regimen dictated by ACTG 076 is unaffordable and impractical. This study strongly



indicates that abbreviated regimens are still substantially effective in reducing the rate of transmission from mother to infant, and that such abbreviated regimens are effective, although optimal cost benefit analysis will be difficult to conduct.

JOSEPH A. CHURCH, MD  
Los Angeles, CA

#### A NOVEL FACTOR PRODUCED BY PLACENTAL CELLS WITH ACTIVITY AGAINST HIV-1

Sharma UK, Trujillo J, Song H-F, et al. *J Immunol.* 1998;161:6406–6412

*Purpose of the Study.* The factors controlling human immunodeficiency virus (HIV) transmission from mother to infant are not clearly defined. Maternal viral load, disease stage, and immune status have all shown an effect on transmission, yet no analysis of maternal factors fully explains why approximately 75% of children born to infected mothers escape infection. Indirect evidence suggests the existence of placental protective mechanisms that inhibit viral replication in utero. This investigation was to characterize the antiviral activity of a placental factor present in the supernatant from cultured placental stromal cells, which protected HIV-infected peripheral blood cells from virus-induced death.

*Methods.* First trimester chorionic villus biopsy samples from HIV-seronegative subjects were used as a source of placental stromal cells. These cells were cultured and culture supernatants were obtained. This supernatant was used to assay for antiviral activity and to examine the physical chemical and immunochemical characterization of the placental factor.

*Results.* The inhibitory activity present in the supernatant was not attributable to the presence of any known cytokine previously reported to have anti-HIV effects. The placental factor had no specific suppressive effect on the infectivity of cell-free HIV, and envelope-mediated membrane fusion appeared to be uninfected. However, infected peripheral blood mononuclear cells treated with placental factor revealed reduced expression of all viral proteins and the production of virions with 10- to 100-fold reduced infectivity.

*Conclusions.* The placental factor described is a small, heat and pH stable molecule with broad suppressive activity against different strains of HIV. The factor does not share identity with any known cytokines. This factor could play an important role in the protection of the fetus and newborn from HIV infection and further studies to purify and characterize this factor are in progress.

*Reviewer's Comments.* How so many infants escape HIV infection in utero has remained a mystery. It is generally presumed now that most perinatal infections occur peripartum rather than during early and mid-gestation. This supports the author's claim that some feature of placental physiology impacts the transmission of HIV to the developing fetus. Further, active infection is not prevented by this factor, although direct cytopathology and individual virion infectivity is decreased. If this factor can be isolated and characterized, it may provide the basis for the development of a new class of HIV interventions.

JOSEPH A. CHURCH, MD  
Los Angeles, CA

#### ANALYSIS OF THE PERSISTENCE OF HUMORAL AND CELLULAR IMMUNITY IN CHILDREN AND ADULTS IMMUNIZED WITH VARICELLA VACCINE

Zerboni L, Nader S, Aoki K, Arvin AM. *J Infect Dis.* 1998;177:1701–1704

*Purpose of the Study.* To evaluate the persistence of humoral and cellular immunity to varicella-zoster virus (VZV) in children and adults immunized with live attenuated VZV vaccine.

*Study Population.* Two hundred healthy children (ages 2–12 years) and forty healthy adults (ages 13–45 years) were vaccinated and identified as seroconverters who did not develop breakthrough varicella. Of these individuals, 60 children and 18 adults agreed to be reevaluated.

*Methods.* Serum was collected at the time of vaccination and then serially for 5 years postvaccination. The presence of anti-VZV IgG antibodies was determined by enzyme-linked immunosorbent assay (ELISA) and cell-mediated immunity to VZV was detected by lymphocyte proliferation assay. Peripheral blood mononuclear cells were stimulated with VZV antigen and supernatants were then assayed for interleukin-2, interferon-gamma, and interleukin-10 response.

*Results.* At a mean of 5 years after vaccination, 93% of children and 94% of adults had immunoglobulin G (IgG) antibodies to VZV as determined by ELISA. VZV antibody concentrations were significantly higher at 5 years than at 1 year after immunization in children and adults. Cell-mediated immunity to VZV was detected in 87% of children and 94% of adults at 5 years. The mean stimulation index was significantly higher at 5 years than at 1 year among children and adults. Cytokine responses to VZV, including interleukin-2, interferon-gamma, and interleukin-10 were equivalent between children and adults at 5 years.

*Conclusions.* Varicella immunization induced long-term humoral and cellular immunity, and initial differences between cell-mediated responses in children and adults diminished over time.

*Reviewer's Comments.* As more of the population receives the varicella vaccine, the opportunities for exogenous exposure to wild-type VZV will decrease. It is unclear if these exposures are a major mechanism for preserving immunity to VZV, but if so, then it may be necessary to boost immunity with the varicella vaccine at some future point. However, at 5 years, both humoral and cellular immunity appear to be intact.

LEON S. GREOS, MD  
Aurora, CO

#### SAFETY AND IMMUNOGENICITY OF A PURIFIED F PROTEIN RESPIRATORY SYNCYTIAL VIRUS (FPF-2) VACCINE IN SEROPOSITIVE CHILDREN WITH BRONCHOPULMONARY DYSPLASIA

Groothuis JR, King SJ, Hogerman DA, Paradiso PR, Simoes EA. *J Infect Dis.* 1998;177:467–469

*Purpose of the Study.* To assess the safety, immunogenicity, and efficacy of PFP-2 (purified fusion [F] protein) vaccine in a high-risk population of young seropositive children with bronchopulmonary dysplasia (BPD).

*Study Population.* Twenty-one children (age >12 months) with BPD and culture or serologically proven respiratory syncytial virus (RSV) infection in a previous respiratory season.

**Methods.** Children were randomized to receive one dose of PFP-2 vaccine or influenza vaccine (placebo). Children were followed for adverse reactions and RSV illness over two respiratory seasons. Sera were obtained for determination of immunoglobulin G (IgG) titers to RSV F protein and neutralizing antibody titers before and 1, 6, and 12 months after vaccination.

**Results.** Adverse reactions were few. Fourfold F protein rises occurred in 9 of 10 PFP-2 and 0 of 11 placebo recipients. Six PFP-2 recipients had low prevaccination neutralizing antibody titers (<1:450); all had fourfold rises. By 12 months, F protein and neutralizing antibody titers in all 21 children were similar. RSV illness occurred in 6 of 11 placebo versus 1 of 10 PFP-2 recipients ( $P = .06$ ); 1 placebo child required hospitalization.

**Conclusions.** PFP-2 vaccine appears safe and immunogenic and may protect children with BPD against serious RSV disease on reinfection.

**Reviewer's Comments.** The development of severe pulmonary disease on primary RSV infection in infants who received RSV-formalin vaccine in previous trials has impeded RSV vaccine development. Studies in animals, the elderly, and patients with cystic fibrosis using the fusion protein vaccine have consistently demonstrated good effect, and thus, this approach offers new hope for prevention of this serious disease.

LEON S. GREOS, MD  
Aurora, CO

#### **AVIDITY OF IGG FOR STREPTOCOCCUS PNEUMONIAE TYPE 6B AND 23F POLYSACCHARIDES IN INFANTS PRIMED WITH PNEUMOCOCCAL CONJUGATES AND BOOSTED WITH POLYSACCHARIDE OR CONJUGATE VACCINES**

**Anttila M, Eskola J, Ahman H, Kayhty H. *J Infect Dis.* 1998;177:1614–1621**

**Purpose of the Study.** To assess possible differences in avidity maturation of antipneumococcal polysaccharide (PS) antibodies between infants boosted with the conjugate and those boosted with the PS vaccine.

**Study Population.** Seventy-five healthy infants were vaccinated, and sera were analyzed from 71 infants.

**Methods.** Infants were immunized at 2, 4, and 6 months of age with pneumococcal PS-diphtheria toxoid conjugate vaccine, and boosted at 14 months with the homologous conjugate or a pneumococcal PS vaccine. Relative avidity of immunoglobulin G (IgG) to *Streptococcus pneumoniae* type 6B and 23F PSs was measured in sera of these children using an EIA and the chaotropic agent thiocyanate. Sera were also analyzed from previous immunogenicity studies in another group of infants primed and boosted with pneumococcal PS-meningococcal protein conjugate and compared with a group boosted with PS vaccine after priming with the pneumococcal PS-tetanus toxoid conjugate.

**Results.** The concentrations of antibodies to 6B and 23F PSs increased significantly after the booster with both vaccines. A significant increase in the avidity of anti-6B and anti-23F antibodies was observed after the booster with conjugate but not with PS vaccine. Avidity also increased in the other group of infants primed and boosted with pneumococcal PS-meningococcal protein conjugate but not in the group boosted with PS vaccine after priming with pneumococcal PS-tetanus toxoid conjugate. In the latter group, the avidity of anti-6B was high before boosting.

**Conclusions.** The relative avidity of IgG to *S pneumoniae* type 6B and 23F PSs increased in infants primed with

conjugate vaccines when boosted with conjugated but not PS vaccine.

**Reviewer's Comments.** Protein conjugate vaccines are T cell-dependent whereas PS vaccines are T cell-independent. As observed in *Haemophilus influenzae* type b conjugate vaccines, induction of T cell response allows pneumococcal conjugate vaccines to be immunogenic in infants, to induce immunologic memory and to enhance avidity with booster doses.

LEON S. GREOS, MD  
Aurora, CO

#### **MOLECULAR MIMICRY BY HERPES SIMPLEX VIRUS-TYPE 1: AUTOIMMUNE DISEASE AFTER VIRAL INFECTION**

**Zhao ZS, Granucci F, Yeh L, Schaffer PA, Cantor H. *Science.* 1998;279:1344–1347**

**Purpose of the Study.** The onset of autoimmune disease sometimes follows an acute viral infection. One possible explanation for this phenomenon is "molecular mimicry." According to this hypothesis, a virus could trigger autoimmunity if one of the viral proteins is very similar in structure to a host protein. Thus, an immune response to the viral protein would also initiate an autoimmune response to a similar host protein.

**Study Population.** A mouse strain in which herpes simplex virus-type 1 (HSV-1) infection induces a chronic autoimmune keratitis.

**Methods and Results.** The authors cloned autoreactive T cells that target corneal antigens from mice with autoimmune herpes stromal keratitis. These T cell clones were found to also recognize part of the coat protein of herpes simplex virus-type 1 (HSV-1). Mutant HSV-1 viruses that were engineered to omit this particular protein segment (epitope) did not induce autoimmune disease.

**Conclusions.** An immune response initiated by part of the HSV-1 coat protein caused the activation of T cells that were virus-specific, but also attacked host corneal proteins that are structurally similar to the viral protein, resulting in autoimmune keratitis.

**Reviewer's Comments.** This is a convincing demonstration of molecular mimicry, and similar studies may yield groundbreaking information regarding the pathogenesis of autoimmune diseases in humans (see next review).

JAMES E. GERN, MD  
Madison, WI

#### **IDENTIFICATION OF LFA-1 AS A CANDIDATE AUTOANTIGEN IN TREATMENT-RESISTANT LYME ARTHRITIS**

**Gross DM, Forsthuber T, Tary-Lehmann M, et al. *Science.* 1998;281:703–706**

**Purpose of the Study.** In most individuals, the symptoms of Lyme arthritis resolve after the acute infection is eradicated. However, infection with *Borrelia burgdorferi*, the agent of Lyme disease, can sometimes trigger chronic arthritis that resembles an autoimmune disorder. This treatment-resistant Lyme arthritis is associated with immune reactivity to outer surface protein A (OspA) of *B burgdorferi*, and the major histocompatibility complex class II allele DRB1\*0401. The purpose of this study was to try to define autoantigens that could be involved in the pathogenesis of chronic arthritis triggered by Lyme disease.

**Study Population.** Individuals with treatment-resistant Lyme disease, and control subjects with other forms of chronic arthritis.

*Methods and Results.* The immunodominant epitope of OspA for T helper cells was identified. Examination of the bacterial protein sequence revealed homology to a human adhesion molecule, leukocyte function-associated antigen-1 (hLFA-1). Individuals with treatment-resistant Lyme arthritis, but not other forms of arthritis, generated responses to OspA, hLFA-1, and their highly-related peptide epitopes.

*Conclusions.* The authors conclude that identification of the initiating bacterial antigen and a cross-reactive autoantigen may provide a model for development of autoimmune disease.

*Reviewer's Comments.* The authors have made a convincing case of molecular mimicry as a cause of chronic Lyme arthritis. In this scenario, an immune response to the OspA bacterial protein triggers an immune response to LFA-1, a human protein with a similar structure. This work opens up new possibilities for the treatment of chronic arthritis after Lyme disease with peptides, or other immune modulators, that can block the interaction of auto-reactive T cells with LFA-1.

JAMES E. GERN, MD  
Madison, WI



## Meta-Analysis of Outcomes of Pediatric Functional Endoscopic Sinus Surgery

Yael Raz and David E. Tunkel

*Pediatrics* 1999;104:369

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## Meta-Analysis of Outcomes of Pediatric Functional Endoscopic Sinus Surgery

Yael Raz and David E. Tunkel

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