FOUR-YEAR INCIDENCE OF ALLERGIC SENSITIZATION AMONG SCHOOLCHILDREN IN A COMMUNITY WHERE ALLERGY TO CAT AND DOG DOMINATES SENSITIZATION: REPORT FROM THE OBSTRUCTIVE LUNG DISEASE IN NORTHERN SWEDEN STUDY GROUP


Purpose of the Study. To evaluate the incidence of type 1 sensitization during a 4-year period among schoolchildren in northern Sweden (a dust mite- and cockroach-free environment) and to examine the risk factors for sensitization, including cat and dog ownership.

Study Population. A total of 1870 schoolchildren, 7 to 8 years of age at the beginning of the study, were derived from a longitudinal cohort of 2454 children living in 2 municipalities in northern Sweden in 1996.

Methods. Skin prick tests for tree, grass, weed, dust mite, mold, cat, dog, and horse allergens were conducted. The same children were retested 4 years later. A positive reaction was recorded if the wheal was ≥3 mm after 15 minutes. The participation rate was 88% during both collection periods. CAP system immunoglobulin E antibodies to cat, dog, tree, and grass allergens were determined in sera collected from 923 children during the second data collection period. A parental questionnaire was used to screen for risk factors at the onset of the study and again annually, to determine the status of dog and cat ownership from year to year.

Results. The prevalence of sensitization to any allergen increased from 20.6% at 7 and 8 years of age to 30.4% at 11 and 12 years of age. In both age periods, the most common allergen was cat allergen, followed by dog, birch, and timothy grass allergens. The cumulative incidence during the 4-year period was 13.8%. The strongest risk factor for sensitization at 7 to 8 years, as well as development of sensitization during the 4-year period, was a family history of allergy. A significant inverse association between cat and dog ownership and the prevalence of type 1 allergy was found, especially for children living with cats and/or dogs before 7 and 8 years of age, and was most pronounced among children who persistently had lived in a house with a cat.

Conclusions. The authors concluded that, despite the presence of a cockroach- and dust mite-free environment, the incidence of allergic sensitization between the ages of 7 to 8 years and 11 to 12 years was high in northern Sweden. The major risk factor for incident and prevalent cases was a family history of allergy. Although cat allergen was the most common allergen of sensitization, keeping a cat or dog at home was not related to an increased risk of sensitization to these allergens. Therefore, avoiding cats and dogs at home is not protective against sensitization.

Reviewers’ Comments. It should be noted that steps were taken in the analysis of the data to avoid risk for bias of pet ownership selection, in terms of primary prevention (avoidance of pets in a family with a known history of allergy) as well as secondary prevention (removal of pets after allergy diagnosis). Furthermore, although only sensitization was addressed in this article, additional data concerning clinical outcomes within the same longitudinal cohort were published and showed a lower prevalence of asthma among children with cats in the home.

CHILDHOOD FARM ENVIRONMENT AND ASTHMA AND SENSITIZATION IN YOUNG ADULTHOOD

Kilpeläinen M, Terho EO, Helenius H, Koskenvuo M. Allergy. 2002;57:1130–1135

Purpose of the Study. To examine the relationship between childhood farm environments and allergic sensitization and asthma in young adulthood.

Study Population. The 296 participants were Finnish first-year university students (median age, 21.5 years) recruited by questionnaire. One hundred fifty-two subjects (51%) had a history of asthma or wheezing and 144 (49%) had no history of asthma or wheezing.

Methods. Physicians in both pulmonary and dermatology subspecialties, who were blinded with respect to original questionnaire data concerning prior symptoms and farm environment, conducted baseline examinations. Pulmonary function tests and methacholine challenge tests were performed. Participants were considered to have current asthma if they had experienced clinical symptoms consistent with asthma, such as wheezing, cough, associated with typical provoking factors, during the preceding 12 months and the results of methacholine challenge or pulmonary function tests were indicative of asthma. Skin prick tests and allergen-specific immunoglobulin E (IgE) tests with multiple indoor, outdoor, food, and latex allergens were performed. Data were analyzed to examine the effects of childhood farm environments on current asthma and allergic sensitization, with adjustment for early childhood pet ownership.

Results. Approximately 10% of subjects experienced childhood farm environments at 0 to 6 years of age, and the incidence of current asthma in the total study population was 10.7%. Significantly fewer patients with histories of farm environments had current asthma, compared with nonfarm participants (odds ratio [OR]: 0.22, 95% confidence interval [CI]: 0.07–0.70). No difference in bronchial hyperreactivity or skin test reactivity between groups was seen, although trends in favor of childhood farm environments were observed, with less bronchial hyperreactivity and fewer positive skin test results in this group. Farm environments had a protective effect on cat-specific IgE (OR: 0.10; 95% CI: 0.02–0.47), and participants in this group were more likely to have dust mite-specific IgE (OR: 3.29; 95% CI: 1.21–8.96).

Conclusions. Childhood farm environments were protective against asthma in young adulthood. Sensitization to cat allergens was more likely among participants from nonfarm environments, whereas dust mite sensitivity was more common among those from farm environments.

Reviewers’ Comments. Although this study confirms previously described protective effects of farm environments on the development of asthma and allergic sensitization, results should be interpreted cautiously. The number of patients with a history of childhood farm exposure was small, making it difficult to make generalizations about larger populations with similar environmental histories. In addition, the conflicting findings on the protective effects of farm environments against sensitization to cat and dust mite allergens warrant more investigation.

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AIRWAY INFECTIONS IN INFANCY AND THE PRESENCE OF ALLERGY AND ASTHMA IN SCHOOL AGE CHILDREN


**Purpose of the Study.** To determine whether a history of otitis media (OM) and respiratory tract infection (RTI) was associated with allergic sensitization and asthma among school-aged children.

**Study Population.** A total of 4,585 children from 4 cities in Norway were surveyed for this study. Children recruited from 2 cities had the diagnosis of asthma or had wheezed without the diagnosis of asthma in the past 12 months. In the third city, children were randomly recruited. Control groups came from the same areas. The final study population included 502 children with complete data sets. Group 1 (n = 166) included those with current asthma or previous asthma, group 2 (n = 155) included those who had wheezed within the past year but had no diagnosis of asthma, and group 3 (n = 181) included those without asthma or wheezing.

**Methods.** The initial survey was from the International Study of Asthma and Allergies in Childhood. A second clinical study with the study groups investigated early exposures and health outcomes. The children also underwent skin prick testing and clinical examinations. Skin prick testing was performed with house dust mites, mold, animal dander, birch tree pollen, timothy grass pollen, mugwort pollen, cow’s milk, and egg. Questions addressed OM and RTI, all involving recall of physician diagnoses. Information was also obtained about confounders such as breastfeeding, day care, and smoke exposure.

**Results.** The prevalence of allergic sensitization was different among children of atopic parents versus nonatopic parents (49.3% vs 31.9%). The prevalence of OM did not differ significantly between those born of atopic versus nonatopic parents (8.0% vs 7.4%). The associations between OM with or without RTI during infancy and allergic sensitization among school-aged children of atopic parents demonstrated odds ratios of 0.13 and 0.31, respectively. The association between RTI and asthma among school-aged children depended on whether lower RTI was included. Among children of nonatopic parents, a history of RTI/lower RTI was significantly associated with a history of asthma (odds ratio: 4.21). There was no association among children born to atopic parents. Confounding variables had no effect on this relationship.

**Conclusions.** In this study, a history of OM in infancy was negatively associated with allergic sensitization among school-aged children born to atopic parents, whereas a history of lower RTI was positively associated with asthma among children of nonatopic parents.

**Reviewer’s Comments.** The “hygiene hypothesis” has been put forth as a potential explanation for the increase in allergic conditions. Studies on RTIs have yielded inconsistent results with respect to allergic sensitization. However, studies on RTI as a risk factor for asthma seem to be more consistent in their conclusions. The finding of less allergic sensitization among those with OM in infancy is new. The strongest association between subsequent asthma and early childhood infections was found among nonatopic children. This should be an area of continuing investigation, ideally with large prospective studies.

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**Purpose of the Study.** To determine whether breastfeeding has an association with the development of recurrent wheeze, asthma, or both among children up to 72 months of age and whether the duration or exclusivity of breastfeeding has an effect on this association.

**Study Population.** Children (n = 8,261), 2 to 71 months of age, were sampled from the Third National Health and Nutrition Examination Survey, a nationally representative, cross-sectional survey conducted between 1988 and 1994 and designed to provide health estimates for the US population.

**Methods.** Data used in this study were obtained with the Third National Health and Nutrition Examination Survey Household Youth Questionnaire. Data were tested for significant associations between breastfeeding and physician-diagnosed asthma or recurrent wheeze (≥3 episodes of wheeze within the previous 12 months), with and without adjustments for confounding variables.

**Results.** Of the original cohort, 7,766 children had available data on breastfeeding duration, recurrent wheeze, and all covariates. Prevalences of physician-diagnosed asthma and recurrent wheeze were 5.9% and 7.6%, respectively. Approximately one-half of the children were reported to have ever been breastfed. Unadjusted model results showed that children who had ever been breastfed were less likely to be diagnosed with asthma or to have recurrent wheeze, compared with those who had never been breastfed, whereas those were breastfed for a longer time (>4 months) had the lowest odds of asthma or wheeze. After adjustment for potential confounders, these results were not statistically significant. However, the investigators showed that children who had ever been breastfed had a decreased likelihood of recurrent wheeze or asthma before the age of 24 months, compared with children who had never been breastfed. Children with environmental tobacco smoke (ETS) exposure (37.9%) had a higher prevalence of asthma than did those from smoke-free homes. Children between the ages of 2 and 71 months with ETS exposure who had ever been breastfed were less likely to develop recurrent wheeze or asthma than were children who had not been breastfed, especially if the duration was ≥4 months.

**Conclusions.** Breastfeeding might delay the onset of or actively protect children <24 months of age against asthma and recurrent wheeze and might reduce the prevalence of asthma and wheeze among children exposed to ETS.

**Reviewers’ Comments.** Recurrent wheeze and asthma are leading reasons for hospitalization and emergency department visits among children in the United States. Appropriate asthma diagnosis and treatment is especially difficult among children <24 months of age. In addition, ETS exposure is prevalent among young asthmatic patients and can compromise clinical outcomes. This study indicates that breastfeeding may have important effects on asthma and may provide protection from the ill effects of ETS. Broad-based public health strategies are needed to better educate individuals about preventive measures, such as breastfeeding and reduction of ETS exposure.

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520 ALLERGY

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TRANSFORMING GROWTH FACTOR-Î² IN HUMAN MILK IS ASSOCIATED WITH WHEEZE IN INFANCY


Purpose of the Study. To determine whether the cytokines in breast milk could account for some of the apparent protective effects of breastfeeding against wheeze in the first 1 year of life.

Study Population. Mothers and their infants participating in the Infant Immune Study in Tucson, Arizona, were studied.

Methods. Data on breastfeeding and infant wheeze, from birth to 1 year, were collected prospectively from 243 mothers. Breast milk samples obtained at a mean postpartum age of 11 days were assayed, with enzyme-linked immunosorbent assays, for concentrations of transforming growth factor-Î² (TGF-Î²), interleukin-10, tumor necrosis factor-Î±, and the soluble form of CD14. The dose of each cytokine was assessed for a relationship with wheeze, in bivariate and logistic regression analyses.

Results. Greater duration of breastfeeding was significantly associated with decreased prevalence of wheeze (P = .039). There was wide variability in the levels of each cytokine in milk, as well as variability among women in the amount of each cytokine produced. There was a significant inverse association between the dose of TGF-Î² received through milk and the incidence of wheeze (P = .017); the relationship was linear (P = .006). None of the other cytokines showed a linear relationship with wheeze. In multivariate analyses, the risk of wheeze was significantly decreased (odds ratio: 0.22; 95% confidence interval: 0.05–0.89; P = .034) with increasing TGF-Î² dose (long breastfeeding and medium/high TGF-Î² level, compared with short breastfeeding and low TGF-Î² level).

Conclusions. This analysis shows that the dose of TGF-Î² received from milk has a significant relationship with infant wheeze, which might account for at least some of the protective effects of breastfeeding against wheeze.

Reviewer’s Comments. It was previously shown that longer duration of breastfeeding was associated with reduced wheeze in both developing and industrialized countries, but it was unclear which components of breast milk conferred this protective effect. Cytokines secreted in human milk might play important roles in newborn health and in the development of infant immune responses. TGF-Î² has a potent immunosuppressive effect in the gut and acts with interleukin-10 to promote specific immunoglobulin A production, which might reduce susceptibility to both enteric and respiratory infections. A second mechanism might involve effects on infant lung development, because TGF-Î² appears to regulate the signaling mechanisms of proliferation and differentiation of lung cells in mice. More importantly, a single human study found a correlation between breastfeeding and lung function among 124 infants who underwent pulmonary function testing before 6 months of age.

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EFFECT OF PROBIOTIC LACTOBACILLUS STRAINS IN CHILDREN WITH ATOPIC DERMATITIS


Purpose of the Study. To evaluate the clinical and anti-inflammatory effects of probiotic supplementation among children with atopic dermatitis (AD).

Studie Population. Subjects were 43 children (1–13 years of age) in Denmark with known AD.

Methods. A randomized, double-blind, crossover design placed patients into 2 treatment groups, group A (placebo followed by probiotics) and group B (probiotics followed by placebo). Dosing was twice daily for 6 weeks, with a 6-week washout period between treatment arms. The probiotics used included Lactobacillus rhamnosus 19070-2 and Lactobacillus reuteri DSM 12246, strains previously shown to adhere to intestinal mucosa. The placebo was skim milk powder and dextrose. Patients were evaluated 2 weeks before study onset, with the scoring AD (SCORAD) system (consisting of itch score, intensity, and extent of eczema) and measurement of serum immunoglobulin E levels. Skin prick test results and serum immunoglobulin E levels were used to divide patients into allergic and nonallergic groups. At weeks 0, 6, 12, and 18, SCORAD indices, serum eosinophilic cationic protein levels, and cytokine (interleukin-2, interleukin-4, interleukin-10, and interferon-Î³) levels were measured. Subjective evaluations of the status of AD were obtained from patients/parents at 6, 12, and 18 weeks. Patients continued to receive topical corticosteroids, with the quantity of medication being recorded at each visit.

Results. The SCORAD indices at study onset were 18 to 64 (scale: 0–80), indicating moderate to severe AD in the study groups. Thirty-nine patients completed subjective evaluations, with 22 (56%) indicating improvement after active therapy, compared with 6 (15%) after placebo. In the total study group (n = 43), a 24.7% reduction in the extent of eczema after active treatment was seen (P = .02), whereas itch scores and intensity only trended toward lower values. The overall SCORAD index improved slightly during active treatment (from a score of 35.6 to 31.6, P = .06), but no improvement was seen with placebo. For patients whose subjective evaluations indicated improvement during active treatment, the total SCORAD index was significantly improved, compared with placebo (P < .0001). Serum eosinophilic cationic protein levels decreased during active treatment, compared with placebo (P = .03). Cytokine levels did not change during any treatment. In the allergic group (n = 27), the total SCORAD index and the extent of disease score both decreased (P = .04 and P = .008, respectively). Topical corticosteroid use was similar for all patients.

Conclusions. The use of probiotic Lactobacillus strains produced improvement in moderate to severe eczema, with respect to both subjective evaluations and extent of eczema. Results were more pronounced in the allergic group.

Reviewers’ Comments. This study supports current evidence that intestinal inflammation and subsequent disruption of the intestinal mucosa occur in AD and that probiotics may work to reduce intestinal inflammation. The results indicate another therapy for the treatment of AD. The long-term effectiveness of probiotic use for treatment of AD remains to be addressed.

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THE EFFECT OF HYDROLYZED COW’S MILK FORMULA FOR ALLERGY PREVENTION IN THE FIRST YEAR OF LIFE: THE GERMAN INFANT NUTRITIONAL INTERVENTION STUDY, A RANDOMIZED, DOUBLE-BLIND TRIAL


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Purpose of the Study. Feeding extensively or partially hydrolyzed formulas to infants might reduce their risk of developing allergic disorders, but the scope of benefit remains unclear. The authors sought to assess the preventive effect of different hydrolyzed formulas versus cow’s milk in a prospective study among high-risk infants.

Study Population. The subjects were 2252 infants with hereditary risk of atopy, defined as at least 1 biological parent or sibling with an allergic disease.

Methods. Infants were randomly assigned at birth, in a blinded manner, to 1 of 4 formulas, ie, cow’s milk formula (CMF), partially hydrolyzed whey formula, extensively hydrolyzed whey formula, or extensively hydrolyzed casein formula (eHF-C). However, all mothers were encouraged to breastfeed exclusively for the first 4 to 6 months. Study formula was provided for the first 6 months. Avoidance of solid foods for the first 4 months was advised, with subsequent avoidance of cow’s milk, eggs, soy, fish, peanuts, nuts, tomatoes, and citrus fruits during the first year. Mothers maintained diaries of milk sources for the first 6 months. Children were examined at 1, 4, 8, and 12 months of age. The primary end point at 1 year of age was the presence of allergic manifestation, which was defined as atopic dermatitis (AD), gastrointestinal manifestations of food allergy, allergic urticaria, or a combination of these. Both immunoglobulin E-mediated and non—immunoglobulin E-mediated reactions were considered for gastrointestinal manifestations of food allergy, and symptoms needed to disappear with elimination of the suspected formula and to recur with challenge for diagnosis. Asthma and allergic rhinitis were excluded from consideration as allergic manifestations, because diagnoses are usually difficult to establish in the first year of life.

Results. Of the 2252 infants enrolled, 889 were exclusively breastfed for the first 4 months, whereas 865 were monitored for the entire study period. Of the 1249 infants assigned to a study formula, 418 left before completion of enrollment data, left thereafter, or were excluded because of noncompliance. A total of 945 infants who adhered to the study formula protocol for the entire 12 months remained. Among the hydrolyzed formulas, only eHF-C was associated with a significant decrease in allergic manifestations, compared with CMF. However, when the outcome of AD was analyzed specifically, both eHF-C and partially hydrolyzed whey formula were associated with more favorable outcomes, compared with CMF. A family history of AD was associated with lesser benefit, with only eHF-C approaching statistical significance, compared with CMF (P = .077). The results for exclusively breastfed infants were not included in the analysis, because it was not possible to randomize to breastfeeding for ethical reasons and mothers who chose to nurse differed from the mothers of formula-fed infants with respect to important variables, including greater family prevalence of AD, less smoking, and fewer pets.

Conclusions. The expression of allergic diseases in the first year of life is favorably modified by the use of less allergenic milk sources, especially in the absence of a family history of AD. Individual hydrolysate formulas must be studied more extensively in this role.

Reviewer’s Comments. The findings of this study are consistent with various observations on the role of hypoallergenic formulas in ameliorating allergic disease early in life. Of course, this study was not designed to look beyond the first year of life, and most evidence to date suggests that the protective benefits of such early food allergen avoidance are limited to AD and immunologic reactions to food proteins, without significant effects on lifetime risks for asthma and allergic rhinitis.

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THE RELATIONSHIP BETWEEN EXHALED NITRIC OXIDE AND ALLERGIC SENSITIZATION IN A RANDOM SAMPLE OF SCHOOLCHILDREN


Purpose of the Study. To determine whether there is a relationship between levels of exhaled nitric oxide (eNO) and sensitization to common allergens.

Study Population. A convenience sample of 450 schoolchildren (7–12 years of age), of a total random sample of 2504 children in the Netherlands, were enrolled.

Methods. Children were recruited from 7 public schools and were assessed for allergen sensitization with skin prick testing and/or specific immunoglobulin E (IgE) radioallergosorbent testing (RAST) with common environmental allergens, including dust mite, cat, tree, grass, dog, and mold allergens. eNO was measured with a standard protocol. Families were also asked to complete a questionnaire regarding the home environment, family composition, education, and passive smoke exposure. Associations between eNO levels and sensitization to common allergens were analyzed with adjustments for age, gender, gas cooking, unvented water heaters, passive smoke exposure, and having a cold during sampling.

Results. Of the total 450 children studied, 9% had a lifetime history of asthma, with 10% reporting wheeze in the previous year, 8.2% had a history of hay fever, and 29.1% had a history of eczema ever. Of the 319 children who underwent skin prick testing, 29.5% had 1 positive test result, 21.9% for indoor allergens and 15% for outdoor allergens. Of the 229 children who underwent specific IgE RAST, 32.3% had 1 positive test result, 23.1% for indoor allergens and 21.8% for outdoor allergens. The geometric mean level of eNO was ~1.5 times higher among children sensitized to indoor allergens, compared with nonsensitized children (P < .05), and this was increased to 2 times higher when a cutoff value of ≥2 positive tests was used for either indoor or outdoor allergen sensitivity. eNO levels gradually increased with increases in positive allergen tests. There was no association between eNO levels and current pet ownership. The association between allergen sensitization and eNO was much stronger among children with a history of wheezing, compared with children without wheezing (relative increases of 1.24–1.47 among non-wheezees and 1.56–3.44 among wheezees).

Discussion. This study found a positive association between eNO levels and levels of allergen sensitivity in a random sample of schoolchildren in the Netherlands. The association was stronger among children with sensitization to indoor allergens and children with a history of wheezing. Association with sensitization to outdoor allergens was not as strong, which the authors proposed might be related to the larger particle size of pollens preventing their entry into lower airways. The mechanism of these elevated eNO levels is not known, but the authors proposed that exposure to allergens could lead to inflammatory changes in the lower airway without causing signs of clinical asthma.

Conclusion. The authors concluded that allergen sensitization was associated with elevated levels of eNO in a random sample of children, most without outward signs of asthma.
FOOD ALLERGY

FACTORS ASSOCIATED WITH THE DEVELOPMENT OF PEANUT ALLERGY IN CHILDHOOD


Purpose of the Study. Because peanut allergy has increased in prevalence and is an important cause of life-threatening reactions, the authors sought to investigate possible determinants of peanut allergy.

Study Population. Data were obtained from the Avon Longitudinal Study of Parents and Children. This geographically defined cohort included 13,971 preschool-aged children. Forty-nine of those children had a history of peanut allergy. Thirty-six of those 49 underwent skin testing, and 29 demonstrated positive results. Peanut allergy was confirmed for 23 children with double-blind, placebo-controlled, food challenge.

Methods. Pregnant women were enrolled and questioned about their allergy history before delivery and were given serial questionnaires throughout their children’s infancy and childhood. The authors prospectively identified 49 children with a history of reactions to peanuts. Twenty-three children were then confirmed as being allergic to peanuts with skin testing and double-blind, placebo-controlled, food challenge. There were 2 control groups, including children with eczema in the first 6 months of life whose mothers also had eczema and 140 children without allergic reactions with formal peanut challenge at the start of the study, were studied.

Results. Peanut allergy was found to be independently associated with eczematous dermatitis (rash over joints and creases or oozing crusted rash) in the first 6 months of life, intake of soy products, family history of peanut allergy, and the use of skin preparations containing peanut oil. Neither maternal peanut consumption during pregnancy and lactation nor duration of breastfeeding was found to be associated with the development of peanut allergy. Additional evidence not supporting previous concepts of in utero sensitization came from undetectable peanut-specific IgE and normal total IgE levels in cord blood.

Conclusions. Sensitization to peanut antigens appeared to be through inflamed atopic skin, rather than via the gastrointestinal tract, possibly from the use of skin preparations with even trace amounts of peanut oil. With respect to the independent association between intake of soy products and peanut allergy, soy protein fractions have shown homology to major peanut proteins and cross-sensitization could result from exposure to a common T cell epitope.

Reviewer’s Comments. eNO has been shown in many studies to be a useful marker of inflammation among asthmatics, but this study demonstrated an association between atopy and eNO levels. It has been suggested that eNO may be a useful screening test for asthma, and perhaps some of these asymptomatic atopic patients are evolving asthmatics. Although eNO devices have received Food and Drug Administration approval, their cost has limited their use to research settings to date.

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EFFECT OF ANTI-IMMUNOGLOBULIN E THERAPY FOR PATIENTS WITH PEANUT ALLERGY


Purpose of the Study. To determine whether subcutaneous administration of a humanized anti-immunoglobulin E (IgE) antibody, TNX-901, raises the threshold of sensitivity to peanuts among patients with peanut allergy.

Study Population. Eighty-four patients between 12 and 60 years of age, with a history of allergic reactions to peanuts, total IgE levels between 30 and 1000 IU/mL, positive skin prick tests for peanuts, and documented reactions with formal peanut challenge at the start of the study, were studied.

Methods. A randomized, double-blind, placebo-controlled, dose-range study was performed. During the screening process, peanut allergy was confirmed and the threshold for reactivity was determined with a double-blind, placebo-controlled, oral food challenge with encapsulated peanut flour. Patients were subsequently randomized to receive subcutaneous injections of placebo or TNX-901 (150, 300, or 450 mg) at 4-week intervals, for a total of 4 doses. Two to 4 weeks after the initial injection, a final peanut challenge was performed, to determine the threshold of reactivity to peanuts after the treatments. Serum samples were obtained at 4-week intervals, to monitor trough total IgE levels.

Results. From mean baseline thresholds of sensitivity of 178 to 436 mg of peanut flour in the various groups, the mean increases in the oral food challenge threshold were 710 mg in the placebo group, 913 mg in the group given 150 mg of TNX-901, 1650 mg in the group given 300 mg of TNX-901, and 2627 mg in the group given 450 mg of TNX-901 (P < .001 for comparison of the 450-mg dose with placebo; P < .001 for trend with increasing dose). Patients who received 450 mg had a mean threshold of reactivity of 2805 mg of peanut protein (equivalent to ~9 peanuts), compared with 178 mg (equivalent to one half of a peanut) before the injections.

Conclusions. Subcutaneous administration of TNX-901 increases the threshold of reactivity to peanuts in a dose-dependent manner, which may translate into protection against most accidental ingestions of peanuts.
ANAPHYLAXIS

RISK OF ANAPHYLAXIS AFTER VACCINATION OF CHILDREN AND ADOLESCENTS


Purpose of the Study. Anaphylaxis is a risk of vaccination. This study retrospectively quantified the risk in a population of pediatric patients.

Study Population. Children and adolescents enrolled in 4 West Coast health maintenance organizations that participated in the Vaccine Safety Data Link Project between 1991 and 1997 were studied.

Methods. A total of 7,644,049 vaccine doses were administered to 2,226,907 children between the ages of 0 and 17 years at 3 sites and between 0 and 6 years at a fourth site. Potential cases of anaphylaxis were identified by using International Classification of Diseases, 9th revision, codes suggesting anaphylaxis. A total of 657 cases were reviewed, of 664 cases of interest. Missing chart information excluded 7 cases. Criteria including organ systems involved in reactions, timing of reactions after vaccination, and treatments were reviewed, to identify possible or probable cases of anaphylaxis. Two analyses were performed. One included all sites, and 1 included a single site for which more detailed data on outpatient diagnoses were available.

Results. Six possible cases of anaphylaxis were identified. After a more detailed chart review, 2 cases were considered unlikely to be anaphylaxis, 1 case was unlikely to be secondary to vaccination, and 1 case of anaphylaxis predated and was not attributable to vaccination. The final risk of anaphylaxis was calculated as 0.26 case per 1,000,000 doses (2 cases per 7,644,049 doses). At the single site with more complete data on outpatient diagnoses, a risk of 1.53 cases per 1,000,000 doses was calculated. Rates for individual vaccines ranged from 0 to 14.4 cases per 1,000,000 doses. Most reactions were seen with diphtheria- and tetanus-containing vaccines, hepatitis B vaccine, measles-mumps-rubella vaccine, and oral polio vaccine. These vaccines were also more commonly administered. No reactions were seen with diphtheria-tetanus-acellular pertussis vaccine, influenza vaccine, inactivated polio vaccine, adult diphtheria-tetanus vaccine, hepatitis A vaccine, or varicella vaccine. However, these vaccines were less commonly administered. No deaths resulted from the anaphylactic episodes. No association was made with atopic status.

Conclusions. The frequency of vaccine-associated anaphylaxis is very low. Nonetheless, providers should be prepared to provide immediate treatment should it occur.

Reviewer’s Comments. Vaccination remains one of the most effective preventative treatments provided for children. Some advocates for better access to vaccination lobby for administration of vaccines at locations where acute health care is absent (eg, pharmacies). Although the risk of anaphylaxis is extremely low, it is not negligible. Providers of vaccines must be prepared to provide immediate treatment if anaphylaxis should occur, and society must determine when the need for vaccine access outweighs this risk.

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ANAPHYLAXIS: RISK FACTORS FOR RECURRENCE

Mullins RJ. Clin Exp Allergy. 2003;33:1033–1040

Purpose of the Study. To determine the incidence of anaphylaxis and risk factors for recurrence.

Study Population. Four hundred thirty-two patients with anaphylaxis who were referred to a community-based specialist practice in the Australian Capital Territory were studied. Twenty-seven percent were of school age (5–18 years of age).

Methods. Patients referred to an allergist for evaluation of anaphylaxis were enrolled during a 5.5-year period and evaluated prospectively. Medical record review, patient questionnaires, allergy skin testing, and challenge testing (for a small subset of patients) were used.

Results. Of 432 patients (48% male, 73% atopic; mean age: 27.4 years; SD: 19.5 years; median: 26 years) with anaphylaxis, 260 patients were examined after the first episode; 172 experienced 584 previous reactions. Fifty-four percent of index episodes were treated in a hospital. Causes were identified for 91.6% of patients, ie, food (61%), stingings insects (20.4%), or medication (8.3%). The minimal occurrence and incidence of new cases of anaphylaxis were estimated as 12.6 and 9.9 episodes/100,000 patient-years, respectively. Follow-up data were obtained for 304 patients (674 patient-years). One hundred thirty patients had additional symptoms (45 serious), 35 required hospitalization, and 19 were administered epinephrine. Accidental ingestion of peanuts or tree nuts caused the largest number of relapses, but the highest risk of recurrence was associated with sensitivity to wheat and/or exercise. Rates of overall and serious recurrence were 57 and 10 episodes/100 patient-years, respectively. Among patients prescribed epinephrine, three-fourths of the patients carried it, two-thirds of the doses were in a date, and only one-half of the patients faced with serious symptoms administered epinephrine. Five patients developed new triggers for anaphylaxis.

Conclusions. In any 1 year, 1 of 12 patients who have suffered anaphylaxis will experience recurrence and 1 of 50 will require hospital treatment or will use epinephrine. Compliance with carrying and using epinephrine is poor. Patients occasionally develop new triggers.

Reviewer’s Comments. There are few studies on the incidence or recurrence of anaphylaxis, but the limited data suggest that the incidence of anaphylaxis and food allergy...
are increasing. In this study, allergic reactions to peanuts and tree nuts were the most common cause of anaphylaxis and the most common reason for recurrence, but other foods, such as eggs, fruits, vegetables, wheat, fish, and shellfish, were also common triggers. Compliance with the use of self-injectable epinephrine was only 50%. Because of the high risk of recurrence, each anaphylactic event should be reviewed and patients should be reeducated regarding trigger avoidance, recognition of symptoms, and use of epinephrine.

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The Upper Airway

LACK OF EFFECT OF FLUTICASONE PROPIONATE AQUEOUS NASAL SPRAY ON THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS IN 2- AND 3-YEAR-OLD PATIENTS


Purpose of the Study. To determine the effects of fluticasone propionate (FP) (200 μg daily) on the hypothalamic-pituitary-adrenal (HPA) axis among patients 2 to 3 years of age.

Study Population. Children 2 to 3 years of age who demonstrated positive skin test responses to ≥1 seasonal allergen and the presence of nasal symptoms for ≥1 hour daily on most days or the use of rhinitis medication on most days during the relevant allergen exposure season were studied.

Methods. Children were administered FP (200 μg daily) (N = 33) or vehicle placebo (N = 32) for 6 weeks. Twelve-hour urine samples were collected, for determination of urinary cortisol levels, at the end of the 6-week treatment and at baseline. Routine chemical analyses, hematologic assessments, and electrolyte measurements were also performed at screening and at the last treatment visit. The secondary safety measures included the incidence of clinically significant alterations in laboratory test results, in the case of adverse effects.

Results. There were no differences in urinary cortisol levels between the children who received FP and those who received placebo. The most common adverse events reported for either group were cough and fever. Vomiting was observed more frequently for the FP group (18% vs 0%). However, there were no statistically significant differences in any of these findings.

Conclusions. FP (200 μg/day) was equivalent to placebo with respect to its effects on HPA axis function, as determined by 12-hour urinary free cortisol levels, among 2- to 3-year-old children. FP was otherwise well tolerated by these 2- to 3-year-old children with allergic rhinitis.

Christopher Randolph, MD
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EFFICACY OF THE TOPICAL NASAL STEROID Budesonide ON IMPROVING SLEEP AND DAYTIME SOMNOLENCE IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS


Purpose of the Study. To determine the efficacy of topical nasal corticosteroids in the improvement of sleep and daytime somnolence among patients with perennial allergic rhinitis (PAR).

Study Population. Twenty-two subjects (18–65 years of age) with positive skin test responses to perennial allergens but not seasonal allergens were enrolled in the study.

Methods. The study was a double-blind, placebo-controlled, crossover study that incorporated Balaam’s design. Patients were randomized to 1 of 4 treatment groups, ie, active-placebo, placebo-active, active-active, or placebo-placebo. Patients received 2 sprays of the active medication (budesonide, 128 μg/day) or placebo once daily for 4 weeks. After a 1-week washout period, patients crossed over to the second arm of the study, according to the randomization sequence. Patients completed daily diaries, commenting on nasal symptoms, sleep, daytime somnolence, quality of sleep, and medication response. At weeks 1, 4, 5, and 8, patients completed subject questionnaire during clinic visits, to assess quality of life, somnolence, and fatigue.

Results. Analyses of data obtained from the daily diaries showed that patients receiving active medication demonstrated significant improvements in daytime fatigue, somnolence, sleep problems, and quality of life, compared with those receiving placebo. There was no significant difference in nasal congestion or other symptoms of rhinitis between the treatment groups. Patients receiving active medication were significantly less likely to fall asleep during normal daily activities, but there was no difference in the numbers of hours of sleep or nighttime arousals. Those in the active group also had significantly more restorative sleep and reported feeling more refreshed, compared with those receiving placebo.

Conclusions. Patients with PAR who were receiving the topical nasal corticosteroid budesonide demonstrated significant improvements in daytime somnolence, fatigue, and sleep problems.

Reviewers’ Comments. Patients with allergic rhinitis frequently complain of nocturnal symptoms, such as nasal congestion and rhinorrhea, that interfere with sleep, and previous studies showed that patients with allergic rhinitis have significantly more difficulty with daytime somnolence and sleep problems. This study offers encouraging data on the usefulness of topically applied nasal corticosteroids in improving sleep-related problems among patients with PAR and provides more evidence supporting the recommendation of topically applied nasal corticosteroids as the primary treatment for allergic rhinitis.

Tamara T. Perry, MD
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Baltimore, MD

THE EFFECTS OF INTRANASAL TRIAMCINOLONE ACETONIDE AND INTRANASAL FLUTICASONE PROPIONATE ON SHORT-TERM BONE GROWTH AND HYPOTHALAMIC-PITUITARY-ADRENAL AXIS IN CHILDREN WITH ALLERGIC RHINITIS

**Purpose of the Study.** To evaluate the effects of triamcinolone acetone (TAA) and fluticasone propionate (FP) aqueous nasal sprays on short-term, lower-leg growth velocity and hypothalamic-pituitary-adrenal (HPA) axis function among pediatric subjects.

**Study Population.** The subjects were 59 children (4–10.5 years of age) who were within normal limits for height and had a ≥1-year history of allergic rhinitis that required treatment and positive prick skin test responses to an inhalant allergen. Patients who had used corticosteroids in the previous 60 days were excluded from the study.

**Methods.** The study was a randomized, 4-way, crossover trial comparing 2 doses of TAA nasal spray, 1 dose of FP nasal spray, and placebo among pediatric patients with perennial allergic rhinitis. The study was conducted from October 1998 through September 1999, at Children’s Hospital of Pittsburgh (Pittsburgh, PA). After a 2-week baseline period, subjects entered 4 treatment periods, each lasting 2 weeks, with a 2-week washout period between treatments. Lower-leg growth velocity was measured kinemetrically. HPA axis function was assessed by measuring 12-hour (overnight) urine samples for cortisol/creatinine ratios. Three clinic visits occurred during each treatment period.

**Results.** Of the 59 subjects, 49 completed the study in all 4 treatment periods. Four subjects discontinued participation because of adverse events (110-mcg TAA group: broken foot, nasal burning sensation, asthma exacerbation; placebo group: asthma exacerbation), 3 were lost to follow-up monitoring, 1 withdrew consent, and 2 were non-compliant. In terms of lower-leg growth velocity, no differences were found between either dose of TAA and FP or between the treatment group and the placebo group. In terms of HPA axis function, the urinary cortisol/creatinine ratios from the beginning to the end of the 2-week treatment period did not differ significantly between the TAA doses and placebo; however, the mean value for the FP group was lower than that seen for all other treatment groups (statistically significant). Because the coefficient of variation for the cortisol measurements was quite high, the clinical relevance of this finding is unclear.

**Conclusions.** This study showed that daily use of nasal sprays with TAA at 110 μg, TAA at 220 μg, or FP at 200 μg did not produce any clinically meaningful effects on lower-leg growth velocity during the 2 weeks of treatment. FP was shown to produce a statistically significant level of HPA axis suppression, compared with placebo; however, the clinical relevance of this finding is unclear.

**Reviewer’s Comments.** Many pediatricians and parents have concerns regarding the effects of corticosteroid use, whether for treatment of allergic rhinitis (as a nasal spray) or for treatment of asthma, on the growth and HPA axis function of children. This study provides additional reassurance that short-term use of nasal corticosteroid sprays at standard doses does not affect growth or the HPA axis.

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**INTRACAPSULAR TONSILLAR REDUCTION (PARTIAL TONSILLECTOMY): REVIVING A HISTORICAL PROCEDURE FOR OBSTRUCTIVE SLEEP-DISORDERED BREATHING IN CHILDREN**


**Purpose of the Study.** To compare the safety and efficacy of intracapsular tonsillar reduction (partial tonsillectomy) with those of conventional tonsillectomy for treating obstructive sleep-disordered breathing among children.

**Study Population.** The authors reviewed the medical records for a total of 350 children who underwent either partial (243 children) or standard (107 children) tonsillectomy for treatment of obstructive sleep-disordered breathing. The diagnosis of sleep-related obstruction was made on the basis of history findings.

**Methods.** This was a retrospective chart review of patient records for all children with obstructive sleep-disordered breathing who underwent either partial or standard tonsillectomy, performed by 1 of 3 primary surgeons. The choice of surgical technique was made by the parents, who were told that the new partial tonsillectomy might be associated with less postoperative discomfort but might have a greater chance of recurrence, compared with standard tonsillectomy. Subjective assessments of outcomes and quality of life, recorded in a telephone survey of parents, included postoperative pain assessment, measurement of the days to return to a normal diet, measurement of analgesic use, and assessment of relief of sleep-related obstructive symptoms. Analyses of patient records included measurements of operative time, estimated blood loss, and incidence of delayed postoperative complications, such as bleeding and tonsil regrowth. Partial tonsillectomy was performed by using a microdebrider to remove the bulk of the tonsil tissue while leaving the surrounding capsule intact. Standard tonsillectomy was performed by using electrocautery to remove the palatine tonsils and their capsules in their entirety.

**Results.** The children who underwent partial tonsillectomy were younger than those who underwent standard tonsillectomy (mean age: 6.1 years vs 9.1 years; *P* < .001). The children who were treated with the new technique experienced significantly less postoperative pain, fewer days to normal activity and diet, and less analgesic use, compared with the children who underwent standard tonsillectomy. Partial tonsillectomy was associated with small but significantly greater intraoperative blood loss, after adjustment for patient age, and the new procedure required a slightly longer time to perform (an average of 3 minutes longer for experienced surgeons). The microdebrider instrumentation was more expensive than that used for conventional tonsillectomy. The frequency of delayed postoperative bleeding appeared lower with partial tonsillectomy (4.7% and 1.7% for standard and partial tonsillectomy, respectively), but this difference was not statistically significant. Quality of life measurements showed similar rates of improvement for children treated with the 2 procedures, with >93% of the parents in both groups reporting marked improvements after surgery. Tonsillar regrowth after partial tonsillectomy was not observed for any patient during the 2-year follow-up period.

**Conclusions.** Partial tonsillectomy is a safe reliable technique that results in less postoperative pain, more rapid return to normal function, and equivalent improvements in sleep-related airway obstruction and quality of life, compared with standard tonsillectomy, among children.

**Reviewers’ Comments.** The most common indication for adenotonsillectomy among children is an obstructive sleep disorder. Tonsillectomy is associated with considerable postoperative discomfort and a small but finite risk of perioperative bleeding. The authors support the concept that subtotal tonsil removal (usually combined with adenoidectomy) may be curative, with less postoperative pain and other morbidities. This study has the limitations of all retrospective analyses. The study groups may not be directly comparable, because of selection biases. Additional
bias may occur with telephone surveys of patients and families after a surgical procedure. Finally, the diagnosis of obstructive sleep-disordered breathing on the basis of history findings, with similar assessments of improvement after surgery, does not have the quantitative accuracy of preoperative and postoperative polysomnographic evaluations. Despite these limitations, this study succeeded in showing that intracapsular tonsillar reduction (partial tonsillectomy) shows great promise as a safe effective treatment for children with obstructive sleep-disordered breathing and appears to cause less morbidity than standard tonsillectomy. Additional studies with more long-term follow-up monitoring are required to assess the recurrence rates for both obstructive and infectious tonsillar disease, after this procedure is performed among young children.

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Asthma

PATHOPHYSIOLOGY

EARLY THICKENING OF THE RETICULAR BASEMENT MEMBRANE IN CHILDREN WITH DIFFICULT ASTHMA


Purpose of the Study. To determine whether reticular basement membrane (RBM) thickening is present among children with difficult-to-control asthma and to compare the findings with those for adults with asthma.

Study Population. Subjects were 19 children (6–16 years of age) with difficult-to-control asthma. Control subjects were 10 children (7–16 years of age) without asthma, 10 adults with mild asthma, 6 adults with severe asthma, and 8 healthy adults.

Methods. The 19 asthmatic children underwent bronchoscopy and endobronchial biopsy as part of an asthma evaluation. Patients were treated with oral prednisolone therapy (40 mg/day) for 2 weeks before the biopsy. Exhaled nitric oxide levels were measured before and after the course of corticosteroids. Endobronchial samples were obtained from third-order or higher bronchi on either side of the lung. The control subjects were pediatric patients undergoing bronchoscopy because of other indications. The adults with mild asthma were corticosteroid-naive. Adults with severe asthma underwent biopsy while intubated because of a severe asthma attack. The 8 adult control subjects were nonsmokers. Three biopsy specimens for each patient were fixed immediately and stained for light-microscopic evaluation.

Results. Children with asthma had an average RBM thickness of 8.2 μm (range: 5.4–11.2 μm). Adults with mild asthma had a mean RBM thickness of 8.1 μm (range: 5.8–10.0 μm); adults with severe asthma had a mean RBM thickness of 7.2 μm (range: 2.8–10.0). Adult control subjects had an average RBM thickness of 4.4 μm (range: 3.2–6.3 μm; P < .01); pediatric control subjects had an average RBM thickness of 4.9 μm (range: 3.7–8.3 μm; P < .01). There was no correlation of RBM thickness with duration of asthma or age. The exhaled nitric oxide concentrations before and after prednisolone treatment were 16.9 ppb (range: 1.2–33.4 ppb) and 8.1 ppb (range: 1.3–24.5 ppb), respectively (normal values at the study center: <12.5 ppb). There was no correlation between RBM thickness and exhaled nitric oxide levels.

Conclusions. The authors concluded that RBM thickening is a feature of childhood asthma that is not present among normal control subjects. RBM thickening is a common feature of asthma among adults and children but is not correlated with age, severity, or duration.

Reviewer’s Comments. This study demonstrated that histologic changes in the airways of children with severe asthma, as evidenced by RBM thickening, are similar to those seen among adults. This is one of the few such studies among children and is novel for the inclusion of child and adult control subjects. The authors were unable to show a link between RBM thickness and severity of asthma or a marker of inflammation (exhaled nitric oxide). This information raises questions regarding the timing and appropriateness of antiinflammatory treatment delivered with the hope of preventing airway remodeling among children with asthma. Clinical trials are needed to establish whether it is possible to prevent these changes and whether such prevention is important.

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LIPOPOLYSACCHARIDE-ENHANCED, TOLL-LIKE RECEPTOR 4-DEPENDENT, T HELPER CELL TYPE 2 RESPONSES TO INHALED ANTIGEN


Purpose of the Study. To evaluate the dose-dependent effects of lipopolysaccharide (LPS) (endotoxin) inhalation and LPS-induced activation of toll-like receptor 4 (TLR4) on the generation of T helper (Th) cell type 2-dependent allergic inflammatory responses to an inhaled antigen, ovalbumin (OVA).

Study Population. Wild-type or TLR4-deficient, 6- to 10-week-old, female mice were studied.

Methods. Mice were sensitized with intranasal exposure to LPS-depleted OVA or OVA with either a low (0.1 μg) or high (100 μg) dose of LPS. After intranasal OVA challenge, pulmonary inflammatory responses were assessed through enumerating bronchoalveolar lavage cells, performing histopathologic analyses, measuring OVA-dependent cytokine production by lung-draining lymph node cells, and determining OVA-specific serum antibody levels. Dendritic cell responses to OVA with LPS were evaluated in cytokine production, activation marker expression, and cell migration studies.

Results. After antigen challenge, mice sensitized to OVA with low-dose LPS exhibited a Th2-associated response, with pulmonary eosinophilia, airway mucus secretion, Th2 cytokine (interleukin-5 and -13) production by lymph node cells, and production of high levels of OVA-specific immunoglobulin E and immunoglobulin G1. In contrast, mice sensitized to OVA with high-dose LPS developed a Th1-associated response, with a predominance of neutrophils, no airway mucus secretion, Th1 cytokine (interferon-γ) production by lymph node cells, and production of high levels of OVA-specific immunoglobulin G2a. No pulmonary inflammatory responses were observed with mice sensitized to LPS-depleted OVA. OVA sensitization of TLR4-deficient mice with either low- or high-dose LPS failed to generate inflammatory responses. However, treatment with tumor necrosis factor, which is secreted by LPS-stimulated dendritic cells, compensated

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for deficient dendritic cell activation, restoring the responses of TLR4-deficient mice to OVA with either low- or high-dose LPS.

Conclusions. The authors concluded that inhalation of low doses of LPS with OVA antigen was necessary to induce allergic or Th2-dependent responses in the lung, whereas inhalation of high doses of LPS with antigen induced nonallergic or Th1-dependent responses. The LPS-mediated effects on allergic sensitization were dependent on signaling through TLR4 on dendritic cells.

Reviewers’ Comments. The effects of endotoxin exposure on the development of atopy and asthma are seemingly paradoxical. Although studies show that exposure to endotoxin early in life inhibits the development of asthma and atopic disease, other studies demonstrate adverse effects of endotoxin on airway function. Although endotoxin is ubiquitous in children’s environments, the exposure level can vary and may be the factor influencing the development of atopy. For example, this dosage effect may help explain the protection from atopy associated with growing up on a farm, where endotoxin exposure is excessive. The results of this study are an intriguing advance toward understanding the basis for these conflicting data, suggesting a mechanism through which the dose of endotoxin present during ovalbumin exposure could influence the incidence of allergic sensitization.

Louis A. Rosenthal, PhD
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ESSENTIAL ROLE OF NATURAL KILLER T CELLS PRODUCING INTERLEUKIN-4 AND INTERLEUKIN-13 IN THE DEVELOPMENT OF ALLERGEN-INDUCED AIRWAY HYPERREACTIVITY


Purpose of the Study. To determine the role of natural killer T (NKT) cells in the development of asthma.

Methods. NKT cell-deficient mice were used to determine the relative contribution of NKT cells to the development of T helper type 2 (Th2) responses and allergen-induced airway hyperreactivity (AHR).

Results. The investigators found that AHR, a cardinal feature of asthma, did not develop in the absence of NKT cells. The failure of NKT cell–deficient mice to develop AHR was not attributable to an inability of the mice to produce Th2 responses, because NKT cell-deficient mice that were immunized subcutaneously at nonmucosal sites produced normal Th2-biased responses. The failure to develop AHR could be reversed with the adoptive transfer of tetramer-purified NKT cells producing interleukin-4 and interleukin-13 to Jα281−/− mice, which lack the invariant T-cell receptor of NKT cells, or with the administration to Cal days −/− mice of recombinant interleukin-13, which directly affects airway smooth muscle cells.

Conclusions. Pulmonary NKT cells crucially regulate the development of asthma and Th2-biased respiratory immunity against nominal exogenous antigens. Therapies that target NKT cells may be clinically effective in limiting the development of AHR and asthma.

Reviewer’s Comments. The contribution of different cell types to the development of asthma is an area of intense interest. This elegant study points to the likely importance of NKT cells in the development of allergen-induced airway hyperreactivity, a cardinal feature of asthma.

Robert A. Wood, MD
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THE ROLE OF INTERLEUKIN-13 IN ESTABLISHED ALLERGIC AIRWAY DISEASE


Purpose of the Study. To determine the effects of blocking interleukin-13 (IL-13) on early- and late-phase airway responses in previously sensitized and challenged mice.

Study Population. Ovalbumin-sensitized and -challenged mice were studied.

Methods. Ten- to 12-week-old mice were sensitized with intraperitoneal injections of ovalbumin on days 1 and 14 and then challenged with nebulized ovalbumin for 3 days on days 28 to 30. The mice received a second challenge of nebulized ovalbumin 6 weeks after the first challenge, to assess inflammatory and histologic outcomes, airway reactivity, and early- and late-phase responses. A soluble fusion protein consisting of the extracellular domain of the high-affinity IL-13 receptor (IL-13R) and human immunoglobulin G (hIgG) (sIL-13Ra2-hlgG) was administered 24 hours and 1 hour before the second ovalbumin challenge, when early- and late-phase responses, respectively, were assessed, and was also administered 24 hours after the challenge, when inflammatory and histologic outcomes and airway reactivity at 48 hours were assessed. hlgG was administered to control mice.

Results. Levels of IL-13 in bronchoalveolar lavage (BAL) fluid were increased after the second ovalbumin challenge in previously sensitized mice, and sIL-13Ra2-hlgG significantly reduced BAL fluid levels of IL-13. The sIL-13Ra2-hlgG fusion protein also inhibited the development of the late-phase response but not the early-phase response. Airway hyperresponsiveness, assessed as changes in lung resistance and dynamic compliance after methacholine inhalation, was inhibited by sIL-13Ra2-hlgG fusion protein. sIL-13Ra2-hlgG decreased the number of cells in BAL fluid, particularly eosinophils, but did not completely eliminate them. Treatment with sIL-13Ra2-hlgG significantly reduced BAL fluid levels of IL-5 but not interferon-γ, IL-12, or IL-10.

Conclusions. IL-13 appears to play a critical role in the development of the late-phase response in previously sensitized mice. Blockade of IL-13 may be an important strategy to pursue in the development of new treatments for allergic asthma.

Reviewer’s Comments. Although this study was performed in mice, the results provide the foundation for pursuing IL-13 as a target for asthma treatment. The hope is that targeted therapy may be associated with fewer side effects than corticosteroid therapy and that treatment may be able to be tailored to specific asthma phenotypes.

Elizabeth C. Matsui, MD
Baltimore, MD

LUNG FUNCTION AND RESPIRATORY HEALTH IN ADOLESCENTS OF VERY LOW BIRTH WEIGHT


Purpose of the Study. Very low birth weight (VLBW) infants (birth weight of <1500 g) are typically preterm and usually require respiratory support in the nursery, placing them at risk for lung injury, which might have long-term consequences. Do these children have reduced lung function and respiratory disease when they reach adolescence?
ROLE OF GASTROESOPHAGEAL REFLUX IN OLDER CHILDREN WITH PERSISTENT ASTHMA


Purpose of the Study. To determine the effect of gastroesophageal reflux (GER) treatment on asthma outcomes.

Study Population. Forty-six children (5–10.5 years of age) who had received treatment for moderate persistent asthma for at least 2 years and who were being cared for by gastroenterologists, to rule out GER disease with esophageal pH (dual-channel) monitoring (for 20–24 hours). Those with abnormal pH probe study results began treatment, including lifestyle changes, proton pump inhibitor treatment, and, if indicated, surgical intervention. Those with normal pH study results were given the option of beginning medical treatment. The subjects were monitored at regular 4-week intervals for an 18-month period, for asthma assessment and adjustment of medications if necessary. The pulmonologist was not blinded with respect to the treatment.

Results. A total of 482 subjects were screened during a 2.5-year period. Twenty-seven of the 46 enrolled patients (59%) had abnormal pH study results, with 18 opting for medical treatment and 9 opting for surgical treatment. Of the 19 with normal pH study results, 8 opted to begin medical treatment. There were no differences in age or gender for any of the groups. The 27 patients who underwent treatment because of abnormal pH study results all were able to reduce (~50%) the amount of asthma medication used. There was no statistical difference in outcomes between the medical and surgical intervention groups. Of those with normal pH study results, the 11 patients who did not begin GER treatment experienced no changes in their asthma medications; however, 2 of 8 patients with normal study results who began empiric GER treatment were able to reduce (70%) their requirements for bronchodilators and inhaled corticosteroids. Among patients with abnormal pH study results, the probability of improvement of asthma after GER treatment was 100%; among those with normal pH study results receiving treatment, the probability of improvement was 25%. The study found what has been shown in adult studies, that treatment of GER disease with either proton pump inhibitors or surgical intervention can improve asthma, in this case by reducing the need for rescue and controller medications. This has not been found for treatment with ranitidine. The authors found pH probe study results to be useful predictors of responses to anti-GER treatment. The study did not answer several questions, including the following. How long should medical GER treatment continue for these patients? Is the prokinetic necessary? How long will asthma improvement continue, with or without treatment? Is surgical intervention superior to medical treatment? What, if anything, in the patient history could indicate the presence or absence of GER and suggest the response to treatment? What effect does this treatment have on lung function and long-term outcomes?

Conclusions. Screening for the presence of GER disease among children with moderate persistent asthma, with pH probe studies, is a useful screening approach. Treatment of asthmatic children with aggressive acid suppression may improve asthma outcomes.

Reviewer’s Comments. Although the exclusion criteria for this study were extensive, resulting in a rather select study population, this study does demonstrate what has been found among adults, that GER disease may play a role in a significant number of asthma cases and that treatment of GER disease may lead to improvement in asthma outcomes. It also demonstrates that pH probe studies are useful screening tests for such patients, although patient histories would have been helpful in this study.

Mary Beth Bollinger, DO
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NATIONAL TRENDS IN ASTHMA VISITS AND ASTHMA PHARMACOTHERAPY, 1978–2002


Purpose of the Study. To analyze asthma clinic visits and changes in asthma (oph) treatment during a 25-year period.

Study Population. Subject data from the National Disease and Therapeutic Index, from 1978 to 2002, were used to evaluate asthmatics examined by office-based physicians.

Methods. The National Disease and Therapeutic Index provides data on diagnostic and prescribing information
from physicians across the United States. Approximately 3500 physicians participate each 3-month period and provide information on patients they examine in 2 consecutive workdays. Information focuses on specific diagnoses and medications, not on patient adherence. This study analyzed the number of asthma visits (based on International Classification of Diseases, 9th revision, codes) and medications used to treat asthma each year from 1978 to 2002, primarily in an outpatient setting. Medications were classified as controllers (eg, inhaled corticosteroids) or relievers (eg, short-acting, $\beta_2$-receptor agonists).

### Results

The annual number of patient visits for treatment of asthma doubled from 1978 (8.5 million) to 1990 (17.7 million) and then demonstrated a plateau, with a mean of 16 million cases per year, from 1991 to 2002. The treatment of asthma changed tremendously during the 25-year study period. Prescription rates for controllers increased; in 2001, controllers were prescribed more than relievers (83% vs 80%) for the first time. Prescriptions for relievers increased from 1978 to 1993 but decreased thereafter. From 1978 to 1988, prescriptions for inhaled corticosteroids remained at 8% with respect to the annual total of asthma visits. This number increased to 48% in 2002. The use of long-acting, $\beta_2$-receptor agonists alone peaked in 2000 and declined to 9% in 2002, most likely because of increased use in combination with inhaled corticosteroids (20% of visits). The use of leukotriene modifiers steadily increased after their release in 1997, to 24% in 2002, whereas xanthine use decreased to 2% and cromone use decreased to <1%. Oral corticosteroid use was constant at 20%. The number of medications was stable, at a mean of 2 per patient, during the past decade.

### Conclusions

The study concluded that, although the number of asthma visits increased during the study period, the number of return visits for treatment of asthma decreased. Prescriptions for controller medications increased, whereas prescriptions for relievers decreased. This pattern suggests that asthma treatment is changing to be more consistent with current guidelines.

### Reviewers’ Comments

Consensus guidelines for asthma are helpful for adequate diagnosis and treatment of this disease. Trends in asthma pharmacotherapy are changing, so that controller medications are prescribed more often, leading to decreased need for relievers and better control of asthma. This study did not include asthma-related visits to emergency departments or hospital-based clinics; therefore, more severe cases of asthma might not have been adequately analyzed.

**Jenny Campbell, MD**  
**Stacie M. Jones, MD**  
Little Rock, AR

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### ASTHMA MEDICATION USE AND DISEASE BURDEN IN CHILDREN IN A PRIMARY CARE POPULATION


#### Purpose of the Study

To describe the use of asthma medications and the disease burden among children with persistent asthma and to estimate asthma control.

#### Study Population

A total of 638 children (3–15 years of age) with persistent asthma, drawn from private insurance claims and pharmacy databases, who were recruited for the Pediatric Asthma Care Patient Outcomes Research Team II study from 42 primary care practices in 3 urban locales were studied.

**Methods.** A single telephone interview with parents of eligible children was used to assess 1) classes of medications (controller and reliever) in use and frequency of use in the previous 4 weeks; 2) asthma symptoms during days, but not nights, in the previous 2 weeks; 3) visits to specialists, outpatient doctors, or emergency departments or hospitalizations; and 4) the existence and use of a written action plan.

**Results.** Of the children who participated, 68% had 0 to 4 symptom days in the previous 2 weeks, 16% had 5 to 9 symptom days, and 16% had 10 to 14 symptom days. Sixty-five percent had a health care visit in the previous 1 year; 23% went to an emergency department, 14% saw an asthma specialist, and 4% were hospitalized. Most children with frequent symptom days were receiving controller medicines and used reliever medicines. Poor adherence to controller medicines was common (40%), especially among those with few symptom days. Sixty-four percent of children with persistent asthma had excessive symptoms or high reliever medication use and were considered to have inadequately controlled conditions. Approximately one-third of these patients had not been prescribed controllers. Written care plans were received by 21% of patients, and the existence of a plan was not protective against inadequate control.

**Conclusions.** Inadequate asthma control, defined as frequent symptoms or high reliever medication use, was common even when controller medications were prescribed. Nonadherence to controller medications and over-reliance on reliever medications were common.

**Reviewers’ Comments.** This is an important study emphasizing that asthma control remains a significant problem for children. This study highlights 2 factors that contribute to poor asthma control, namely, lack of adherence to controller medications and lack of appropriate prescription of controllers. Younger age and being treated by an asthma specialist were associated with better asthma control. The study excluded important groups, including children <3 of age, children treated by a specialist, and patients with intermittent or severe persistent asthma. Patients themselves were not interviewed (only the parents were interviewed), which is a known limitation in adolescent studies. Surveyed controller and reliever use was not compared with actual prescription refills or mechanical dose-counting results. Nonetheless, this is another study suggesting that asthma among children is not well controlled and that we need to assist our patients with medication adherence and to make sure that patients with persistent asthma are prescribed controller medications.

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### DIAGNOSIS AND MANAGEMENT

#### EFFECTS OF EDUCATIONAL INTERVENTIONS FOR SELF-MANAGEMENT OF ASTHMA IN CHILDREN AND ADOLESCENTS: SYSTEMATIC REVIEW AND META-ANALYSIS


#### Purpose of the Study

To determine the effectiveness of educational programs for the self-management of asthma among children and adolescents.

#### Study Population

Eligible studies were published, randomized, controlled trials of educational programs for the self-management of asthma among children and adoles-
Results. Thirty-two of 45 identified trials were eligible, with a total of 37,006 patients 2 to 18 years of age. Education regarding asthma was associated with improvements in lung function (standardized mean difference: 0.50; 95% confidence interval [CI]: 0.25–0.75) and self-efficacy (mean difference: 0.36; 95% CI: 0.15–0.57) and reductions in absenteeism from school (mean difference: −0.14; 95% CI: −0.23 to −0.04), number of days of restricted activity (mean difference: −0.29; 95% CI: −0.33 to −0.09), and number of visits to an emergency department (mean difference: −0.21; 95% CI: −0.33 to −0.09). When pooled with a fixed-effects model but not a random-effects model, education was also associated with a reduced number of nights disturbed by asthma. The effects on morbidity were greatest for programs with strategies based on peak flow, interventions targeted at the individual, and participants with severe asthma.

Conclusions. Educational programs for the self-management of asthma among children and adolescents improve lung function and feelings of self-control and reduce absenteeism from school, number of days of restricted activity, number of visits to an emergency department, and possibly number of disturbed nights. Educational programs should be considered part of the routine care of young people with asthma.

Reviewer’s Comments. In the early 1990s, a meta-analysis found no evidence of reductions in morbidity or utilization of health care resources associated with educational programs. However, several rigorous evaluations of educational programs have been completed in the past decade. This meta-analysis provides encouraging evidence that our educational efforts regarding self-management of asthma improve lung function, reduce morbidity, and decrease utilization of emergency health care resources. Such programs should be considered routine in the care of children and adolescents with asthma.

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PROACTIVE ASTHMA CARE IN CHILDHOOD: GENERAL PRACTICE-BASED, RANDOMIZED, CONTROLLED TRIAL


Purpose of the Study. To assess the feasibility and effectiveness of a general practice-based, proactive system of asthma care among children.

Study Population. A total of 174 children with moderate/severe asthma who were cared for by 24 general practitioners in the Australian Capital Territory were studied.

Methods. The study was a randomized, controlled trial with cluster sampling according to general practice. The intervention involved a system of structured asthma care called the 3+visit plan, which included families being reminded to visit the general practitioner. Visit 1 was a baseline visit in which the concept of a “contract” for care was discussed. Visit 2 was used to assess asthma status, history, drug treatment, and management. Education and review of medications were performed. Visit 3 occurred 2 weeks later and included spirometric evaluation and a review of patient and peak flow records. An asthma action plan was completed. Allergy skin testing or radioallergosorbent testing was used to identify triggers. Visit 4 occurred 4 weeks later; progress was assessed and the asthma action plan was reviewed. Allergy test results were discussed and education was reinforced. Main outcome measures were rates of asthma consultations with the general practitioner, written asthma plans, completion of the 3+visit plan, lung function test results, emergency department visits for treatment of asthma, days absent from school, asthma symptoms, and medication use.

Results. The intervention group had more asthma consultations (odds ratio [OR] for ≥3 asthma consultations: 3.8; 95% confidence interval [CI]: 1.9–7.6; P < .01), asthma action plans (OR: 2.2; 95% CI: 1.2–4.1; P = .01), and 3+visit plans (OR: 24.2; 95% CI: 5.7–103.2; P < .01) than did the control group. The intervention group experienced less reduction in forced expiratory volume in 1 second after cold air challenge (2.6%; range: 1.7–3.5%; P < .01) than did the control group. The intervention group experienced less speech-limiting wheeze (OR: 0.2; 95% CI: 0.1–0.4; P < .01) and was more likely to use spacers (OR: 2.8; 95% CI: 1.6–4.7; P < .01), compared with the control group. No differences in days absent from school or symptom-free days were observed.

Conclusions. Proactive care with active recall for children with moderate/severe asthma is feasible in general practice and seems to be beneficial.

Reviewer’s Comments. Delivering optimal health care for chronic illnesses such as asthma requires health systems to move from a reactive approach to a proactive approach. The study nicely evaluates the role of a general practice-based, proactive approach to pediatric asthma care. Studies such as this are often quite difficult to conduct and interpret in a controlled manner; however, this study represents 1 step in evaluating proactive primary care strategies. Reinforcement of education through frequent follow-up visits and encouragement of active recall appear to be feasible and beneficial in a general practice setting.

PEDIATRICIAN SELF-EFFICACY FOR COUNSELING PARENTS OF ASTHMATIC CHILDREN TO QUIT SMOKING


Purpose of the Study. Although environmental tobacco smoke is a known risk factor for asthma exacerbations among children, pediatricians infrequently advise parents who smoke to discontinue smoking. It has been shown that high physician self-efficacy or self-confidence in the counseling of parents regarding smoking discontinuation is related to increased physician screening and counseling on this issue. It is unclear, however, which factors are associated with high physician self-efficacy for counseling (eg, previous training in smoking cessation counseling or number of years in pediatric practice). The objective was to identify parameters related to physician self-efficacy in smoking cessation counseling.

Methods. This was a cross-sectional survey of a national random cohort of 829 primary care physicians.

Results. The response rate was 55% (457 of 829 physicians). The percentages of physicians with high levels of self-efficacy for screening parents and children to identify...
smokers were 87% and 84%, respectively. The percentages of physicians with high levels of self-efficacy for advising parents and patients about smoking cessation were 59% for both. Previous training in smoking cessation counseling was associated with higher levels of self-efficacy for all 4 skills assessed, including inquiring about the patient’s smoking status (odds ratio [OR]: 3.91; 95% confidence interval: 1.63–9.37), inquiring about patients’ smoking status (OR: 2.51), counseling the patient to quit smoking (OR: 5.30), and counseling a parent to quit smoking (OR: 4.96). The number of years since completing residency training was not related to greater self-efficacy.

Conclusions. The authors concluded that formal training in smoking cessation had significant effects on physician self-efficacy with respect to smoking discontinuation, throughout physicians’ professional careers.

Reviewer’s Comments. The study clearly demonstrated that levels of physician self-efficacy in both screening for and counseling about smoking cessation were significantly enhanced by formal training in this area. The study was limited in that it might not be representative of all pediatricians, because the respondents were more likely to be board-certified in pediatrics than were nonrespondents. In addition, the response rate was 55%, which could limit generalizability. Although there are many examples of formal training programs in smoking cessation counseling, less than one-half of pediatric residency programs currently offer any formal training in smoking cessation counseling. This study suggests that this should be made a priority for all training programs.

Christopher Randolph, MD
Waterbury, CT

EFFECTIVENESS OF ACUTE ASTHMA CARE AMONG INNER-CITY ADULTS


Purpose of the Study. To identify processes of asthma care that result in improved peak expiratory flow rate (PEFR) 2 to 3 weeks after an emergency department visit.

Study Population. A total of 365 adults with asthma who were discharged from a public hospital emergency department after an asthma exacerbation were studied.

Methods. Eligible patients were identified from an administrative database and were invited for a follow-up visit 2 to 3 weeks after discharge from the emergency department. Information regarding 6 processes of care was obtained from emergency department records and questionnaires. These processes of care were 1) inhaled β-receptor agonist at discharge, 2) inhaled corticosteroids at discharge, 3) systemic corticosteroids, 4) a follow-up visit, 5) patient education regarding an inhaler device, and 6) patient education regarding asthma medication use. Each process was examined as a potential predictor of percentage changes in predicted PEFR.

Results. Three hundred sixty-five of 448 eligible patients enrolled in the study, and 309 returned for the follow-up visit. The study population was economically disadvantaged and predominantly African American and Hispanic. The range of percentage PEFR changes was −16% to 590%, with a median of 80%. Male subjects had significantly greater percentage PEFR changes than did female subjects (115% vs 74%, P = .002), and patients with mild asthma had significantly greater percentage PEFR changes than did those with moderate or severe asthma (148% vs 87% and 22%, respectively; P < .001). After adjustment for gender, ethnicity, and asthma severity, appropriate use of systemic corticosteroids at discharge was associated with a 31.6% increase in the predicted PEFR (95% confidence interval: 8.1–55.1%). Asthma severity did not modify the effect of systemic corticosteroids on percentage changes in PEFR.

Conclusions. These findings suggested that, among poor minority adults with asthma, systemically administered corticosteroids improved PEFR 2 to 3 weeks after discharge from an emergency department.

Reviewer’s Comments. Although the results were not surprising, this study demonstrated that at least 1 aspect of acute asthma care might have improved outcomes in a high-risk patient population. Whether the improvements in PEFR seen a few weeks after discharge represent markers for improved asthma outcomes in the longer term remains to be determined.

Elizabeth C. Matsui, MD
Baltimore, MD

MORBIDITY PATTERNS AMONG LOW-INCOME WHEEZING INFANTS


Purpose of the Study. Although information is available regarding wheezing and asthma among low-income, school-aged children, less is known about morbidity related to wheezing or asthma among infants and toddlers. The objective of this study was to evaluate biological, environmental, and psychosocial associates of morbidity in wheezing illness in a multiethnic sample of low-income infants <2 years of age.

Study Population. A total of 177 infants, 9 to 24 months of age, and their families, recruited from pediatric departments of local hospitals and clinics in the metropolitan Denver area, were studied.

Methods. The protocol required the children to have had ≥3 health contacts with documented wheezing and to have undergone a complete evaluation as part of an environmental intervention program. Baseline evaluations of children included total immunoglobulin E level measurement, environmental assessment of tobacco smoke exposure, assay of urine samples for cotinine, psychosocial assessments (with the Rand Mental Health Battery) of anxiety, depression, positive effect, and emotion and stability of the caregiver, and assessment of health care utilization. Caregiver reports were included in the evaluation. At study entry, prior morbidity attributable to wheezing illness was assessed, primarily on the basis of caregiver reports and medical record documentation of hospitalizations and emergency department visits.

Results. Of the infants in this study, 46% had ≥1 hospitalization and ~60% had ≥2 emergency department visits from birth for treatment of wheezing conditions. Foreign-born Hispanic families took their infants to the emergency department significantly more than did other groups, including United States-born Hispanic families, white families, and black families, although they used fewer controller medications and documented lower illness severity. Overall, 72% of the children were receiving bronchodilators, whereas 28% were receiving controllers. The highest percentage of children receiving controller medications occurred in the white group. There was no relationship between receiving controller medications and experiencing ≥2 emergency department visits. Corticosteroid bursts were, however, associated with hospitalization (P < .001) and emergency department visits (P < .001). Multivariate analyses demonstrated 3 biological factors,
namely, respiratory syncytial virus, elevated immunoglobulin E levels, and cockroach allergy in the home, that were independently associated with hospitalizations within this group. Emergency department visits were associated with caregivers with a status of single parent or smoker ($P = .037$ for single parent and $P = .034$ for smoker).

**Conclusions.** The authors concluded that ethnic and immigrant status played significant roles in morbidity related to infant wheezing illness. In addition to respiratory infection, allergic processes and social variables played roles, as evidenced by health care utilization.

**Reviewer’s Comments.** Additional studies of this nature with larger populations, including suburban families, would be of interest to validate these findings. The relationships of ethnic, biological, and social factors to asthma morbidity are certainly consistent, however, with the paradigm of inner-city asthma that has been established for older children and adolescents.

Christopher Randolph, MD
Waterbury, CT

A LONGLITUDINAL, POPULATION-BASED, COHORT STUDY OF CHILDHOOD ASTHMA FOLLOWED TO ADULTHOOD


**Purpose of the Study.** To describe risk factors that may predict the severity and duration of childhood asthma in adult life.

**Study Population.** A complete birth cohort of 1390 children born between April 1972 and March 1973 in Dunedin, New Zealand, was studied. Of those children, 1037 (91%) were present for the follow-up assessment at 3 years.

**Methods.** The children were examined every 2 years from 3 to 15 years of age and then at 18, 21, and 26 years. Respiratory questionnaire assessment and pulmonary function testing were performed at ages 9, 11, 13, 15, 18, 21, and 26 years and methacholine challenge testing was performed at all except the 18- and 26-year visits, when bronchodilator responses were studied. Allergic diathesis was measured with immunoglobulin E assays at 11 years, skin tests at 13 years, and both at 21 years.

**Results.** A total of 613 patients (59%) provided data at every assessment. Seventy-three percent reported ≥1 episode of wheezing, whereas 51% reported ≥1 episode of wheezing. At age 26 years, 27% of the cohort was currently wheezing, with 15% experiencing persistent symptoms and 12% relapsing after a symptom-free period. The predictors of persistent wheezing included severity of house dust mite sensitivity, increased bronchial hyperreactivity, smoking at 21 years of age, and earlier age of symptom onset. Pulmonary function test results were consistently lower for patients with persistent wheezing and those who experienced relapses. The degree of pulmonary function abnormality was measured as the forced expiratory volume in 1 second (FEV$_1$)/forced vital capacity (FVC) ratio. Among male patients with persistent wheezing, those who experienced relapses began with a FEV$_1$/FVC ratio of 82% at 9 years of age, which decreased to ~75% by 26 years of age. Similar but less profound abnormalities were seen in the female cohort. Patients with no wheeze ever, intermittent wheezing, or transient wheezing maintained FEV$_1$/FVC ratios at or just below 85% through the study.

**Conclusions.** More than 5% of children who wheezed experienced persistence of symptoms into adulthood. The abnormalities in pulmonary function among patients with persistent wheezing and relapse of wheezing occurred early in life (<9 years of age) and persisted throughout life. Patients with transient wheezing or resolved wheezing did not experience progressive loss of lung function.

**Reviewer’s Comments.** These data confirm that early airway damage attributable to infection, allergen exposure, or both may lead to abnormalities in pulmonary function that persist throughout life. The chance to intervene in asthma may well occur before our patients are able to tell us that they have any difficulty breathing.

Bradley E. Chipp, MD
Sacramento, CA

WHO GETS DIAGNOSED WITH ASTHMA?
FREQUENT WHEEZE AMONG ADOLESCENTS
WITH AND WITHOUT A DIAGNOSIS OF ASThma


**Purpose of the Study.** To evaluate factors related to the failure to make an asthma diagnosis among children with frequent wheezing symptoms and to assess risk factors for frequent wheezing.

**Study Population.** The study included 122 829 children, 12 to 18 years of age, enrolled in 499 public middle schools in North Carolina during the 1999–2000 school year.

**Methods.** The study was based on results from the North Carolina School Asthma Survey, a self-reported questionnaire on respiratory disease adapted from the International Study of Asthma and Allergies in Childhood.

**Results.** Characteristics that were independently related to undiagnosed frequent wheezing, compared with asymptomatic children, included female gender (odds ratio [OR]: 1.45), current smoking (OR: 2.6), exposure to household smoke (OR: 1.6), low socioeconomic status (OR: 1.5), and African American (OR: 1.25), Native American (OR: 1.4), and Mexican American (OR: 1.3) race/ethnicity. There was a minimal negative association with urban residents, with an OR of 0.91. Documentation of allergies was less likely among frequent wheezers (70%), compared with diagnosed asthmatics (86%), but was much higher than among asymptomatic children (36%). Thirty-three percent of children with undiagnosed frequent wheezing reported ≥1 physician visits in the previous year for treatment of wheezing or breathing conditions, compared with 71% of children with diagnosed asthma and 4% of asymptomatic children. The prevalence of any inhaler therapy in the previous 12 months was 12% for undiagnosed frequent wheezers, compared with 78% for diagnosed asthmatics.

**Conclusions.** The authors concluded that undiagnosed frequent wheezing was independently related to female gender, current smoking, exposure to household smoke, low socioeconomic status, and African American, Native American, and Mexican American race/ethnicity. Children with undiagnosed frequent wheezing were not receiving sufficient health care for their asthmatic conditions.

**Reviewer’s Comments.** These are rather striking findings that clearly demonstrate the degree to which asthma is underdiagnosed in some populations.

Christopher Randolph, MD
Waterbury, CT

HEALTH CONSEQUENCES ASSOCIATED WITH FREQUENT WHEEZING IN ADOLESCENTS
WITHOUT ASTHMA DIAGNOSIS

Purpose of the Study. To evaluate the association between undiagnosed frequent wheezing and health consequences among adolescents.

Study Population. The North Carolina School Asthma Survey population of 122,829 children, 12 to 14 years of age, was studied. The target population was enumerated from 1999–2000 enrollment records maintained by the North Carolina Department of Public Instruction and included 565 public middle schools, with 192,248 children.

Methods. The questionnaire was adapted from the International Study of Asthma and Allergies in Childhood. Three mutually exclusive groups were compared, ie, 1) children with frequent wheezing symptoms and no diagnosis, 2) children who reported wheezing symptoms and a physician diagnosis of asthma, and 3) children with no symptoms or diagnosis ever. A fourth group, defined as infrequent wheezers (children with infrequent wheezing symptoms and no physician diagnosis, n = 38,424), was included for reference. Outcome variables were defined as the numbers of school absences, activity limitations, and sleep disturbances attributable to asthma-like symptoms. Health care utilization variables included the numbers of physician visits, emergency department visits, and hospitalization admissions for treatment of asthma-like symptoms.

Results. The odds of wheezing-related sleep disturbances, limited activities, and missed school were higher among undiagnosed frequent wheezers, compared with diagnosed asthmatics. The frequencies of emergency department visits and hospitalizations did not differ substantially between the undiagnosed wheezing group and the diagnosed asthma group, although the undiagnosed group was less likely to have visited a physician for treatment of wheezing in the previous year. Undiagnosed frequent wheezers were more likely to experience sleep disturbances, limited activities, missed school, and greater health care utilization for treatment of wheezing, compared with asymptomatic children. Compared with asymptomatic children, diagnosed asthmatics were 10 to 24 times more likely to experience limited activities, sleep disturbances, and missed school. They were also 20 times more likely to visit a physician and 3–9 times more likely to report ≥3 emergency department visits or hospitalization for treatment of wheezing, compared with asymptomatic children.

Conclusions. Children with frequent wheezing symptoms but no asthma diagnosis experience substantial illness-related morbidity, similar to that of diagnosed asthmatics. Undiagnosed frequent wheezers require more recognition from primary care physicians and need active disease management to reduce health consequences.

Reviewer’s Comments. This study nicely evaluates multiple aspects of functional consequences and health care use among children with undiagnosed frequent wheezing from a population-based sample. This study suggests that undiagnosed frequent wheezers require better recognition by primary care physicians and need active disease management. It also suggests that the effects of asthma in the pediatric population may be underestimated, because of undiagnosed disease.

Wanda Phipatanakul, MD
Boston, MA

LOWER PHYSICIAN ESTIMATE OF UNDERLYING ASTHMA SEVERITY LEADS TO UNDERTREATMENT


Purpose of the Study. To determine how physician estimates of patients’ underlying asthma severity affect asthma care.

Study Population. A total of 4005 adult asthma patients enrolled in managed care organizations and the physicians who were primarily responsible for their asthma care were studied.

Methods. Patient- and physician-reported data were used to examine the relationship between physician estimates of underlying asthma severity and asthma care. Asthma patients were asked about asthma symptoms and asthma medical care. Asthma care questions included questions regarding medication use, self-monitoring, self-management, and allergy history and treatment. The physicians were instructed to evaluate the severity of their patients’ asthma, and 4005 patients had complete physician estimates of underlying severity. Relationships between physician severity classifications, patient-reported symptoms, and asthma care were examined, and multivariate logistic regression analyses were used to adjust for age, gender, race, and education.

Results. The mean age of the respondents was 44.8 years; 83.5% were white and 70.1% were female. Almost 40% of respondents reported moderate symptoms and 50.1% reported severe symptoms, but 44.6% of physicians classified their patients’ underlying asthma severity as mild and 44.5% as moderate. After adjustment for patient-reported symptoms, the odds of receiving each component of asthma care were greater when the physician estimate of severity was moderate (odds ratio: 1.92; 95% confidence interval: 1.65–2.22) or severe (odds ratio: 4.97; 95% confidence interval: 3.58–6.89) than when the physician estimate was mild. The more severe the patient-reported symptoms, the more likely patients were to receive inhaled corticosteroids and peak flow meters but the less likely they were to have self-management knowledge, even after adjustment for physician estimates of severity. Physician-estimated severity was a stronger predictor of asthma care than were patient-reported symptoms.

Conclusions. In a population of adult asthmatic patients, physician estimates of asthma severity determined the asthma care reported by patients but physicians might underestimate asthma severity, resulting in suboptimal care.

Reviewer’s Comments. These results suggested that physician underestimation of asthma severity may lead to the delivery of asthma care that is not consistent with national guidelines. Because the participants were predominantly white female adults, these results may not be applicable to other populations. In addition, physician estimates of underlying severity were obtained 1 to 6 months after patients reported symptoms, resulting in a time lag that might explain at least some of the discrepancy between patient-reported symptoms and physician estimates of underlying severity. Studies of pediatric asthmatic patients are needed, to determine the prevalence of physician underestimation of asthma severity and its effects on asthma care and ultimately on asthma outcomes.

Elizabeth C. Matsui
Baltimore, MD

HOSPITAL READMISSIONS FOR CHILDHOOD ASTHMA


Purpose of the Study. To determine the magnitude of readmissions for children with asthma and to examine
measurable risk factors for readmissions for asthma treatment.

Study Population. All hospitalized children with a primary discharge diagnosis of asthma (International Classification of Diseases, 9th revision, code 493) at 2 large hospitals in St. Louis, Missouri, between January 1, 1990, and December 31, 1999, were included.

Methods. This was a retrospective analysis of children with asthma hospitalizations between January 1, 1990, and December 31, 1999. Data for admissions of patients with asthma were extracted from the billing databases of 2 hospitals for the 10-year period. Patient attributes of age, gender, race/ethnicity, residence, payer status, length of stay, and month of admission were compared between patients admitted once during that period and patients admitted multiple times. Extensive measures were undertaken to ensure that each patient’s hospital admissions for asthma were counted as accurately as possible. The main outcome measures were the total number of admissions and the time to readmission during the study interval.

Results. During the study period, there were 8761 children with 14 905 hospitalizations because of asthma. Of these, 6142 were admitted only once and 2619 (30%) were admitted more than once. There were a total of 6144 admissions (41.2% of total asthma admissions); 3525 of these were third admissions or more (23.6% of all asthma admissions). The largest numbers of admissions, both single and multiple, occurred among patients between 1 and 4 years of age. The ratio of African American patients to all other patients was 2.16 for single admissions and 4.38 for multiple admissions ($\chi^2$ test, $P < .0001$). The ratio of Medicaid or self-pay insurance to commercial insurance was 1.94 for the multiple-admission group and 1.29 for the single-admission group ($\chi^2$ test, $P < .001$). Prior admission was a more specific indicator of readmission, with greater predictive value, than ethnicity, insurance status, or their combination.

Conclusions. Readmissions for asthma treatment represented a substantial proportion of admissions, and there was a disproportionate association with African American race/ethnicity and low income, as indicated by insurance status. In addition, there was increasing risk for readmission with each subsequent asthma admission.

Reviewer’s Comments. This is a very interesting study with practical clinical applications. As noted, any readmission for asthma treatment should be used as an impetus for intervention. Inpatient hospital services represent the largest direct medical expenditures for asthma treatment; therefore, identification of asthmatics at high risk for readmission is critical. Interventions to improve overall asthma management, including environmental controls, adherence to a written asthma action plan with appropriate medications, and specific attention to psychosocial issues, should help decrease readmissions. Continued research in this area, with particular emphasis on successful interventions to prevent readmissions for asthma treatment, will be very welcome.

John M. James, MD
Fort Collins, CO

Sensitivity of Spirometric Measurements to Detect Airway Obstruction in Infants


Purpose of the Study. To demonstrate the ability of forced expiratory flow (FEF) volume curves from increased lung volumes to discriminate among infants with differing severities of respiratory symptoms and to compare the ability of variables used to quantify the flow volume curves to detect airway obstruction.

Study Population. Infants referred to a pediatric pulmonary clinic were classified into 2 groups. Group 1 patients had previous respiratory symptoms but were asymptomatic on the date of evaluation. Group 2 patients were symptomatic with current respiratory symptoms, such as coughing, rhonchi, or wheezing on the date of evaluation. A control group included 153 healthy infants.

Methods. Before spirometry, infants received 50 to 75 mg/kg chloral hydrate orally; measurements were obtained while the infants were sleeping in the supine position. Forced expiratory maneuvers were performed with the increased-volume, rapid-thoracic compression technique. Flow volume curves were quantified with forced vital capacity (FVC), FEF at 50% of FVC, FEF at 75%, forced expiratory volume in 0.5 second (FEV 0.5), and FEV 0.5/FVC, which were expressed as $z$ scores.

Results. All variables except FVC had $z$ scores that were significantly less than 0 and distinguished groups 1 and 2 with progressively lower $z$ scores. The mean $z$ scores for the flow variables (FEF at 50%, FEF at 75%, and FEF at 25–75%) were more negative than the $z$ scores for the timed expired volumes (FEV 0.5 and FEV 0.5/FVC) for both groups. In general, measures of flow identified a greater number of infants with abnormal lung function than did measures of timed volume; FEF at 50% had the best performance in detecting abnormal lung function.

Conclusions. Forced expiratory maneuvers performed with the increased-volume, rapid-compression technique could discriminate among groups of infants with respiratory symptoms of differing severity. Measures of forced expiratory flow were better than timed expiratory volumes in detecting abnormal airway function.

Reviewer’s Comments. Because routine, standardized, spirometric measurements among infants with respiratory diseases were not readily available in the past, several investigations used the increased-volume, rapid-thoracic compression technique to assess lung function in this age group. This study extends the body of evidence obtained with this technique and highlights the importance of forced expiratory flow measurements as being better than timed expiratory volumes in detecting abnormal airway function in this age group. The challenge remains to develop this technique into a more practical procedure that can be incorporated into routine clinical practice.

John M. James, MD
Fort Collins, CO

Environmental Exposures

Effects of Ambient Air Pollution on Symptom Severity and Medication Use in Children with Asthma


Purpose of the Study. To investigate the short-term effects of ambient air pollution on asthma symptoms and medication use among children with persistent asthma.

Study Population. A total of 133 children (5–13 years of age) with mild/moderate asthma were studied. The mean duration of asthma was 5.3 years. The children were enrolled from 1 center participating in the Childhood Asthma Management Program study. During the run-in period of the Childhood Asthma Management Program study, before being placed on 1 of the study controller medications...
or placebo, the subjects had preventative therapy suspended and were monitored for 28 to 112 days while using only albuterol as needed and orally administered prednisone for treatment of severe exacerbations.

Methods. The children and their caregivers completed daily diary cards for an average of 58 days, recording medication use and asthma severity. Air pollution and temperature data were collected by the Puget Sound Clean Air Agency (Seattle, WA). Particulate matter (PM) and carbon monoxide (CO) were measured. PM is a complex aerosol of solid and liquid, organic and inorganic materials, including dust, soot, smoke, pollen, acid droplets, and secondary aerosols. PM with an aerodynamic diameter of ≤10 μm (PM_{10}) and PM with an aerodynamic diameter of ≤2.5 μm (PM_{2.5}) were measured. Recent research has indicated that PM_{2.5} may be more strongly associated with asthma than larger particles. PM_{2.5} and PM_{10} concentrations were measured nephelometrically. CO monitoring sites were located in areas of high traffic volume. CO data were averaged, to diminish the influence of random sources of air pollution on any given day.

Results. Asthma severity and medication use were both associated with elevated PM_{2.5}, PM_{10}, and CO concentrations. Increasing asthma severity was most significantly seen 1 day after pollution exposure. With adjustment for confounders, 1 day after a 10 μg/m^3 increase in PM_{2.5} levels, there was a 1.2-fold increase in the odds of having a serious asthma attack and a 1.08-fold increase in β-receptor agonist use. The association of air pollutants with medication use was weaker than that with asthma severity. Stronger associations with asthma severity and rescue inhaler use were found with CO levels than with PM levels.

Conclusions. Increases in PM and CO levels were associated with higher risks of increasing asthma severity and rescue medication use among children with moderate/severe asthma in the Seattle area.

Reviewer’s Comments. The authors noted that there is no biological plausibility of a direct association between CO levels and asthma exacerbations. The primary effect of CO exposure is anoxia, which results in confusion, headache, and nausea. The authors speculated that CO levels may serve as a marker for exposure to combustion byproducts, particularly diesel and gasoline exhaust particles.

Alan B. Goldsobel, MD
San Jose, CA

PROSPECTIVE STUDY OF AIR POLLUTION AND BRONCHITIC SYMPTOMS IN CHILDREN WITH ASTHMA


Purpose of the Study. To examine the effects of air pollutants, including particulate matter (PM), organic carbon (OC), elemental carbon, and other traffic-related pollutants, on bronchitic symptoms among children with asthma.

Study Population. Twelve Southern California communities were studied. In 1993, fourth graders and seventh graders were recruited from schools in 12 neighborhoods. Children with a history of asthma who completed ≥2 years of study questionnaires (1996–1999) were included in the analysis. There were 475 children in the study.

Methods. Questions regarding bronchitic symptoms were asked each year. Positive responses included daily cough for 3 consecutive months, 3 consecutive months of congestion or phlegm, or the occurrence of bronchitis. Other questions addressed smoke exposure and participation in team sports. A number of demographic questions were also asked. Air pollution monitoring stations were established in the 12 neighborhoods. The following were measured: ozone, PM of <10 μm, nitrogen dioxide (NO₂), PM of <2.5 μm (PM_{2.5}), OC, and elemental carbon. Annual averages for these pollutants were calculated, and 4-year mean levels (1996–1999) for each community were established.

Results. Of the 475 children in the study with asthma, 184 (38.7%) experienced bronchitic symptoms during the first year. Children with a history of wheezing in the year before the study or with allergy were significantly more likely to report symptoms. During the 4 years of the study, the average pollutant concentrations varied 4- to 10-fold among the communities. There was very little variation within each community from year to year. The odds ratio (OR) for bronchitic symptoms among children with asthma varied from 0.80 for ozone to 1.81 for PM_{2.5} among the communities. Within communities, the ORs were >1 for every pollutant. In special models for 2 pollutants, ie, OC and NO₂, ORs were only modestly decreased when other pollutants were controlled for and the effects of OC and NO₂ were not altered by other pollutants. NO₂ effects were modified by participation in team sports, with an increase in the OR for bronchitic symptoms among participating children.

Conclusions. Among children with asthma, there were associations of bronchitic symptoms with PM_{2.5}, OC, NO₂, and ozone levels. Importantly, OC and NO₂ effects were not confounded by other pollutants. These 2 pollutants deserve greater attention with respect to bronchitic symptoms associated with air pollution among patients with asthma.

Reviewer’s Comments. This is another important study that helps to establish the effects of air pollution on children with asthma. The study was conducted in California, and the air pollution components that were investigated were derived from vehicular traffic more than industry. This article also demonstrates the need to investigate more extensively the effects of NO₂ and OC among children with asthma.

FREDERICK E. LEICKLY, MD
Indianapolis, IN

RELATIONSHIP OF OUTDOOR AIR QUALITY TO PEDIATRIC ASTHMA EXACERBATION


Purpose of the Study. To determine the relationship of outdoor air quality parameters to asthma exacerbations among children.

Study Population. Pediatric patients who had experienced an emergency department visit or an inpatient hospitalization at Cincinnati Children’s Hospital for treatment of acute asthma were studied.

Methods. The number of emergency department visits and hospitalizations for treatment of asthma were determined by review of emergency department logs and a hospital computer database. Air quality data were obtained from a centrally located monitoring station. Ozone concentrations were continuously monitored, and data were recorded as daily averages and the highest 1-hour average concentration for each day. Concentrations of airborne particulates <10 μm in diameter were obtained by using a volumetric air sampler with a size-selective inlet, and 24-hour average values were calculated. Pollen and
fungal counts were obtained by using a Rotorod sampler (Multidata, Inc, Plymouth Meeting, PA). Multiple-regression models were developed to examine all potential exposure measures as predictors of the number of daily asthma visits. Poisson regression analysis was used to model the daily number of asthma visits as a function of air quality data and temporal variables. In the data analyses, air quality measures from 0 to 5 days before the asthma visit date were used, to account for delayed effects.

Results. A series of Poisson regression models was used to identify predictors of changes in the number of asthma visits. Initially, the logarithm of pollen counts and the month of the year (April to October) were significant predictors of the number of asthma visits. The number of asthma visits per day was associated with pollen counts reported for the same day (P = .014). The effect was increasingly strong, however, for pollen counts recorded 1, 2, and 3 days before the visit. The logarithm of the pollen counts lagged 3 days was the most significant predictor of asthma visits (P < .001). This effect was very strong during the summer and spring months; however, in the autumn, when pollen counts and asthma visits were both high, daily variations in pollen counts did not account for the variations in daily asthma visits as they did during other seasons. The analyses also showed a synergistic effect between pollen and particulate levels, in that the exposure-response to pollen counts was moderately high on days when particulate matter levels were low but was significantly higher on days when particulate matter levels were >33 μg/m³. Fungal spore counts and average ozone concentrations were not significant predictors of asthma visits.

Conclusions. Ambient concentrations of pollens and small particles were strongly associated with emergency visits for treatment of pediatric asthma in Cincinnati, Ohio. Concentrations of ozone did not appear to be associated with pediatric asthma exacerbations.

Reviewer’s Comments. Several studies have demonstrated associations between particulate matter levels and emergency department visits, and several have shown correlations between pollen counts and asthma symptoms. This study shows the added effects of both on asthma symptoms. It would be interesting to evaluate particulate matter levels and pollen counts in various urban, suburban, and rural settings, to assess their influence. In addition, examination of particulate matter levels inside and outside households, schools, and offices might give us a better understanding of the conditions that influence asthma. The fact that pollen counts influenced asthma admissions in the spring and summer but not the autumn might be secondary to other factors that dominate during that season (eg, cold weather and respiratory infections).

HELEN SKOLNICK, MD
Princeton, NJ

ASSOCIATION OF LOW-LEVEL OZONE AND FINE PARTICLES WITH RESPIRATORY SYMPTOMS IN CHILDREN WITH ASTHMA


Purpose of the Study. Exposure to ozone and particulate matter of ≥2.5 μm (PM2.5) in air at levels above current US Environmental Protection Agency (EPA) standards is a risk factor for respiratory symptoms among children with asthma. This study sought to examine the simultaneous effects of ozone and PM2.5 at levels below EPA standards, on daily respiratory symptoms and rescue medication use among children with asthma.

Study Population. Daily respiratory symptoms and medication use were examined prospectively for 271 children, <12 years of age, with physician-diagnosed, active asthma who were residing in southern New England.

Methods. Exposure to ambient concentrations of ozone and PM2.5 from April 1, 2001, through September 30, 2001, was assessed with peak 1-hour and 8-hour ozone levels and 24-hour PM2.5 levels. Logistic regression analyses with generalized estimating equations were performed separately for maintenance medication users (n = 130) and nonusers (n = 141). Associations between pollutant levels (adjusted for temperature and controlling for same- and previous-day levels) and respiratory symptoms and rescue medication use were evaluated. Major outcome measures were respiratory symptoms and rescue medication use, as recorded on calendars by the subjects’ mothers.

Results. Mean ± SD levels were 59 ± 19 ppb (1-hour average) and 51 ± 16 ppb (8-hour average) for ozone and 13 ± 8 μg/m³ for PM2.5. In copollutant models, ozone but not PM2.5 levels were significantly associated with respiratory symptoms and rescue medication use among children using maintenance medication; a 50-ppb increase in 1-hour ozone levels was associated with increased likelihood of wheeze (by 35%) and chest tightness (by 47%). The highest levels of ozone (1-hour or 8-hour averages) were associated with increased shortness of breath and rescue medication use. No significant, exposure-dependent associations were observed for any outcome with any pollutant among children who did not use maintenance medication.

Conclusion. Asthmatic children using maintenance medication were particularly vulnerable to ozone, controlling for exposure to fine particles, at levels below EPA standards.

Reviewer’s Comments. This is an excellent study that provides persuasive evidence regarding the adverse effects of air pollution in childhood asthma, even at levels that are generally regarded as safe.

ROBERT A. WOOD, MD
Baltimore, MD

PERSONAL EXPOSURE TO NITROGEN DIOXIDE AND THE SEVERITY OF VIRUS-INDUCED ASTHMA IN CHILDREN


Purpose of the Study. Nitrogen dioxide (NO2) exposure has been linked to respiratory tract illness. This study examined the relationship between the level of personal exposure to NO2 and the severity of asthma exacerbations caused by respiratory viral infections.

Study Population. The subjects were 114 asthmatic children, 8 to 11 years of age (63 male subjects and 51 female subjects).

Methods. The cohort of 114 children collected daily upper and lower respiratory tract symptom scores and peak expiratory flow (PEF) values for up to 13 months. During this time, NO2 collection tubes were worn on the children’s outer clothing, placed in the subjects’ bedrooms at night, and changed weekly. Symptom scores determined the likelihood of an upper respiratory tract infection and prompted the collection of nasal aspirates, for assessment of the presence of common respiratory viruses and atypical bacteria with reverse transcription-polymerase chain reaction assays. NO2 exposure levels were divided into tertiles of low (<7.5 μg/m³), medium (7.5–14 μg/m³), and high (>14 μg/m³). Exposure levels in the week before
or after an upper respiratory tract infection were analyzed in relation to the severity of asthma in the week after an infection.

Results. Two hundred nineteen episodes of upper respiratory tract infection occurred among 99 subjects. Lower respiratory tract symptom scores were increased and PEF values were decreased with increasing personal exposure to NO\textsubscript{2} in the week before infection for all upper respiratory tract infections combined and for piconavirus and respiratory syncytial virus individually. There was no significant change in lower respiratory tract symptom scores or PEF values with high NO\textsubscript{2} exposure in the week after infection.

Conclusions. Higher levels of NO\textsubscript{2} exposure in the week before the beginning of a respiratory tract infection were associated with increases in the severity of resulting asthma exacerbations.

Reviewer’s Comments. NO\textsubscript{2} exposure may be derived from indoor sources, such as gas-burning stoves or wood-burning fireplaces. The levels of NO\textsubscript{2} in this study were well within the standards for air quality safety. NO\textsubscript{2} exposure itself, in the range experienced by the study cohort, was not associated with adverse symptom scores or lower PEF values. The highest levels of exposure were associated with worsening of asthma symptoms and decreased PEF values in the presence of upper respiratory tract infection. The results should be interpreted with caution, however, because there were no control aspirates from subjects with stable symptom scores and PEF values.

Michael S. Kaplan, MD
Los Angeles, CA

ASSOCIATION OF RECURRENT WHEEZING WITH SENSITIVITY TO COCKROACH ALLERGEN IN INNER-CITY CHILDREN

Purpose of the Study. To assess the prevalence of positive allergy skin test results for common inhaled allergens and the association with wheezing among inner-city children being examined in a general pediatric clinic.

Study Population. Seventy-five children, 2 months to 10 years of age, were studied. The children were undergoing well-child or follow-up visits in the general pediatric clinic at a teaching hospital in Chicago, Illinois. Children who had not been previously diagnosed as having asthma or other atopic diseases, as documented in their medical records, were selected.

Methods. Demographic data were collected for suburban versus urban residents. A questionnaire was administered regarding episodes of wheezing in the previous year and the presence of other allergic symptoms, family history, exposure to smoking and pets, and the presence of cockroaches in the home. Each child underwent standard allergy skin testing performed with the puncture method, with the Quintest skin test device (Hollister Stier Laboratories, Spokane, WA). Testing was performed for dust mites, cockroach mixture, cat hair, dog dander, mold mixture, grass mixture, and ragweed, with positive and negative control samples.

Results. A total of 37% of the children demonstrated positive skin test results for \( \geq 1 \) allergen; 29% of the children were sensitive to dust mites, 15% to cockroach mixture, 9% to cat hair, 7% to mold, 4% to grass, 3% to ragweed, and 1% to dog dander. Cockroach allergen was the only allergen that was correlated significantly with previous episodes of wheezing. Sixty-four percent of children with positive skin test results for cockroach allergen had a history of wheezing, compared with 33% of those with negative results for cockroach allergen (\( P = .05 \)). None of the families acknowledged seeing cockroaches in their homes. No significant correlation between exposure to cigarette smoke at home and a history of wheezing was noted.

Conclusions. Among a population of inner-city children not previously identified as atopic, more than one-third of the children showed sensitivity to \( \geq 1 \) environmental allergen. Although dust mite allergen was the most common allergen to which children were sensitized, cockroach allergen sensitivity was the only response that was...
correlated significantly with previous episodes of wheezing.

Reviewer’s Comments. Although this study was conducted in a general pediatric population, there are 3 messages that are very consistent with others that have focused on inner-city children with diagnosed asthma. First, wheezing is very common; second, allergic sensitization is extremely common, especially considering the age group included in this study; and third, cockroach is the allergen that is most associated with asthma morbidity in inner-city children.

ALAN B. GOLDSOBEL, MD
San Jose, CA

COCKROACH ALLERGEN EXPOSURE AND SENSITIZATION IN SUBURBAN MIDDLE-CLASS CHILDREN WITH ASTHMA


Purpose of the Study. To evaluate the prevalence of cockroach allergen exposure in middle-class suburban environments and its relationship to sensitization.

Study Population. A total of 339 children (6–17 years of age) with physician-diagnosed asthma were recruited from 3 pediatric practices located in suburban and rural counties surrounding Baltimore, Maryland, and from 1 practice located within Baltimore city. The children were required to have currently active asthma, and the families needed to agree to a home visit.

Methods. The families completed a demographic questionnaire, and an environmental technician conducted a house inspection and collected dust samples, which were analyzed for cat, dog, cockroach, and dust mite allergens. The children underwent skin testing with a sampling of perennial and seasonal allergens, including cat, dog, cockroach, and dust mite allergens.

Results. Of the study children, 44% were male and 49% were white. Seventy-seven percent lived in rural or suburban areas, 53% of the families had an annual income of more than $50,000, and 49% of the mothers had college degrees. Thirty percent of the suburban-rural homes were found to have measurable cockroach antigen, whereas dust mite, cat, and dog allergens were detected for 40%. Only 5% of the suburban-rural homes with measurable cockroach antigen had evidence of cockroach infestation. Sensitization testing with perennial allergens revealed that 71% of subjects were sensitized to dust mite allergen, 29% to cat allergen, 76% to ≥1 seasonal outdoor allergen, and 10% to dog allergen. Cockroach allergen sensitization did discriminate between urban and suburban dwellers, identifying 35% of urban residents, compared with 21% of suburban-rural residents. A kitchen cockroach allergen (Bla g 1) level of >1 U/g was significantly associated with cockroach sensitization and was found in both urban and suburban groups.

Conclusions. The presence of cockroach allergen occurs more frequently in suburban middle-class homes than previously thought, and low-level exposure to this antigen is a risk factor for sensitization.

Reviewer’s Comments. Cockroach antigen was demonstrated for a surprisingly high percentage of middle-class suburban homes. The results show that even low levels of exposure can cause sensitization. Interestingly, only a small percentage of homes in which cockroach antigen was identified exhibited evidence of infestation when examined by the environmental technician. The reason for this is not totally clear. This study suggests that reliance on ques-

THE PREVALENCE OF RAT ALLERGEN IN INNER-CITY HOMES AND ITS RELATIONSHIP TO SENSITIZATION AND ASTHMA MORBIDITY


Purpose of the Study. To determine the prevalence of rat allergen in the homes of inner-city children with asthma and to examine the relationship between rat allergen exposure, sensitization, and asthma morbidity.

Study Population. Children enrolled in the National Cooperative Inner-City Asthma Study were studied.

Methods. Dust samples collected from the homes of 1528 asthmatic children from 8 major inner-city areas were analyzed with the use of a new monoclonal antibody-based enzyme-linked immunosorbent assay, to determine the prevalence of rat allergen in dust samples from inner-city homes of the National Cooperative Inner-City Asthma Study population. Home characteristics were evaluated to identify variables that were associated with the presence of rat allergen. Data were also analyzed to assess the relationships between the presence of rat allergen, sensitization, and asthma morbidity.

Results. Thirty-three percent of inner-city homes had detectable rat allergen (Rat n 1). The presence of rat allergen was associated with reported rat and mouse infestation, as well as evidence of mouse infestation in home inspections. Twenty-one percent of the participants were sensitized to rat allergen; however, sensitization was not more common when rat allergen was found in the home. The numbers of hospitalizations, unscheduled medical visits, and days with decreased activity because of asthma were significantly increased for individuals who were both sensitized and exposed to rat allergen.

Conclusions. Rat allergen sensitization and exposure were associated with increased asthma morbidity among inner-city children.

Reviewer’s Comments. Rodent allergens are known to cause immunoglobulin E-mediated hypersensitivity in occupational settings. Recently, mouse allergen was identified as an important allergen among asthmatic children. This is the first study to investigate the prevalence and significance of rat allergen in inner-city homes. The most remarkable finding in this study was the relationship between rat allergen and morbidity among inner-city asthmatic children. These results suggest that rat allergen exposure is an important public health concern and control measures should be implemented in inner-city neighborhoods. Rat allergen reduction measures might have significant effects on asthma morbidity and might reduce overall health care utilization for inner-city children with asthma.

ANNA NOWAK-WEGRZYN, MD
New York, NY

EFFECT OF MATTRESS AND PILLOW ENCASINGS ON CHILDREN WITH ASTHMA AND HOUSE DUST MITE ALLERGY

Purpose of the Study. Allergy to house dust mite (HDM) is an important contributor to childhood asthma, and these investigators sought to determine whether the use of mattress and pillow encasings resulted in effective long-term control of mattress HDM levels, thus reducing the need for maintenance asthma medication.

Study Population. The subjects were 60 children (5–15 years of age) with asthma and HDM allergy, in the absence of any other clinically relevant allergy. Inclusion criteria included physician-diagnosed asthma, positive HDM puncture skin test results, positive HDM bronchoprovocation results, and total HDM concentrations of ≥2000 ng/g dust from the child’s mattress. All except 4 of the study patients were treated with inhaled corticosteroids.

Methods. In this prospective, double-blind, placebo-controlled, 1-year study, children were randomized to the use of active (allergy control) or placebo mattress and pillow encasings. Baseline measures included mattress dust sampling, spirometry, and adjustment of medications. Symptom scores and peak flows were recorded throughout the study. Clinical assessments, including medication adjustments, and dust sampling were performed every 3 months. Bronchoprovocation was performed at the time of inclusion and at completion of the study.

Results. Twenty-six children in the active treatment group and 21 children in the placebo group completed the study. A significant perennial reduction in levels of HDM allergen recovered from mattresses was noted only for the active treatment group. Significant decreases in the doses of inhaled corticosteroids also were noted only for the active treatment group. There were no significant differences between the active treatment and placebo groups in any of the secondary endpoints, including peak flow and forced expiratory volume in 1 second, symptoms, and HDM bronchoprovocation results.

Conclusions. The use of mattress and pillow encasings led to significant long-term reductions in HDM allergen levels in mattresses and in the need for inhaled corticosteroids among children with asthma and HDM allergy.

Reviewer’s Comments. Another study in the same issue showed no difference in allergic rhinitis symptom control among patients randomized to receive allergen-impermeable bed covers, as opposed to sham covers. It may be postulated that there is no single intervention strategy that, by itself, significantly affects immunoglobulin E-mediated upper and lower airway involvement. This does not exclude the possibility that control of house dust mite exposure, in addition to other active treatments and more comprehensive environmental control measures, may have beneficial effects for selected patients.

BRADLEY E. CHIPPS, MD
Sacramento, CA

KNOWLEDGE AND PRACTICE OF DUST MITE CONTROL BY SPECIALTY CARE


Purpose of the Study. To compare the knowledge and practice of environmental control measures in families of children with asthma who were treated by either an allergist or a pediatrician.

Study Population. The subjects were 114 asthmatic children (age range: 6–17 years; mean age: 11.2 years) with positive skin test results for house dust mites. The children were recruited from 4 pediatric practices in the Baltimore metropolitan area.

Methods. A cross-sectional study using secondary analyses of data from a clinical trial of parents and their children with asthma was performed. In the initial visit, skin testing was performed and the parent answered baseline questions related to the child’s health history. A baseline home environment evaluation consisted of 35 questions addressing the family’s cleaning habits, knowledge of environmental control measures, and self-reported changes in the home to reduce the child’s exposure to indoor allergens. A home inspection evaluated the home characteristics, as well as evidence of dust mite environmental controls (eg, mattress encasement, pillow encasement, removal of wall-to-wall carpeting, and removal of stuffed animals). Dust samples were collected and analyzed for indoor allergens with standard methods. The children were divided into 2 groups, according to whether they had been treated by an allergist. The study then
determined whether the 2 groups had ever been advised to make changes in their homes to reduce dust mite exposure (knowledge) and whether they had made any changes in their homes to reduce dust mite exposure (practice).

**Results.** The study families were predominately white (50%) or African American (35%). All of the children demonstrated positive skin test results for dust mite allergen, 61% (n = 69) had been examined and skin-tested by an allergist before enrolling in the study, and 4% were currently receiving immunotherapy. Fifty-six of the 69 families (81%) that had visited an allergist reported receiving advice regarding general indoor environmental control, compared with 22 families (49%) that had not visited an allergist (P < .0001). With respect to specific dust mite recommendations, families that had been evaluated by an allergist had significantly more dust mite knowledge (70% vs 18%, P < .0001). Families that had visited an allergist demonstrated a significantly greater frequency of knowledge regarding the need for mattress encasement (61% vs 13%, P < .001) and pillow encasement (51% vs 11%, P < .0001), compared with the non-allergist-treated group. Families that had visited an allergist demonstrated somewhat greater implementation of dust mite control recommendations, compared with families that had visited a pediatrician (68% vs 56%, P = .063). The use of mattress and pillow encasements was significantly greater (38% vs 11%, P = .001, and 36% vs 16%, P = .009, respectively) in the allergist-treated group than in the pediatrician-treated group. To evaluate adherence, comparisons of each family’s knowledge of specific recommendations with the changes made in the household were made. Of the families that had visited an allergist, 70% had knowledge of dust mite control measures and 60% of those families made at least 1 of the 4 observable changes in their households to reduce dust mite allergen exposure. Of the families that had visited a pediatrician, 18% had knowledge of dust mite control recommendations and 63% of those families made changes in their households.

**Conclusions.** Parents of dust mite-sensitive, asthmatic children who visited an allergist were more aware of dust mite allergen control recommendations and made more indoor environmental changes. Allergists are able to perform specific tests to determine allergies and can offer directed education regarding environmental control measures.

**Reviewer’s Comments.** This study emphasizes the importance of identifying allergy triggers. Without knowledge of specific allergy triggers, guidelines for environmental controls can only be vague. When given specific advice, patients appeared to be equally motivated, regardless of which physician provided the environmental control advice. However, a limitation of the study, as the authors noted, was that the subjects in the study were predominantly middle-class children; patients in lower socioeconomic groups might have different outcomes. In addition, depending on the type of insurance (if any), patients might not have easy accessibility to an allergist.

**Helen Skolnick, MD**
Princeton, NJ

**Fungal Levels in the Home and Lower Respiratory Tract Illnesses in the First Year of Life**


**Purpose of the Study.** Previous studies found a relationship between home dampness and lower respiratory tract symptoms among children. Is this relationship attributable to exposure to fungi, which thrive in damp conditions?

**Study Population.** A birth cohort of 499 children with a history of asthma or allergy for at least 1 parent was studied.

**Methods.** During a home visit, when the child was 2 or 3 months of age, a technician determined household and socioeconomic characteristics and obtained air and dust samples. Every 2 months thereafter, a follow-up telephone questionnaire, regarding respiratory symptoms and illnesses experienced by the child, was administered to the child’s primary caregiver. In-home fungal concentrations were evaluated as predictors of lower respiratory tract illnesses (LRIs) (croup, pneumonia, bronchitis, and bronchiolitis) in the first 1 year of life.

**Results.** In multivariate analyses, after controlling for gender, the presence of water damage or visible mold/mildew, being born in winter, breastfeeding, and being exposed to other children through siblings, the authors found a significantly increased relative risk (RR) of LRI with high levels (>90th percentile) of airborne Penicillium (RR: 1.73; 95% confidence interval [CI]: 1.23–2.43), dust-borne Cladosporium (RR: 1.52; 95% CI: 1.02–2.25), Zygomycetes (RR: 1.96; 95% CI: 1.35–2.83), or Alternaria (RR: 1.51; 95% CI: 1.00–2.28), or any fungus (RR: 1.86; 95% CI: 1.21–2.88).

**Conclusions.** Exposure to high fungal levels increased the risk of LRI in infancy. The actual mechanisms remain unknown. Sensitivity to inhaled allergens, including mold, as measured with skin testing or radioallergosorbent testing, is uncommon in infancy, and this association in infancy is likely to be nonallergic.

**Reviewer’s Comments.** These are interesting and potentially useful findings, but more study is required. It should be noted that no increase in LRI was associated with high levels of exposure to a large number of other individual fungi evaluated. As the authors pointed out, “People are routinely exposed to >200 different species of fungi. Exposure occurs universally and is impossible to avoid completely. Often there are no adverse effects from these exposures.” It is hoped that solid scientific work such as this will not be misconstrued to bolster the mold hysteria prevalent in many parts of the country, resulting in expensive and unnecessary mold removal projects.

**John M. Kelso, MD**
San Diego, CA

**β-Adrenergic Agonist Therapy**

**Comparison of Racemic Albuterol and Levalbuterol for Treatment of Acute Asthma**


**Purpose of the Study.** Inhaled β-receptor agonists are widely used to treat bronchospasm and acute asthma exacerbations. Recently, a new β agonist, levalbuterol, which is the R-isomer of albuterol, was introduced. This study was conducted in an acute setting, to compare albuterol and levalbuterol.

**Methods.** This was a randomized, double-blind, controlled trial conducted in the emergency department and inpatient asthma care unit of a children’s hospital. Children were 1 to 18 years of age; the study group included 482 patients, with a total of 547 enrollments. Patients received a nebulized solution of either 2.5 mg of racemic albuterol or 1.25 mg of levalbuterol every 20 minutes, for a maximum of 6 doses. Children subsequently admitted to
the asthma care unit were treated in a standardized manner, with continued administration of the drugs assigned in the emergency department. The primary outcome parameter was hospitalization rate.

**Results.** The hospitalization rate was significantly lower for the levalbuterol group (36%) than for the racemic albuterol group (45%, \( P = .02 \)). The adjusted relative risk of admission for the racemic albuterol group, compared with the levalbuterol group, was 1.25 (95% confidence interval: 1.01–1.57). There was no difference in the lengths of hospital stays, and there were no significant adverse events in either group.

**Conclusion.** Substituting levalbuterol for racemic albuterol in the emergency department treatment of acute asthma significantly reduced the number of hospitalizations.

**Reviewer’s Comments.** Additional prospective trials, including pulmonary function studies and economic analyses, will be necessary to justify the use of levalbuterol, rather than albuterol, as standard practice.

**Christopher Randolph, MD**
*Waterford, CT*

### COMPARATIVE EFFICACY OF TERBUTALINE SULFATE DELIVERED BY TURBUHALER DRY POWDER INHALER OR PRESSURIZED METERED-DOSE INHALER WITH NEBUHALER SPACER IN CHILDREN DURING AN ACUTE ASTHMATIC EPISODE


**Purpose of the Study.** Several previous studies demonstrated that the bronchodilator effect of a metered-dose inhaler (MDI) with spacer was just as good as that of a nebulizer for treatment of acute asthma exacerbations among children. What about a MDI with spacer versus a dry powder inhaler (DPI)?

**Study Population.** A total of 112 children with asthma, 6 to 16 years of age, who presented to an emergency department with asthma exacerbations were studied. Baseline forced expiratory volume in 1 second (FEV₁) values were 25 to 60% of predicted values.

**Methods.** Patients were randomized to receive terbutaline through either a MDI with spacer or a DPI (Turbuhaler, AstraZeneca, Lund, Sweden). Doses were administered at 0 and 30 minutes, and FEV₁ values were measured at 0, 30, and 60 minutes.

**Results.** No differences in increases in FEV₁ were seen at 30 minutes (MDI with spacer: 35%; DPI: 33%) or 60 minutes (MDI with spacer: 50%; DPI: 49%). There were also no differences in oxygen saturation or heart rates.

**Conclusion.** For treatment of acute asthma exacerbations among children ≥6 years of age, delivery of a bronchodilator with a DPI works just as well as delivery with a MDI with spacer.

**Reviewer’s Comments.** The Environmental Protection Agency and the Food and Drug Administration are mandating that current MDIs be phased out, because of the adverse environmental effects of chlorofluorocarbon propellants. Inhaler manufacturers have complied either by using more environmentally friendly propellants (such as hydrofluoroalkanes) or by eliminating the propellant entirely in DPIs. It is reassuring to know that, even in acute asthma exacerbations, children ≥6 years of age can effectively use a DPI for delivery of bronchodilator.

**John M. Kelso, MD**
*San Diego, CA*

### RANDOMIZED, DOUBLE-BLEND, PLACEBO-CONTROLLED TRIAL OF ORAL ALBUTEROL IN INFANTS WITH MILD-TO-MODERATE ACUTE VIRAL BRONCHIOLITIS


**Purpose of the Study.** To determine whether oral albuterol therapy is effective in reducing symptoms of mild/moderate acute viral bronchiolitis.

**Study Population.** A total of 129 previously healthy infants (≤12 months of age) discharged directly home from the emergency department (ED), with a clinical diagnosis of acute viral bronchiolitis, were studied.

**Methods.** At discharge from the ED, patients were randomly assigned to receive either oral albuterol therapy (0.1 mg/kg per dose) or oral placebo treatment. Infants were treated 3 times daily for a maximum of 7 days or until complete resolution of bronchiolitis symptoms, whichever happened first. Overall health, medication compliance, feeding and sleeping patterns, follow-up visits, parental life disruptions, and adverse events were discussed in daily telephone interviews until the resolution of symptoms or for 14 days. The primary outcome of interest was the time from study enrollment until the resolution of illness, as determined by the primary caregiver. Secondary outcomes of interest included duration of cough, coryza, and noisy breathing, time to normal feeding, and time to normal sleeping.

**Results.** During the study, 1039 infants were discharged from the hospital ED with acute viral bronchiolitis. Of those, 231 were eligible and 129 were randomized into the study. The mean ages were 5.4 months for the albuterol group and 5.1 months for the placebo group. Respiratory syncytial virus was the pathogen found most frequently (albuterol: 81%; placebo: 79%) in nasopharyngeal aspirates collected from 61 infants in the 2 groups. The median number of days of illness before ED presentation for both groups was 4.0 days. The mean times to the resolution of illness were similar for the 2 groups (albuterol: 8.9 days; placebo: 8.4 days). There were no significant differences in secondary outcomes between the groups. Hospitalization for treatment of respiratory distress was eventually required for 4 infants in the albuterol group and 5 in the placebo group. There were similar median numbers of health care revisits for the 2 groups (albuterol: 1; placebo: 0). There were also similar median numbers of days in which trembling and vomiting were observed (albuterol: 0; placebo: 0 and 1, respectively).

**Conclusions.** There was no significant difference in symptom resolution for newly diagnosed bronchiolitis treated with orally administered albuterol versus placebo. The authors did not recommend the use of orally administered albuterol for this patient population.

**Reviewers’ Comments.** Although previous studies found similar results, most outcomes in this study were based solely on subjective evaluations by the primary caregiver at home. The authors present compelling evidence that orally administered albuterol, at the dose used in this study, has little role in the treatment of bronchiolitis among infants. However, the dose of albuterol was at the low end of the recommended dose range of 0.1 to 0.2 mg/kg per dose, administered 3 times daily.

**Joseph Shapiro, MD**
*Los Angeles, CA*

**Michael S. Kaplan, MD**
*San Diego, CA*
A MULTICENTER, RANDOMIZED, DOUBLE-BLIND,CONTROLLED TRIAL OF NEBULIZED EPINEPHRINE IN INFANTS WITH ACUTE BRONCHIOLITIS


Purpose of the Study. To explore the role of racemic epinephrine, administered via inhalation, in acute bronchiolitis.

Study Population. Infants with corrected ages of <12 months who were admitted for a first episode of wheezing were studied. A clinical diagnosis of bronchiolitis was required, with upper respiratory congestion and evidence of turbulent airflow in the lower airway.

Methods. Standard therapy, including hydration, oxygen administration, and upper airway suctioning, was administered to all patients. Treatment with a Jet nebulizer, driven with 6 L/minute oxygen, was used for 3 doses of 4 mg of epinephrine or placebo. Measurement of oxygen saturation, heart rate, and respiratory score was performed before and after treatment.

Results. There was no statistical difference between the groups with respect to time to readiness for discharge, as defined by no oxygen requirement for 10 hours, good hydration, and no retractions. A requirement for supplemental oxygen was the strongest predictor of disease severity and length of hospitalization. Increased heart rate after epinephrine treatment (20 beats/minute) was observed for the treatment group but there were no changes in respiratory rates, blood pressure, or respiratory effort scores.

Conclusions. The use of nebulized epinephrine did not reduce the time to readiness for discharge among infants with bronchiolitis.

Reviewer’s Comments. These results support a recent meta analysis. A recent study suggested that the use of 3% normal saline with 1.5 mg of epinephrine, administered via inhalation, was superior to the use of 0.9% normal saline with 1.5 mg of epinephrine. The burden of evidence continues to indicate that supportive therapy, with good hydration, upper airway suctioning, and oxygen administration, is the most important intervention strategy for acute viral bronchiolitis. A trial of inhalation therapy with epinephrine or albuterol could be supported if responses were observed and continued; if not, the trial should be discontinued.

BRADLEY E. CHIPPS, MD
Sacramento, CA

STEROID THERAPY

EFFICACY OF A SHORT COURSE OF PARENT-INITIATED ORAL PREDNISOLONE FOR VIRAL WHEEZE IN CHILDREN AGED 1 TO 5 YEARS: RANDOMIZED CONTROLLED TRIAL


Purpose of the Study. To determine whether a parent-initiated, short course of oral prednisolone treatment for viral wheeze decreased mean 7-day daytime and nighttime lower respiratory symptom scores among children 1 to 5 years of age.

Study Population. Children 1 to 5 years of age who were admitted for treatment of viral wheeze, which was defined as an acute episode of wheezing that occurred within 2 days of coryzal upper respiratory tract symptoms, were studied.

Methods. Children were recruited for this double-blind, randomized, placebo-controlled trial from the University Hospitals of Leicester National Health Service Trust Hospital. A pediatrician confirmed the diagnosis of rhinitis and wheeze. Blood samples were obtained from recruited patients, for determination of eosinophil cationic protein (ECP) and eosinophil protein X (EPX) levels. Patients were stratified with respect to eosinophil priming, to investigate whether high-risk patients would demonstrate greater responses to corticosteroids. On the basis of ECP and EPX levels, patients were stratified to a high-primed stratum (ECP levels of >20 g/L or EPX levels of >40 g/L) or a low-primed stratum (ECP levels of <20 g/L or EPX levels of <40 g/L). Patients in the high-primed stratum were considered at high risk for developing persistent wheeze. Patients were then randomized to receive 5 days of oral prednisolone (20 mg) or placebo treatment. Parents were told to initiate medication for the next episode of viral wheezing. Parents recorded daytime and nighttime lower respiratory tract symptoms for 7 days after the initiation of trial medication. Inhaled salbutamol was administered to patients as needed, and parents were instructed to record use. The children’s physicians could substitute orally administered prednisolone if it was deemed clinically necessary. Patients who did not experience an episode of viral wheezing within 12 months after randomization were withdrawn from the study.

Results. Of the 230 children who were randomized, 121 completed the study protocol and were included in the data analysis. There was no difference in mean 7-day daytime and nighttime symptom scores between the prednisolone group and the placebo group. There was no difference between the 2 groups in salbutamol usage, substitution of trial medication for oral prednisolone therapy, or parental opinions regarding the efficacy of treatment. There was a trend toward increased hospitalizations in the prednisolone group, but this was not significant. Stratification of children into high-primed and low-primed groups did not demonstrate any differences in outcomes.

Conclusions. A parent-initiated, short course of oral prednisolone therapy did not have any benefit among children with viral wheeze, compared with placebo. This was true also when children were stratified into groups with high and low eosinophil priming.

Reviewers’ Comments. Wheezing among preschool-aged children with respiratory tract illnesses is common. Many of these children may be treated with corticosteroids for alleviation of symptoms. However, this study shows that parent initiation of oral corticosteroid therapy for their children is not efficacious. Correctly diagnosing wheeze among preschool-aged children can be difficult. Therefore, parents may be initiating treatment on the basis of faulty diagnoses. At this time, it seems prudent for preschool-aged children who develop wheeze to be examined by their doctors, for diagnosis of wheeze and initiation of treatment.

NAVEENA BOBBA, MD
MICHAEL S. KAPLAN, MD
Los Angeles, CA

INHALED CORTICOSTEROIDS MAY BE SUPERIOR TO SYSTEMIC CORTICOSTEROIDS IN CHILDREN WITH MODERATE-TO-SEVERE ACUTE ASTHMA

Purpose of the Study. To compare the efficacy of inhaled corticosteroids with that of orally or intravenously administered corticosteroids in the treatment of acute moderate/severe asthma.

Study Population. The 135 subjects were 6 to 17 years of age, with at least 1 previous episode of wheezing, and were recruited from 1 of 2 emergency centers (ECs) after presentation with acute asthma symptoms.

Methods. Patients were randomized, after receiving an initial dose of albuterol, to 1 of 3 corticosteroid treatment groups if their Wood asthma scores were 4 or 5. All patients received their corticosteroid dose within 15 minutes after the initial albuterol dose. Group A received triamcinolone (600 μg, 100 μg/puff) via inhaler with a spacer, group B received orally administered prednisone (2 mg/kg), and group C received intravenously administered methylprednisolone (2 mg/kg). The decision to hospitalize was made by the EC attending physician, without input from investigators. After EC discharge, group A patients continued to receive triamcinolone (6 puffs 3 times daily for 1 day and then 4 puffs 3 times daily for 3 days); group B and C patients continued to receive orally administered prednisone (1 mg/kg twice daily for 4 days). Outcomes measured were the number of patients hospitalized from each treatment group and the number of unscheduled return visits 1 week after discharge from the EC.

Results. Seven percent of group A patients were hospitalized, compared with 22% and 29% of patients in groups B and C, respectively (P = .020). There were significantly more unscheduled return visits in groups B and C (41.5% combined), compared with group A (12%; P = .007). Hospitalizations or unscheduled return visits were considered treatment failures; rates were 19%, 62%, and 70% in groups A, B, and C, respectively (P = .001).

Conclusions. Patients who received inhaled triamcinolone were less likely to be hospitalized for treatment of acute asthma, compared with those who received orally or intravenously administered corticosteroids. Patients who received inhaled triamcinolone had significantly fewer unscheduled return visits 1 week after EC discharge, compared with patients in the oral or intravenous corticosteroid treatment groups.

Reviewers’ Comments. This was a small, prospective, clinical trial, suggesting that children with asthma could be effectively treated with inhaled corticosteroids in an acute care setting and might experience fewer treatment failures, compared with those who received orally or intravenously administered corticosteroids. One major limitation of the study was the lack of blinding. The attending EC physician might have been biased and more likely to discharge patients from the EC if they were in the inhaled corticosteroid group. Other limitations included the small number of patients and a poorly defined asthma diagnosis. A larger, prospective, double-blind study in a well-defined asthma population would strengthen these findings and might change acute asthma treatment.

Tamara T. Perry, MD
Robert A. Wood, MD
Baltimore, MD

ORAL PREDNISOLONE IN THE ACUTE MANAGEMENT OF CHILDREN AGE 6 TO 35 MONTHS WITH VIRAL RESPIRATORY INFECTION-INDUCED LOWER AIRWAY DISEASE: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL


Purpose of the Study. Systemic corticosteroid use for the treatment of acute wheezing among preschool-aged children is controversial, with a recent meta-analysis finding only marginal positive effects with orally administered corticosteroids among children < 24 months of age. The objective of this study was to investigate the efficacy of oral prednisolone treatment of virally induced lower respiratory disease among young children.

Study Population. The clinical population included 230 children, 6 to 35 months of age, who presented with virally induced lower respiratory disease. Children with previous asthma or ≥ 2 wheezing episodes were excluded.

Methods. The study was a randomized, double-blind, placebo-controlled trial involving treatment with orally administered prednisolone (2 mg/kg per day) or placebo for 3 days. Measured outcomes included the effects of treatment on symptoms, hospital length of stay, and duration of illness.

Results. Hospitalization rates were similar for the 2 groups. However, for admitted children (n = 123), the median length of stay was 1 day shorter in the prednisolone group (2 days vs 3 days, P = .060). The proportions of children who required ≥ 3 days of hospitalization were 48% in the prednisolone group and 68% in the placebo group (P = .023). There was also a reduction in the need for additional asthma medication (18.0% vs 37.1%, P = .018) in the prednisolone group. The mean duration of symptoms of respiratory distress was 1 day in the prednisolone group, compared with 2 days in the placebo group, for both the hospitalized (P < .001) and nonhospitalized (P = .006) children.

Conclusions. A 3-day course of oral prednisolone therapy effectively reduced disease severity, length of hospital stay, and duration of symptoms among children, 6 to 35 months of age, with virally induced lower respiratory disease.

Christopher Randolph, MD
Waterbury, CT

EFFECTS OF Budesonide Inhalation Suspension, Compared with Cromolyn Sodium Nebulizer Solution, on Health Status and Caregiver Quality of Life in Childhood Asthma


Purpose of the Study. To compare the effects of 2 nebulized antiinflammatory asthma medications on asthma control and caregiver quality of life.

Study Population. Children 2 to 6 years of age, with mild/moderate persistent asthma, were studied.

Methods. This was a 52-week randomized trial in which the children received either budesonide inhalation suspension (0.5 mg once or twice daily) (N = 168) or cromolyn sodium nebulizer solution (20 mg 4 times daily) (N = 167), initially for 8 weeks, after which the dosage was adjusted at the discretion of the investigator. The Pediatric Asthma Caregiver’s Quality of Life Questionnaire, Compliance/Caregiver Satisfaction Questionnaire, and Modified Child Health Questionnaire-Parent Form 50 and Functional Status-II(R) questionnaires were administered at baseline and at weeks 8, 28, and 52. At the conclusion of the
study, global evaluations of the simplicity of asthma management and child health care status were obtained from caregivers and physicians.

Results. Improvements from baseline values in domain-specific (activities and emotional function) and total quality of life scores were greater at each time point (weeks 8, 28, and 52) for caregivers of patients treated with budesonide, compared with caregivers of patients treated with cromolyn sodium. Only the budesonide group met the criterion for clinically important improvement (≥0.5-unit change) in all quality of life domains by week 8, which was maintained at weeks 28 and 52. Budesonide resulted in greater caregiver satisfaction, treatment convenience, ease of use, and compliance, compared with cromolyn sodium. Therefore, 90.7% of caregivers in the budesonide group were completely or very satisfied, compared with 53.4% in the cromolyn sodium group. More than one-half (54.6%) of caregivers in the budesonide group rated budesonide highly or very convenient, compared with 25% for cromolyn sodium; 77% rated budesonide extremely or very easy to use, compared with 47% for cromolyn. Adherence with daily medication regimens was reported for 76% of children in the budesonide group, compared with 57% in the cromolyn sodium group. Child health status showed improvements from baseline values for both groups at weeks 8, 28, and 52. There was a trend for these improvements to be superior in the budesonide group. In addition, budesonide was superior to cromolyn sodium in caregiver and physician global assessments.

Conclusions. Budesonide inhalation suspension improved the quality of life for caregivers of children with asthma. Caregivers of children treated with budesonide reported significantly fewer limitations in daily activities and emotional functioning, compared with caregivers of children treated with cromolyn sodium nebulizer solution. Children treated with budesonide inhalation suspension and cromolyn sodium experienced improvements in health status. Treatment with budesonide inhalation suspension resulted in significantly lower mean rates of asthma exacerbations, significantly longer times to first asthma exacerbation, significantly longer times to first additional use of chronic asthma therapy, and significant improvements in asthma symptom scores and breakthrough medication use, compared with cromolyn sodium therapy. Safety profiles were similar for the 2 treatment groups. Budesonide inhalation suspension was associated with significantly greater caregiver satisfaction, convenience, ease of use, and compliance, compared with cromolyn sodium nebulizer solution.

Reviewer’s Comments. This was a nice study but the results are certainly not surprising. How many of us would have predicted that cromolyn would prove superior to an inhaled corticosteroid?

Christopher Randolph, MD
Waterbury, CT

EARLY INTERVENTION WITH BUDESONIDE IN MILD PERSISTENT ASTHMA: A RANDOMIZED, DOUBLE-BLIND TRIAL


Purpose of the Study. To determine whether treatment with low-dose inhaled budesonide would prevent severe asthma-related events and accelerated lung function decline among patients with recent-onset, mild, persistent asthma.

Study Population. A group of 7241 patients, 5 to 66 years of age, with mild asthma symptoms for 3 months to 2 years, were recruited from 499 sites in 32 countries.

Methods. Patients were randomly allocated to receive 400 µg of budesonide (200 µg for patients <11 years of age) or placebo once daily. The primary outcome measure was time to the first severe asthma-related event (admission, emergency treatment, or death), analyzed with an intent-to-treat approach. Follow-up visits, with spirometry and adverse event monitoring, occurred at 6 and 12 weeks after randomization and then every 3 months for 3 years. Patients recorded asthma-related events between visits. Changes in medication regimens, including the addition of inhaled corticosteroids, were allowed if considered clinically necessary.

Results. Budesonide reduced the risk of severe asthma-related events by 44% (hazard ratio: 0.56; 95% confidence interval: 0.45–0.71; P < .0001) and prolonged the time to the first asthma-related event. Budesonide-treated patients experienced significantly fewer severe asthma-related events, life-threatening exacerbations, days with symptoms, and courses of inhaled or systemic corticosteroids. The improvements in postbronchodilator forced expiratory volume in 1 second (FEV1) after 3 years were more pronounced among adults than among children (P = .004), although the improvements in postbronchodilator FEV1 after 1 year and in prebronchodilator FEV1 were similar. Surprisingly, budesonide did not improve prebronchodilator FEV1 among adolescent patients. Children in the budesonide group exhibited slowed growth (mean height difference: −0.43 cm/year; 95% confidence interval: −0.54 to −0.32 cm/year; P < .0001) to a lesser degree with each successive year.

Conclusions. Long-term, once-daily treatment with low-dose budesonide decreased the risk of severe exacerbations and improved asthma control among patients with mild persistent asthma of recent onset.

Reviewers’ Comments. Data on asthma-related events, symptoms, and medication use were not reported separately for the 2 pediatric age groups included in the study (5–10 years and 11–17 years). However, the morbidity associated with mild persistent asthma and the improvements in prebronchodilator FEV1 with budesonide treatment observed in this study suggest that children with mild persistent asthma may benefit from budesonide treatment early in the course of their disease. As always, the benefits of inhaled corticosteroids among children must be weighed against the potential side effect of mild growth delay.

ELINOR SIMONS, MD
ROBERT A. WOOD, MD
Baltimore, MD

FLUTICASONE PROPIONATE IN ASTHMA: A LONG-TERM, DOSE-COMPARISON STUDY


Purpose of the Study. To compare the efficacy and tolerability of 2 doses of fluticasone propionate (FP), 100 µg and 200 µg, administered twice daily, among children with moderate/severe asthma. This was in effect a dose-response study of FP among children.

Study Population. A total of 528 children, 4 to 11 years of age, who had at least a 6-month history of asthma and required high doses of inhaled corticosteroids (ICSs) were eligible for the study. These children had received budesonide, beclomethasone dipropionate, triamcinolone acetonide, or flunisolide (800–1600 µg/day), FP (400–600 µg/day), or orally administered corticosteroids (≤5 mg/day)
for at least 4 weeks before enrollment. Participants in the study were also required to have experienced at least 1 exacerbation of asthma that required oral/parenteral corticosteroid treatment or hospitalization in the previous 12 months. The children were not receiving any long-acting β-receptor agonists.

Methods. This was a multicenter, double-blind, parallel-group study that involved 39 sites, all in Europe. After a 2-week run-in period, patients were randomized to receive either 100 µg or 200 µg of FP twice daily, delivered with a Diskus inhaler (GlaxoSmithKline, Research Triangle Park, NC). Clinic visits occurred at regular intervals, and daily symptom scores were maintained. Peak flow measures were recorded twice daily. The frequency of rescue medication use was noted. The primary outcome measure was the time to the first asthma exacerbation. Exacerbations were defined as a 20% decline in peak flow for 2 consecutive days, increased use of quick reliever medications (more than twice daily for 2 consecutive days), or the use of systemic corticosteroids.

Results. Demographic characteristics were well matched between the 2 treatment groups. The median dose of ICS at baseline for both groups was 800 µg/day (range: 200–1600 µg/day). A subgroup of children experienced severe asthma (defined as ICS usage of >800 µg/day) in each arm of the study and were studied separately. The risk ratio for an asthma exacerbation with 200 µg FP versus 100 µg FP was 0.85. The risk of experiencing an exacerbation at any time was reduced by 15% for patients receiving the higher dose (200 µg) of FP. This was not statistically significant. In the subgroup analysis, there was a much larger, significant, 33% reduction in the risk of experiencing an exacerbation at any time during the study. Secondary outcomes included improved peak flow measures in the 200 µg FP group. In both groups, symptoms were controlled and few side effects were experienced.

Conclusion. The use of FP at 200 µg twice daily may offer benefits, compared with a lower dose, especially among children with more severe asthma.

Reviewer’s Comments. ICSs, alone and in combination with other agents, are the preferred treatment for all forms of persistent asthma. Increasing the dose of the ICS is frequently performed to help provide control. However, dose-response studies of ICS use among adults have yielded conflicting results, and there have been very few such studies among children. The lack of a clear dose-response relationship may lead to reluctance in optimizing the dose to increase control. This study provides insight into a dose-response relationship for the ICS FP. A difficulty with this study and many like it involves the initial mixtures of ICSs and the reporting of the doses used at baseline. It is also important to note that the modality of drug delivery was the Diskus inhaler, which is not used as frequently as metered dose inhalers. ICS usage, especially among children, has been hampered by a paucity of data providing dose-response information. One dose for all forms of persistent asthma is clearly not the way to treat children. Children with moderate asthma do not benefit from higher doses, but those with more significant disease require higher doses to achieve control.

Frederick E. Leickly, MD
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SURVEY OF ADRENAL CRISIS ASSOCIATED WITH INHALED CORTICOSTEROIDS IN THE UNITED KINGDOM


Purpose of the Study. Rare reports of acute adrenal crisis associated with inhaled corticosteroid (ICS) use have been published. How commonly does this occur? To which patients? At what dose? With which drugs?

Study Population. Patients of pediatricians and endocrinologists in the United Kingdom were studied.

Methods. Questionnaires were sent to the physicians, asking whether they had encountered asthmatic patients with acute adrenal crises associated with ICS use. Physicians who responded positively completed a more detailed questionnaire. Patients receiving orally administered corticosteroids were excluded, and the case definition required both symptoms of an adrenal crisis and abnormal hypothalamic-pituitary-adrenal axis function test results.

Results. Thirty-three patients met the case definition criteria for acute adrenal crises developing in relation to ICS therapy, including 28 children (mean age: 6.4 years; range: 3.3–10 years) and 5 adults. Twenty-three children presented with acute hypoglycemia (13 with decreased levels of consciousness or coma, 9 with coma and convulsions, and 1 with coma, convulsions, and death). The remainder of the children and the majority of the adults presented with a more insidious onset of symptoms, such as lassitude, weakness, nausea, and dizziness. There were 37 total episodes of adrenal crisis among the 33 patients. There was no obvious precipitating cause in 24 cases (65%), there was evidence of infection (mostly respiratory) in 8 cases (21%), the ICS had been stopped, reduced, or changed to a lower-potency ICS in 4 cases (11%), and 1 episode (3%) occurred postoperatively. The vast majority of child and adult patients (30 of 33 patients) were treated with fluticasone; 1 child was treated with both fluticasone and budesonide, and 1 adult and 1 child were treated with beclomethasone. The mean dose of fluticasone among children was 980 µg/day (range: 500–2000 µg/day), and the mean dose among adults was 1380 µg/day (range: 1000–2000 µg/day). The mean durations of ICS treatment were 1.7 years for children and 3.3 years for adults.

Conclusions. The frequency of acute adrenal crises was greater than expected. Despite being the least prescribed and most recently introduced ICS, fluticasone was associated with 94% of the cases.

Reviewer’s Comments. Clearly ICSs can cause adrenal suppression and consequent adrenal crises. This appears to be especially true with fluticasone. The author of an editorial that accompanied this article explained that, although fluticasone has high first-pass hepatic metabolism, which decreases the systemic bioavailability of the swallowed portion of the dose, it also has high lipophilicity, allowing the pulmonary portion of the dose to be easily absorbed, which, “combined with its high receptor affinity and prolonged duration of activity, ensure systemic potency and accumulation.” Once again, we are reminded to use the lowest effective dose of ICS. Furthermore, when higher doses are required, perhaps an ICS other than fluticasone would be a better choice.

John M. Kelso, MD
San Diego, CA

VAScular COMPONENT OF AIRway REMODelInG IN ASTHMA IS REDUCed BY HIGH DOSE OF FLUTicaSONE


Purpose of the Study. To assess the effect of short-term treatment with high-dose (500 µg, twice daily) and low-dose (100 µg, twice daily) inhaled fluticasone propionate...
(FP) on the vascular component of airway remodeling among asthmatic patients.

Study Population. Thirty nonsmoking patients with mild/moderate asthma and baseline forced expiratory volume in 1 second values of ≥70% of predicted values. All patients had experienced no asthma attacks in the previous 2 months and controlled their symptoms with inhaled salbutamol only. Patients did not receive corticosteroids in the 6 months before the study and had not experienced any respiratory infections for 4 weeks before the investigation.

Methods. This was a double-blind, randomized, parallel-group study, with patients receiving FP at either 500 or 100 μg twice daily, with a spacer device. Treatments were administered for 6 weeks, and patients were assessed in the clinic on 5 separate days. Symptom diaries were maintained, spirometry and methacholine challenges were performed, and fiber-optic bronchoscopies were undertaken at specific time points during the investigation. Healthy volunteers underwent bronchoscopies for comparison.

Results. Eighteen of 30 patients completed the study protocol, and adequate paired biopsy material for immunostaining was obtained for 16 patients, 8 in the group that received 500 μg of FP twice daily and 8 in the group that received 100 μg of FP twice daily. At baseline, patients with asthma differed significantly from the healthy volunteers with respect to the number of vessels and the vascular area. Among the asthmatic patients, the number of vessels was correlated with vascular area (P < .01) and the number of mast cells (P < .01). Bronchial responsiveness to methacholine, asthma symptom scores, and numbers of inflammatory cells decreased significantly after both low-and high-dose FP (P < .05); however, basement membrane thickness decreased only after high-dose FP (P < .05).

Conclusions. The results from this investigation demonstrated that, among patients with mild/moderate asthma, a high dose of inhaled FP, administered for 6 weeks, could significantly affect airway remodeling by reducing both submucosal vascularity and basement membrane thickness.

Reviewer’s Comments. The authors claim that this is the first published evidence that short-term treatment with high-dose FP significantly reduced the vascular component of airway remodeling among patients with mild/moderate asthma. The small number of subjects who completed the investigation and the short time of medication administration seem to limit the overall conclusions regarding the effects of high-dose FP on airway remodeling. These data could have significant clinical implications for the use of higher doses of inhaled corticosteroids in the ongoing treatment of patients with mild/moderate asthma, who might be receiving lower doses of these medications to control their disease.

LEUKOTRIENE ANTAGONIST THERAPY

A RANDOMIZED, CONTROLLED TRIAL OF INTRAVENOUS MONTELUKAST IN ACUTE ASTHMA

Camargo CA, Smithline HA, Malice MP, Green SA, Reiss TF. Am J Respir Crit Care Med. 2003;167:528–533

Purpose of the Study. To determine whether the addition of intravenously administered montelukast to standard therapy for patients with acute asthma would cause rapid improvement in airflow obstruction, as well as improvement in clinically relevant outcomes such as hospitalization or prolonged or additional antiasthma therapy.

Study Population. Patients, 15 to 54 years of age, who were presenting with acute asthma were screened for enrollment. Requirements included a history of asthma for ≥1 year, a history of tobacco use of <10 pack-years, and no concomitant therapy with systemic corticosteroids, leukotriene modifiers, anticholinergic agents, or long-acting β-agonist bronchodilators.

Methods. This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study with a screening period and an active study period. Two doses of intravenously administered montelukast (7 and 14 mg) or matching placebo were evaluated. Serial spirometric assessments were performed at 10, 20, 40, 60, and 120 minutes and 3 and 6 hours after intravenous study drug infusion.

Results. A total of 201 patients were randomized, and complete data were available for analysis for 194. During the screening period, there was no difference in forced expiratory volume in 1 second responses between the 7-mg and 14-mg montelukast groups. Montelukast improved forced expiratory volume in 1 second values in the first 20 minutes after intravenous administration (mean percentage change from prerandomization baseline value: 14.8% and 35.9% for the pooled montelukast and placebo treatment groups, respectively; P = .007). This benefit was observed at 10 minutes and for 2 hours after intravenous therapy. Patients treated with montelukast tended to receive less β-agonist and to experience fewer treatment failures, compared with patients receiving placebo. The study drug and placebo were similarly tolerated, and no unexpected adverse effects were observed.

Conclusions. Intravenously administered montelukast, in addition to standard therapy, provided rapid benefits and was well tolerated among patients with acute asthma.

Reviewer’s Comments. A substantial proportion of asthma exacerbations continue to require prolonged management in an emergency department setting or hospitalization. In addition to standard asthma therapies, interventions involving inhaled ipratropium, intravenously administered magnesium, and inhaled helium/oxygen mixtures have been investigated. Intravenously administered montelukast, as an adjunctive therapy for these patients, may provide additional benefits with current treatment options. These results must be confirmed and, in future studies, montelukast use among pediatric patients <15 years of age should be investigated.

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EFFECTS OF MONTELUKAST AND BECLOMETHASONE ON AIRWAY FUNCTION AND ASTHMA CONTROL


Purpose of the Study. The primary objective of asthma therapy is the maintenance of asthma control, and the most common measures of such control in clinical studies reflect pulmonary function; forced expiratory volume in 1 second (FEV1) is often used. The authors sought to use a different parameter, ie, days of asthma control, as the primary measure, because observations regarding the need for both rescue medications and unscheduled asthma-related health care are central to perceived wellness.

Study Population. This multicenter study involved 782 individuals, ≥15 years of age, with a ≥1-year history of moderate persistent asthma (baseline FEV1: 50–85% of predicted values) but no controller therapy at the time of...
enrollment. All patients were required to have a current daily need for inhaled albuterol and documented airway reversibility of ≥15% at the time of entry.

Methods. Patients were randomly assigned to receive montelukast (10 mg, each evening), beclomethasone (200 μg, twice daily), or placebo, with a ratio of 3:3:1. The use of spacers was not required. Compliance was monitored with pill counts and simple patient reports of inhaler use. A day of asthma control was defined as a day with no more than 2 puffs of albuterol treatment, no nocturnal awakenings with asthma, and no need for acute medical attention. An asthma exacerbation was defined as ≥3 consecutive days without asthma control. An occurrence of sustained asthma control was defined as ≥3 consecutive days with control. Subjects completed diary cards during the 2-week, single-blind, run-in period and during the 6-week, double-blind, treatment phase. The primary measure was the percentage of days of asthma control during the treatment phase. Secondary measures included average daily albuterol use, percentages of patients with and without attacks, asthma exacerbations, occurrence of sustained asthma control, rescue corticosteroid use, and changes in FEV1 from baseline values. Clinic visits occurred every 3 weeks during the double-blind phase, and spirometry was performed at that time.

Results. The mean percentages of days of asthma control for patients who received montelukast or beclomethasone were similar and were significantly greater than that for placebo recipients. Both drugs resulted in significant improvements in FEV1, but the benefit was greater with beclomethasone. There was no difference between the active treatment groups in any of the other secondary measures, and both treatments were clearly superior to placebo for most parameters.

Conclusions. Montelukast and beclomethasone were of similar efficacy, as judged by indices of clinical control other than FEV1. The latter parameter may underestimate clinical effectiveness.

Reviewer’s Comments. Considering the severity of asthma among these individuals, it might seem surprising that these drugs performed so similarly during the 6-week active treatment phase. One might be tempted to attribute this to presumed poor compliance with the inhaled corticosteroid, compared with the convenient montelukast tablet, especially because beclomethasone monitoring was through reports alone. However, there is no doubt that beclomethasone outperformed the leukotriene receptor antagonist in FEV1 measures, suggesting reasonable compliance and greater potency in improving pulmonary function. Six weeks is probably too short a period to detect differences in major attacks between the 2 treatment groups, and it is likely that a much longer treatment period would have revealed more favorable results for most parameters, including the primary measure, for the inhaled corticosteroid-treated group. Almost by definition, most of these patients had asthma that was too severe to be treated with just 1 drug; a more interesting comparison would have been among patients with mild persistent disease, without histories of hospitalization or recurrent acute attacks.

James R. Banks, MD
Arnold, MD

Montelukast Improves Asthma Control in Asthmatic Children Maintained on Inhaled Corticosteroids


Purpose of the Study. To evaluate whether montelukast as adjunctive therapy improves asthma control and whether montelukast has corticosteroid-sparing effects among children treated with low or moderate inhaled corticosteroid (ICS) doses.

Study Population. Thirty-six children, 6 to 14 years of age, with mild/moderate persistent asthma who were being maintained with a stable low or moderate dose of ICS were randomly assigned to receive montelukast or matching placebo.

Methods. After a single-blind, run-in period of 2 weeks for assessment of incomplete control of asthma symptoms (period I), qualified subjects were randomized in a double-blind, placebo-controlled, 2-period, parallel-group study designed to investigate the effects of montelukast as 4-week adjunctive therapy (period II) and to investigate its effects on the ability to taper the dose of ICS during a 20-week period (period III). Subjects maintained daily asthma diaries, and spirometry was performed monthly.

Results. In period II, both the mean number of β2-agonist rescue-free days per week and the difference in the number of rescue-free days were significantly greater for the montelukast-treated subjects, compared with the placebo-treated subjects (6 days vs 3.18 days, P = .0002; 4.47 days vs 0.05 days, P = .0001; respectively). In period III, the percentage changes in ICS doses were not statistically significantly different between the montelukast and control groups (P = .10), but subjects receiving montelukast experienced an average 17% reduction in ICS dose, compared with a 64% increase in ICS dose among subjects receiving placebo. Also, although the findings were not statistically different, 32% of subjects receiving montelukast were weaned completely off the ICS, compared with 18% in the placebo group.

Conclusion. Montelukast significantly increased the number of rescue-free days among symptomatic children with mild/moderate persistent asthma.

Reviewer’s Comments. Although this was a pilot study with a small patient population, the results are encouraging for those who care for children with asthma, as well as for parents, who are often concerned about the use of corticosteroid medications. Additional studies with a larger population of patients with mild/moderate asthma and a group of patients with severe asthma are warranted.

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Princeton, NJ

Anti-IgE Therapy

Evaluation of Long-Term Safety of the Anti-Immunoglobulin E Antibody, Omalizumab, in Children with Allergic Asthma


Purpose of the Study. To evaluate safety parameters for 1-year treatment with omalizumab among children 5 to 12 years of age.

Study Population. A total of 225 patients, 5 to 12 years of age, with a mean duration of asthma of 6.1 years (range: 1–12 years) were studied. All patients had allergic asthma, which had been well controlled for ≥3 months before the study with inhaled corticosteroid doses equivalent to 168

548  ASTHMA  Downloaded from www.aappublications.org/news by guest on November 5, 2021
to 420 μg/day beclomethasone dipropionate and rescue albuterol as needed. Ninety percent of the patients were classified as having moderate/severe persistent asthma, and 10% were classified as having severe persistent asthma. The mean total serum immunoglobulin E level was 348 IU/mL (range: 20–1269 IU/mL).

Methods. This report included data from a previously published, 28-week study, which was a randomized, double-blind, placebo-controlled, parallel-group trial comparing the addition of omalizumab versus placebo for symptomatic patients receiving beclomethasone dipropionate. The patients who received omalizumab during the double-blind, 28-week study continued to receive open-label omalizumab without interruption for another 24 weeks and were studied with respect to the safety parameters described in this report.

Results. Approximately 93% of patients treated with omalizumab for 52 weeks reported experiencing an adverse event; 85% of those were rated as mild or moderate. This finding was similar to 89% of patients treated with omalizumab and 87% of patients treated with placebo reporting adverse events during the double-blind study. The only statistically significantly greater adverse event among omalizumab-treated patients, compared with placebo-treated patients, in the 28-week study was injury. The higher prevalence of injury among the actively treated patients was not considered to be attributable to treatment and was not associated with adverse events involving the nervous system. The finding was considered to be possibly attributable to increases in activity with improvements in asthma, leading to greater frequencies of injury and trauma among those patients. Among the patients who were treated for 52 weeks with omalizumab, adverse events were numerically greater (by percentage) in all categories, compared with those reported in the 28-week study for either active drug or placebo, but no statistical analysis was reported. The most frequently reported adverse events in the 52-week study were upper respiratory tract infections and headaches. No episodes of anaphylaxis were noted. Urticaria occurred for 11 patients (5%). Urticaria was considered to be possibly treatment-related for 5 patients but was reported to be severe for only 1 of those patients; for that patient, additional treatment with omalizumab was discontinued. Four serious adverse events were reported, but none was considered to be treatment-related. There was no evidence of omalizumab-related decreases in platelet counts among the patients treated for 52 weeks. Antibodies reactive with the antigen-binding fragment of omalizumab were tested for, and no antibodies were detected. Asthma control parameters were not the primary outcome measures in the 52-week extension study, but it was noted that inhaled corticosteroid dose reductions or discontinuation and reductions in asthma exacerbations were maintained at similar levels throughout the 28-week extension period.

Conclusions. Among children 5 to 12 years of age, 52-week treatment with omalizumab was well tolerated. The overall incidence of adverse events was high but was similar to the values reported in the 28-week study for both active drug and placebo. No anaphylactic reactions were reported. Treatment was discontinued for 1 patient because of severe urticaria, which was considered to be possibly treatment-related.

Reviewer's Comments. Although the exact role of omalizumab in clinical practice is not entirely clear, these short-term safety data are reassuring.

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Immunodeficiency

IMMUNODEFICIENCY DISEASES

PROSPECTIVE AUDIT OF ADVERSE REACTIONS OCCURRING IN 459 PRIMARY ANTIBODY-DEFICIENT PATIENTS RECEIVING INTRAVENOUS IMMUNOGLOBULIN


Purpose of the Study. To determine the incidence of adverse reactions among a large group of patients receiving intravenous immunoglobulin (IVIG) replacement therapy in an institutional setting or at home, with or without supervision by a health care professional.

Study Population. The patients were 92 children (<18 years of age) and 367 adults (total: 459 patients). All had been diagnosed as having a primary antibody deficiency, and all had been receiving IVIG replacement therapy for ≥6 months before entry into the study. The majority of patients (290 total, 72 children) received IVIG therapy at home; 160 patients (19 children) received IVIG therapy as outpatients in a hospital, and 9 patients (1 child) received IVIG therapy in a primary care provider’s office.

Methods. IVIG therapy was administered according to the manufacturer’s guidelines. Prophylaxis (with nonsteroidal antiinflammatory drugs and/or antihistamines) to prevent adverse reactions varied among centers supervising IVIG therapy and was not uniform across the study population. Data were collected prospectively for 2 years (13 508 infusions). For infusions administered in institutional settings, data were recorded by health care professionals. Patients receiving IVIG therapy at home were self-infusing and recorded their own symptom data; these records were reviewed by investigators before assignment of a classification. All adverse reactions were classified as mild, moderate, or severe with uniform criteria for all centers.

Results. A total of 111 adverse reactions were documented (overall rate: 0.8%). Of these, 91 (82%) were mild and 20 (18%) were moderate. One patient accounted for 19 of the mild reactions. No severe adverse reactions were recorded. There was no significant variation in the rate of adverse reactions according to age or the setting in which IVIG therapy was administered. For 45 reactions (41%), there was an associated predisposing factor (infection, delay after previous infusion, or administration error [too rapid]); 47 reactions (42%) occurred despite prophylaxis, although the effect of prophylaxis on the overall reaction rate was not mentioned. Three of the 12 centers had relatively higher rates of adverse reactions; the reasons for this, if known, were not stated.

Conclusions. There was a low overall rate of adverse reactions to IVIG infusion and a very low rate (<0.007%) of severe adverse reactions to IVIG administration. The importance of recognizing and avoiding predisposing factors for adverse reactions was emphasized.

Reviewer’s Comments. Home IVIG infusion is clearly safe. More detailed analyses of the effects of prophylaxis on reaction rates and of the differences among centers would have been helpful.
A COHORT STUDY OF NEURODEVELOPMENTAL OUTCOME IN CHILDREN WITH DIGEORGE SYNDROME FOLLOWING CARDIAC SURGERY

Maharasingam M, Ostman-Smith I, Pike MG. Arch Dis Child. 2003;88:61–64

Purpose of the Study. To examine whether cognitive impairment among patients with DiGeorge syndrome (DGS) is secondary to cardiac pathologic conditions and their treatment or is a feature of the DGS phenotype.

Study Population. Ten patients with 22q11 deletions who had undergone cardiac repair in infancy, along with 2 control subjects for each patient, matched with respect to gender and age and having the same or similar cardiac defects and normal 22q11, were studied. Children ranged from <1 year to ~8 years of age at the time of developmental testing.

Methods. Patient records were reviewed retrospectively for features of DGS (hypocalcemia and immunodeficiency), operative data such as duration of bypass and postoperative ventilation, and episodes of hypotension or hypoxia and acidosis. Determinations of developmental quotients (DQs) were performed (in an unblinded manner, because DGS is associated with characteristic facial features) by a single investigator, using the Ruth Griffiths Abilities of Infants and Young Children tool. Patient and control groups were compared with multiple analyses of variance.

Results. There were no significant differences between patients and control subjects with respect to age at presentation or surgery or with respect to operative characteristics and complications. Associations with DQs of 22q11 deletions with hypocalcemia and immunodeficiency were highly significant (P = .004-.009); the associations were not independent, because all are linked features of DGS. The DQs for DGS patients (mean: 71; 95% confidence interval: 47–95) were much lower than those for control subjects (mean: 113; 95% confidence interval: 108–118; P = .0001). Perioperative acidosis was strongly associated with lower DQs among children with DGS (P = .005) but not among control subjects.

Conclusions. Abnormal neurodevelopmental outcomes in DGS are not solely the result of cardiac lesions and their surgical repair. Also, DGS may predispose patients to worse neurodevelopmental outcomes after cardiac surgery because of factors intrinsic to the disease, 1 of which appears to be hypocalcemia.

Reviewer’s Comments. DGS occurs at a rate of ~1 case per 3000 live births. Previous studies showed developmental delays or cognitive impairment in a subset. This study shows that little is attributable to cardiac complications themselves. However, it suggests that DGS may predispose patients to greater susceptibility to poor neurodevelopmental outcomes after surgery because of associated conditions, such as hypocalcemia.

Francisco A. Bonilla, MD, PhD
Boston, MA

SAFETY OF LIVE VIRAL VACCINES IN PATIENTS WITH CHROMOSOME 22Q11.2 DELETION SYNDROME (DIGEORGE SYNDROME/VELOCARDIOFACIAL SYNDROME)

Perez EE, Bokszczanin A, McDonald-McGinn D, Zackai EH, Sullivan KE. Pediatrics. 2003;112:e325–e327

Purpose of the Study. To investigate the incidence of side effects after live viral vaccine administration in a population with chromosome 22q11.2 deletion syndrome.

Study Population. A total of 174 patients with chromosome 22q11.2 deletions were evaluated at Children’s Hospital of Philadelphia between 1994 and 2002. Of these, 59 patients completed a questionnaire regarding live viral vaccination; these constituted the study population.

Methods. Patient records were reviewed retrospectively. Data acquisition was designed to record the clinical consequences of vaccination or of withholding the vaccines.

Results. Thirty-two patients received varicella vaccine. Of those, 3 (9%) reported mild adverse events (fever alone). Vaccinated patients did not contract wild-type varicella, whereas 63% of unvaccinated patients did. Unvaccinated patients had lower T cell numbers, presumably because vaccine was withheld because of theoretical concerns regarding safety. Despite this, no patient who developed chicken pox required hospitalization. Fifty-two patients received measles-mumps-rubella vaccine. Of those, 12 (23%) reported mild adverse reactions, consisting of fever, rash, and malaise. None of the unvaccinated patients developed wild-type measles, mumps, or rubella infection. For neither varicella vaccine nor measles-mumps-rubella vaccine were T cell counts correlated with the occurrence of adverse events.

Conclusions. Adverse reactions to common, live, attenuated, viral vaccines among patients with 22q11.2 deletions were similar in frequency and severity to those in the general population. Varicella vaccine appeared to be very protective in this population.

Reviewer’s Comments. As the authors noted, this study was limited by size, by its retrospective nature, by comparison with the general population, and by relying on parental recollection of adverse events. Also, T cell counts at the time of immunization were not available for many patients, because the diagnosis was not yet established. However, this analysis provides a very reasonable basis for the general safety and efficacy of these vaccines among patients with 22q11.2 deletions and lays the groundwork for a more definitive prospective study.

Francisco A. Bonilla, MD, PhD
Boston, MA

TARGET CELLS OF EBSTEIN-BARR VIRUS-POSITIVE POSTTRANSPLANT LYMPHOPROLIFERATIVE DISEASE: SIMILARITIES TO EBSTEIN-BARR VIRUS-POSITIVE HODGKIN’S LYMPHOMA


Purpose of the Study. To determine the types of B cells from which posttransplant lymphoproliferative disease (PTLD) arises.

Study Population. Tissue samples and DNA extracted from fresh tumors were obtained from 13 patients with PTLD.

Methods. Tumor suspensions were stained with monoclonal antibodies to surface B-cell (CD20 and CD38) and T-cell (CD3) markers and cell surface and cytoplasmic immunoglobulin heavy and light chains. The presence of Epstein-Barr virus (EBV) was detected with in situ hybridization assays for EBV-encoded RNA. Immunoglobulin heavy chain sequences corresponding to framework regions and complementarity-determining (antigen-binding) regions were determined with polymerase chain reaction assays. The sequences were analyzed for suggestions of antigen-selected genotypes (normal memory B cells).
Results. Twelve tumors were of B cell origin and expressed surface or cytoplasmic immunoglobulin. One tumor was a B cell-T cell composite. All 13 malignant B cell populations were positive for EBV-encoded RNA. Of the 11 biclonal and monoclonal tumors, 4 appeared to arise from memory B cells, 5 seemed to be derived from somatically mutated non-memory B cells, and 2 had inactivated immunoglobulin heavy chain sequences, because of a stop codon and a large deletion causing an out-of-frame mutation.

Conclusions. PTLD can arise from atypical, post-germinal center, B cells that have failed selection into memory cells, like the monoclonal tumors of Hodgkin’s lymphoma, as well as from the antigen-selected memory cells that are usually colonized by EBV in immunocompetent individuals.

Reviewers’ Comments. Although the ages of the patients with PTLD were not reported in this study, young children receiving posttransplant immunosuppressive therapy are at increased risk for this disease, because they are more likely to be EBV-susceptible at the time of transplantation. The suggestion of a common initiation step in the pathogenesis of PTLD and Hodgkin’s lymphoma may lead to future diagnostic and therapeutic breakthroughs.


HUMAN IMMUNODEFICIENCY VIRUS

FAILURE OF 1 WEEK ON/1 WEEK OFF ANTIRETROVIRAL THERAPIES IN A RANDOMIZED TRIAL


Purpose of the Study. Although highly active antiretroviral therapy (HAART) has dramatically improved the duration and quality of life of human immunodeficiency virus (HIV)-infected individuals, an increasing number of serious complications are being identified among patients who are treated with these agents for long periods of time. Strategies that reduce the total drug exposure among infected patients while maintaining the stability of HIV and T cell levels would be welcomed. Scheduled or structured treatment interruptions are being evaluated in an effort to decrease the costs and side effects of HAART.

Methods. In this study, 600 patients receiving successful HAART were randomized to either continuous therapy, CD4+ T cell count-guided therapy, or 1 week on/1 week off therapy.

Results. This report described the preliminary analysis of data for the 1 week on/1 week off arm. Of 36 evaluable patients, 19 had 2 successive HIV RNA plasma concentrations of \( >500 \text{ copies/mL} \) after 1 week off therapy; those cases were classified as virologic failures. Most of the patients who experienced failure were receiving didanosine, stavudine, saquinavir, and ritonavir. Among those patients, there was no evidence of mutations suggesting drug resistance. Plasma saquinavir levels were within the expected range.

Conclusions. The 1 week on/1 week off schedule tested in this study showed an unacceptably high failure rate and was therefore terminated early.

Reviewer’s Comments. Early anecdotal reports suggested that HIV-specific immune responses were boosted after discontinuation of therapy. Clinical trials based on this concept were developed for both acute and chronic HIV infections. The most promising results were from studies involving subjects who were treated for acute HIV infections; specific T cell responses to HIV were enhanced after interruptions in therapy. Similar findings have not been demonstrated for patients with chronic HIV infections. The results of this study are certainly disappointing. However, the definition of virologic failure in this study was a rebound to \( \geq 500 \text{ copies/mL} \). Current guidelines suggest that HIV RNA levels of \(<50,000 \text{ copies/mL} \), with stable CD4+ T cell levels, might be acceptable. The major concern with this approach would be the development of resistance to the antiretroviral therapy if repeated rebounds were allowed to continue in the off weeks. Studies of scheduled or structured treatment interruptions will continue. Perhaps a 2 weeks on/1 week off or 3 weeks on/1 week off schedule would limit the viral rebounds and still reduce the cumulative drug exposure for patients.

Joseph A. Church, MD
Los Angeles, CA

USING POINT-OF-CARE TESTING TO MAKE RAPID HUMAN IMMUNODEFICIENCY VIRUS-1 TESTS IN LABOR REALLY RAPID


Purpose of the Study. The US Food and Drug Administration recently approved the OraQuick rapid human immunodeficiency virus-1 (HIV-1) antibody test (OraSure Technologies, Bethlehem, PA). The test is designed for point-of-care testing for HIV. The test is performed with a tiny amount of blood, and results are available within 20 to 30 minutes. Remarkably, this test is as sensitive and specific as the standard enzyme-linked immunosorbent assay for HIV-specific antibodies. The purpose of this study was to evaluate the differences in turnaround times between hospitals where obstetric staff members performed the rapid test at the point of care and a hospital where testing was performed in the hospital laboratory.

Results. During a 7-month period, 5771 women were evaluated in the labor and delivery areas of the target hospitals, and 514 met the criteria for rapid HIV testing. Of those, a total of 225 women were tested at 3 hospitals that used point-of-care testing and 155 were tested at a hospital that used the laboratory for the same test. Standard enzyme-linked immunosorbent assays confirmed 100% of the rapid test results. Three women were identified as being HIV infected; in those instances, antiretroviral therapy was administered during labor and delivery and/or administered to the neonate. The median turnaround time at the 3 hospitals that used point-of-care testing was 45 minutes (range: 30 minutes to 2.5 hours); the hospital that used the laboratory had a median time of >3.5 hours (range: 94 minutes to >16 hours; \( P < .0001 \)).

Conclusions. The OraQuick rapid HIV-1 antibody test is a highly accurate measure of HIV risk, for use in a number of clinical settings. With the OraQuick test, hospitals can rapidly identify HIV-infected individuals. This study demonstrates that true point-of-care testing dramatically reduces the time needed for test result availability and allows clinical interventions in a timely manner.

Reviewer’s Comments. Same-day access to HIV test results could greatly reduce the number of adults who are tested but never return to the test site for their HIV test results. The availability of the OraQuick test also has the potential to reduce the already low incidence of perinatal HIV transmission. It currently takes days to obtain HIV antibody test results for individuals presenting to a hospi-
tal or clinic. For women who have received no prenatal care and who present in labor, this time frame precludes the implementation of antiretroviral therapy during labor and delays the administration of antiretroviral agents to the newborn. In many cases, the delay exceeds the 48- to 72-hour period within which transmission might be reduced with treatment of the newborn. Finally, the availability of the OraQuick test might reduce the time that caregivers would need to receive antiretroviral agents after accidental sharps exposures, with the source being quickly shown to be HIV-negative. Anyone who has needed to take an antiretroviral “cocktail” for even 2 or 3 days can understand the potential savings in emotional stress and physical discomfort in such situations.

Joseph A. Church, MD
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BROAD ANTIRETROVIRAL DEFENSE BY HUMAN APOBEC3G THROUGH LETHAL EDITING OF NASCENT REVERSE TRANSCRIPTS


Purpose of the Study. Innate intracellular antiretroviral defense mechanisms have been described. Viral infection requires that these lines of defense be overcome, and this task is usually accomplished by specialized viral proteins. The virus infectivity factor (Vif) protein of human immunodeficiency virus (HIV) is required to counter the antiviral activity of a protein expressed in human T cells, ie, APOBEC3G (apolipoprotein B messenger RNA-editing enzyme, catalytic polypeptide-like 3G, which is also known as CEM15). APOBEC3G family members have potent DNA-editing activity, triggering hypermutation in nascent DNA. The purpose this study was to examine potential mechanisms of APOBEC3G effects.

Methods. In vitro experiments, the investigators measured the infectivity of wild-type and vif-deleted virions, in the presence or absence of APOBEC3G. They then tested a series of point mutations, concentrating on residues of the catalytic site of APOBEC3G.

Results. When produced in the presence of APOBEC3G, Vif-defective virus was not infectious. The results of these studies demonstrated that APOBEC3G exerts its antiviral effects during reverse transcription, triggering lethal guanosine-to-adenosine hypermutation in the complementary retroviral DNA. It was also noted that APOBEC3G could act on a broad range of retroviruses, in addition to HIV.

Conclusion. APOBEC3G exerts its anti-HIV activity through lethal editing of DNA reverse transcripts.

Reviewer’s Comments. Immune cells have evolved a remarkable set of mechanisms to defend against microbial invaders, and microbes have coevolved to circumvent these defenses. APOBEC3G is a human factor produced in T cells that inherently inactivates retroviruses. However, as shown in this study, the HIV accessory protein Vif selectively inactivates APOBEC3G. An understanding of the mechanisms of viral infectivity and resistance has generated an increasing number of targets for interventions against HIV infection. For example, strategies aimed at limiting the activity of Vif might allow APOBEC3G to better accomplish its task of virus suppression.

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Los Angeles, CA

LONGITUDINAL ANALYSIS OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 RNA IN BREAST MILK AND OF ITS RELATIONSHIP TO INFANT INFECTION AND MATERNAL DISEASE


Purpose of the Study. Transmission of human immunodeficiency virus (HIV) via breastfeeding may occur throughout lactation. In developing countries, where >90% of HIV-exposed children live, safe alternatives to breastfeeding are not available. An understanding of the dynamics of breast milk virus levels and the correlation of breast milk virus levels with mother-to-child transmission is essential for the development of effective interventions.

Methods. A total of 648 breast milk samples were collected from 275 women enrolled in a clinical trial in Nairobi, Kenya, between 1992 and 1998. Antiretroviral regimens were not available to the women at the time of the study. Breast milk samples were analyzed for virus levels, and infants were monitored for up to 2 years, for assessment of HIV transmission.

Results. The average duration of breastfeeding was 21 months. Of the 275 women, 70 transmitted HIV to their infants and 205 did not. Greater maternal plasma viral loads, lower maternal CD4+ T cell counts, and detection of HIV DNA in maternal genital secretions were significantly associated with elevated breast milk HIV RNA levels. The median viral load in early milk was significantly greater than that in breast milk collected 14 days after delivery. Breastfeeding mothers who transmitted HIV had significantly higher breast milk HIV RNA levels and more consistent viral shedding, compared with mothers who did not transmit HIV.

Conclusions. The risk of infant infection through breastfeeding was increased by higher levels of virus in breast milk; levels were highest early after delivery.

Reviewer’s Comments. In developing countries, the rate of perinatal HIV transmission approaches 50%. This is dramatically higher than the 20% to 25% rate of transmission that was noted in developed countries before the initiation of perinatal antiretroviral therapy. It is now clear that breastfeeding is a significant factor in the transmission of HIV from mother to child and may be responsible for ≥30% of transmissions in developing countries. Unfortunately, safe alternatives to breastfeeding do not exist for most HIV-positive women. Provision of effective perinatal antiretroviral therapy, combined with safe alternative feeding methods, is required to significantly affect the extraordinary rate of HIV disease among children in the developing world.

Joseph A. Church, MD
Los Angeles, CA

LETHAL T CELL IMMUNODEFICIENCY INDUCED BY CHRONIC COSTIMULATION VIA CD27-CD70 INTERACTIONS


Purpose of the Study. During human immunodeficiency virus (HIV) infection, CD4+ T cell levels decline. Studies suggested that this loss is less likely related to direct infection and killing of these cells than to exhaustion of the T cell pool induced by chronic immune activation. The purpose of this study was to determine, in an animal model, whether artificially induced chronic immune activation alone could result in clinically significant T cell deficiency.
Activation of T cells requires stimulation of the antigen-specific T-cell receptor and ligation of coreceptors on the T cell surface. One coreceptor on the surface of T cells is CD27, a member of the tumor necrosis factor receptor family. CD70 is the ligand for CD27. The investigators generated a CD70-transgenic mouse model in which CD70 was constitutively expressed on B cells, resulting in chronic T cell activation in the absence of viral infection.

Results. These mice demonstrated progressive conversion of naïve T cells into effector-memory cells. The end result was depletion of naïve T cells from lymph nodes and spleen. Despite this hyperactive immune response, CD70-transgenic mice died as a result of Pneumocystis carinii pneumonia, which is an acquired immunodeficiency syndrome-defining condition among human patients infected with HIV.

Conclusions. Constant activation of T cells via CD27-CD70 interactions, as may occur among human subjects during chronic active viral infections, may result in exhaustion of the T cell pool and the development of fatal immunodeficiency.

Reviewer’s Comments. It has been unclear how T cell loss occurs during HIV infection. Some T cells are undoubtedly killed by infection with HIV. However, the magnitude of the T cell loss is not explained by this pathway. Very early in the HIV epidemic, it appeared that chronic immune activation was a hallmark of HIV disease. Was the immune activation a cause of T cell loss or simply the effect of chronic viral infection? In other primates, chronic infection with retroviruses may not cause any detectable immune dysfunction if immune activation is not induced. This study clearly demonstrated that immune activation alone might be sufficient to induce T cell deficiency. If the virus cannot be eradicated, then perhaps induction of immunologic tolerance to it may be the next best thing.

Joseph A. Church, MD
Los Angeles, CA

Infectious Disease

RESPONSE TO SMALLPOX VACCINE IN PERSONS IMMUNIZED IN THE DISTANT PAST


Purpose of the Study. There is renewed interest in the use of smallpox vaccine, because of the potential for a bioterrorist attack. One obvious question relates to the current status of people who have been vaccinated in the past. This study sought to evaluate the use of diluted vaccinia virus for vaccination of previously vaccinated (nonnaive) participants.

Study Population. Eighty nonnaive participants, 32 to 60 years of age, were randomized to receive either undiluted or diluted (1:3.2, 1:10, or 1:32) doses of smallpox vaccine, in a single-blinded study. A comparison group of 10 vaccinia-naive participants, 18 to 31 years of age, received undiluted vaccine.

Methods. Participants were enrolled between April 1 and May 15, 2002, at the National Institute of Allergy and Infectious Diseases Vaccine and Treatment Evaluation Unit at St Louis University (St Louis, MO). Smallpox vaccine was administered through scarification, using 15 skin punctures in the deltoid region of the arm. Outcome measures included the presence of a major reaction, defined as a vesicular or pustular lesion or area of palpable induration surrounding a central lesion, after vaccination, measures of viral shedding, and antibody titers.

Results. Initial vaccination resulted in a major reaction for 64 of 80 nonnaive participants. Ninety-five percent of nonnaive participants had major reactions in the undiluted group, 90% in the 1:3.2 dilution group, 81% in the 1:10 dilution group, and 52.6% in the 1:32 dilution group. All of the vaccinia-naive participants (n = 10) experienced major reactions. Compared with vaccinia-naive participants, nonnaive participants had significantly smaller skin lesions (P = .04) and a significantly lower incidence of fever (P = .02). Preexisting antibody was present in 76 of 80 nonnaive participants. Antibody responses were significantly greater and occurred more rapidly among the nonnaive participants, compared with the vaccinia-naive participants (P = .002 for day 28 and P = .003 for 6 months). Vaccinia-naive participants shed virus from the vaccination site 2 to 6 days longer and had significantly higher mean peak viral titers, compared with the nonnaive participants (P = .002).

Conclusions. Previously vaccinated persons could be successfully revaccinated with diluted (≤1:10) smallpox vaccine. Fewer adverse reactions were observed in this study among nonnaive participants, compared with vaccinia-naive participants, which might be attributable to immunologic memory.

Reviewer’s Comments. This is an excellent practical study addressing an important issue. Although we hope that widespread smallpox vaccination will not be necessary, these data should be useful for the design of whatever program might be necessary.

Robert A. Wood, MD
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EFFECT OF CONJUGATE PNEUMOCOCCAL VACCINE FOLLOWED BY POLYSACCHARIDE PNEUMOCOCCAL VACCINE ON RECURRENT ACUTE OTITIS MEDIA: A RANDOMIZED STUDY


Purpose of the Study. To determine whether pneumococcal conjugate vaccine can prevent acute otitis media (AOM) among older children who have experienced previous episodes of AOM.

Study Population. A total of 383 children (1–7 years of age) with ≥2 episodes of AOM in the year before entry were studied.

Methods. Children recruited from a Netherlands general hospital and tertiary care hospital were randomized to receive either 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide or hepatitis A or B vaccines, in a double-blind trial. The randomization was stratified into 4 groups according to age (12–24 months versus 25–84 months) and the number of prior AOM episodes (from parental reports, with physician confirmation) (2 or 3 episodes vs 4 or more episodes). All children were monitored, via parental diaries and clinical examinations, for 18 months for the recurrence of AOM. Cultures of middle ear fluid and nasopharyngeal swabs were performed to assess the association of pneumococcal serotypes with AOM after vaccination.

Results. Of the 383 children enrolled, 190 received pneumococcal vaccinations and 193 received control hepatitis vaccinations. A total of 474 episodes of AOM were diagnosed during the follow-up period after the final vaccination, with 275 recorded for 107 of the 186 children in the pneumococcal vaccine group (58%) and 200 recorded...
for 101 of 181 control subjects (56%). There was no decrease in AOM in the pneumococcal vaccine group, compared with the control group. Data from parental diaries indicated no differences between the pneumococcal vaccine group and the control group with respect to AOM symptom duration, symptom frequency, or use of treatment. Serial nasopharyngeal swabs obtained before and after vaccination in the pneumococcal vaccine group demonstrated a decrease in the conjugated vaccine serotypes but no overall decrease in the nasopharyngeal carriage of pneumococcus, compared with the control group.

Conclusions. There was no reduction in AOM episodes in the pneumococcal vaccine group, compared with the control group. Overall, there was no decrease in the carriage of pneumococcus.

Reviewers’ Comments. Importantly, pneumococcal vaccination decreases the proliferation of conjugate vaccine serotypes and thus decreases nasopharyngeal carriage of the most frequent pneumococcal serotypes until children are older and immunologically more mature. Furthermore, the risk of older children developing recurrent AOM seems independent of receiving the pneumococcal vaccination. This study supports our current clinical practice of early childhood pneumococcal vaccination, without catch-up immunization of older children who might not have received the vaccine previously.

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FOUR-YEAR INCIDENCE OF ALLERGIC SENSITIZATION AMONG SCHOOLCHILDREN IN A COMMUNITY WHERE ALLERGY TO CAT AND DOG DOMINATES SENSITIZATION: REPORT FROM THE OBSTRUCTIVE LUNG DISEASE IN NORTHERN SWEDEN STUDY GROUP
Casey J. Geaney and Laurie Smith
*Pediatrics* 2004;114;519

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