Allergy

**PREDICTION, PREVENTION, AND THE “HYGIENE HYPOTHESIS”**

**Allergen Exposure in Infancy and the Development of Sensitization, Wheeze, and Asthma at 4 Years**


**PURPOSE OF THE STUDY.** To determine to what extent allergen exposure in infancy (3 months old) leads to sensitization, wheeze, and physician-diagnosed asthma at 4 years of age.

**STUDY POPULATION.** This study is of a subsample of a prospective birth cohort (n = 4146 children) recruited in the Netherlands. Subjects were children (n = 1127) classified as high risk (n = 464, atopic mother) and low risk (n = 663, nonatopic mother).

**METHODS.** Mothers were identified during pregnancy as atopic or nonatopic using a validated screening questionnaire on asthma and inhalant allergies. Children were recruited on the basis of high-risk (atopic mothers) and low-risk (nonatopic mothers) for close follow-up including a home visit at 3 months of age and a medical examination at 4 years of age. At the home visit, dust samples were collected from the child’s mattress and analyzed for house dust mite (Der p 1), cat (Fel d 1), and dog (Can f 1) with samples adjusted for season of collection. At 4 years of age, blood samples were drawn for specific IgE levels to inhalant allergens. Data on demographic factors, respiratory symptoms, and risk factors for asthma were collected by yearly questionnaires. Participants were assessed and placed into a diagnostic category: never wheeze, early transient wheeze (at least 1 episode of wheeze within 3 years of life and no wheeze during fourth year), late-onset wheeze (no wheeze in first 3 years of life and at least 1 in fourth year), persistent wheeze (1 episode of wheeze in the first 3 years of life and at least 1 episode in the fourth year), and physician-diagnosed asthma.

**RESULTS.** Allergen sensitization was noted to dust mite, cat, or dog allergens in 14%, 7%, and 4%, respectively. Transient wheeze was noted among 24% and persistent wheeze among 11% of participants, with 4% having physician-diagnosed asthma at 4 years. Allergen exposure was less than detection limits for 42%, 13%, and 68% to Der p 1, Fel d 1, and Can f 1, respectively, with no significant differences between the children of nonatopic and atopic mothers. Of those with allergen exposure, only exposure to house dust mite and cat allergen were found to increase the risk of sensitization at 4 years (odds ratio: 3.22, P = .01; and odds ratio: 2.60, P = .06, respectively). Exposure to allergens was not found to be significantly associated with early transient wheeze. There was an association between cat allergen and persistent wheeze (odds ratio: 2.22; P = .11). In children of atopic mothers, there was a positive association between mite exposure and diagnosed asthma. In children of nonatopic mothers, there was a positive association between dog dander exposure and persistent wheeze. Overall, allergen exposure was not highly associated with physician-diagnosed asthma; however, in children with atopic mothers, dust mite exposure was associated with asthma diagnosis (odds ratio: 3.52; P = .07).

**CONCLUSIONS.** The association between allergen exposure and sensitization was demonstrated for dust mite and cat allergens at 4 years. Cat allergen exposure and sensitization were associated with persistent wheeze. Early mite and dog allergen exposure might lead to asthma and persistent wheeze in subgroups defined by maternal atopy.

**REVIEWER COMMENTS.** Similar to other longitudinal cohort studies, this study demonstrates an association between allergen exposure and sensitization and provides some additional evidence for the link between allergen exposure and persistent asthma. Long-term follow-up of such cohorts is necessary to help us better understand the relationship between early allergen exposure and development of atopy and asthma.

**URL:** www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900D

Josh Kennedy, BA
Stacie M. Jones, MD
Little Rock, AR

**Breast-feeding Reduces the Risk for Childhood Eczema**


**PURPOSE OF THE STUDY.** To investigate the effect of breast-feeding in various phenotypes of eczema.

**STUDY POPULATION.** A birth cohort of 4089 children followed up to 4 years of age.

**METHODS.** Data on breastfeeding, allergic symptoms, and potential confounders were obtained from questionnaires when the children were 2 months and 1, 2, and 4 years old. At 4 years, blood allergen-specific immunoglobulin E was analyzed. Children with symptoms of eczema and asthma during the period of breastfeeding were excluded in most analyses on risk assessment of eczema and asthma, respectively, to avoid disease-related modification of exposure.

**RESULTS.** Exclusive breastfeeding for ≥4 months reduced the risk for eczema at the age of 4 years (odds ratio [OR]:...
The Association of Prolonged Breastfeeding and Allergic Disease in Poor Urban Children


PURPOSE OF THE STUDY. To determine the association between allergic disease in children and prolonged breastfeeding.

STUDY POPULATION. A random sample (n = 861) of 15% of households from 2 poor suburbs of Cape Town, South Africa.

METHODS. Parents completed a validated International Study on Asthma and Allergies in Childhood questionnaire on allergic diseases for children aged 6 to 14 years. Other questions included breastfeeding duration, maternal smoking, and parental allergy. Results were adjusted for possible confounders and possible clustering within the household.

RESULTS. Of the 861 children included in the study, allergic disease in general and hay fever in particular were significantly less frequent in those with prolonged (>6 months) breastfeeding. There was a significant linear inverse association between breastfeeding duration and allergic disease in children without allergic parents but not in children with an allergic predisposition.

CONCLUSIONS. These results from a developing country suggest a protective effect of prolonged breastfeeding on the development of allergic disease, particularly hay fever, in children born to nonallergic parents. This protective effect was not found in children with an allergic predisposition.

Infantile Eczema at One Month of Age Is Associated With Cord Blood Eosinophilia and Subsequent Development of Atopic Dermatitis and Wheezing Illness Until Two Years of Age


PURPOSE OF THE STUDY. To determine if a correlation exists between the prevalence of neonatal skin eruptions at 1 month of age and the later development of atopic dermatitis. In addition, the authors sought to determine if the presence of cord blood eosinophils correlated with the development of later skin disease.

STUDY POPULATION. One hundred five newborn infants born by normal vaginal delivery in Mitoyo General Hospital (Kagawa, Japan) from May 1987 to March 1989.

METHODS. The cord blood eosinophil count was measured at the time of delivery. The neonates were examined at 1 (all subjects) and 24 (98 subjects) months of age by a doctor who was unaware of the cord blood eosinophil count. The subjects’ histories of allergic symptoms or physician-diagnosed wheezing bronchitis or asthma during the first 8 years of life were also determined by direct examination or interviews with the guardians (67 subjects). The age of each subject at the onset of the allergic symptoms was determined. Skin eruptions at 1 month of age were classified into 4 categories: (1) infantile eczema; (2) seborrheic dermatitis; (3) intertrigo; or (4) diaper dermatitis. The diagnosis of atopic dermatitis was made according to the criteria by Hanifin and Rajka (Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Arch Dermatol Venereol. 1980;92:44–47), and each rash was defined carefully by appearance.
RESULTS. At 1 month of age, infantile eczema, seborrheic dermatitis, intertrigo, and diaper dermatitis were diagnosed in a total of 29, 7, 14, and 24 neonates, respectively. No associations (such as family history of allergic disease or mode of feeding) were found for the prevalence of these eruptions. Neonates with infantile eczema had a significantly higher number of eosinophils in the cord blood ($P < .0001$). In contrast, no such tendency was found for any other skin eruption. In neonates with infantile eczema at 1 month of age, the diagnosis of atopic dermatitis had been made significantly earlier, and the prevalence of wheezing illness was significantly higher compared with infants who did not have infantile eczema.

CONCLUSIONS. Infantile eczema, but not other skin eruptions, precedes the development of atopic dermatitis and wheezing illness during early infancy. This may be secondary to the activation of eosinophils before birth.

REVIEWER COMMENTS. Patients with infantile eczema are at increased risk for atopic disease. The measurement of cord blood eosinophils may aid in predicting which infants will develop infantile eczema and, in addition, may have diagnostic utility in predicting which patients are at risk for the development of further allergic disease.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900G

Jennifer M. Maloney, MD
Scott H. Sicherer, MD
New York, NY

Risk Factors for Atopic Dermatitis in New Zealand Children at 3.5 Years of Age


PURPOSE OF THE STUDY. To examine factors associated with a diagnosis of atopic dermatitis (AD) at 3.5 years of age, especially factors implicated by the hygiene hypothesis.

STUDY POPULATION. There were 871 children enrolled at birth for the Auckland Birthweight Collaborative study, 744 (85.4%) participated at 1 year, and 550 (63.2%) at 3.5 years. AD was diagnosed in 87 (15.8%) children at 3.5 years.

METHODS. The Auckland Birthweight Collaborative study is a case-control study of risk factors for small-for-gestational-age infants. Case subjects were born at term with birth weight at ≤10th percentile; controls were appropriate for gestational age, with birth weight >10th percentile. AD was defined as the presence of an itchy rash in the past 12 months with ≥3 of the following by history: flexural involvement, generally dry skin, atopic disease in parents or siblings, or visible flexural dermatitis by photographic protocol.

RESULTS. The prevalence of AD did not differ by birth weight. AD at 3.5 years was associated with raised serum immunoglobulin E, wheezing, asthma, rash, or eczema at 1 year. In multivariate analysis adjusting for parental atopy and breastfeeding, AD at 3.5 years was associated with atopic disease in the parents (maternal atopy only [adjusted odds ratio (aOR): 3.83; 95% confidence interval (CI): 1.2–12.2]; paternal atopy only [aOR: 3.6; 95% CI: 1.09–11.75]; both parents atopic [aOR: 6.12; 95% CI: 2.0–18.5]). There was a higher risk of AD with longer duration of breastfeeding (<6 months [aOR: 6.13; 95% CI: 1.5–25.9]; ≥6 months [aOR: 9.70; 95% CI: 2.5–38.2]) compared with never breastfeeding. AD at 3.5 years had a negative association with cat ownership (aOR: 0.5; 95% CI: 0.2–0.97) but was not associated with owning a dog at 3.5 years, having pets at 1 year, or with older siblings. AD at 3.5 years was not associated with gender, socioeconomic status, maternal smoking, parity, mold exposure, immunizations, BMI, or antibiotic use in the first year of life.

CONCLUSIONS. A personal and a parental history of atopic disease are risk factors for AD at 3.5 years. Duration of breastfeeding was associated with an increased risk of AD. No association was found with factors implicated by the hygiene hypothesis.

REVIEWER COMMENTS. This is one of many studies to look at various risk factors for atopy, here focusing on AD. Similar to other studies, the authors show that family history of atopy is a risk factor for AD. However, compared with other studies, the authors did not find any association with gender, socioeconomic status, environmental risks, or BMI. This discrepancy is probably attributable to differences in populations and different environmental factors. The data on atopy prevention by breastfeeding remain unclear and may be affected by reverse causation (breastfeeding longer in response to observing AD); although this is one of several negative studies, meta-analyses of multiple studies typically show a prevention effect.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900H

Jonathan M. Spergel, MD, PhD
Philadelphia, PA

BCG Immunization at Birth and Atopic Diseases in a Homogeneous Population of Spanish Schoolchildren


PURPOSE OF THE STUDY. To investigate the effect of vaccination with BCG on the development of atopic diseases in a homogeneous population of Spanish schoolchildren.

Downloaded from http://pediatrics.aappublications.org/ by guest on November 7, 2017
STUDY POPULATION. Children aged 6 to 7 years who were living in 3 cities (Bilbao, San Sebastian, and La Coruna) and 1 province (Asturias) of the North Atlantic coast of Spain.

METHODS. The International Study of Asthma and Allergies in Childhood (ISAAC) core and environmental questionnaires were used in 4 different centers of the Spanish North Atlantic coast. Bilbao, San Sebastian, and Asturias have a universal BCG immunization policy during the first days of life, whereas La Coruna discontinued this practice in 1989. Except for this center, immunization coverage was >90%. Parents of children aged 6 and 7 years were surveyed from a random sample of schools of Asturias or all schools in the city district among the remainder of the centers.

RESULTS. The participation rate was >70%. After excluding those children born outside Spain, there were 6762 immunized and 2828 nonimmunized. After adjusting for gender, age, smoking habits of the father and mother, truck traffic near the household, presence of older and younger siblings, and ownership of a cat or a dog during the first year of the child’s life, the adjusted odds ratios of the BCG-immunized children according to disease outcome were 0.87 for asthma (95% confidence interval [CI]: 0.76–1.00), 0.87 for hay fever (95% CI: 0.75–1.01), and 0.89 for atopic dermatitis (95% CI: 0.76–1.05).

CONCLUSIONS. BCG immunization offers weak protection against atopic diseases in Spanish schoolchildren.

REVIEWER COMMENTS. BCG vaccination has received attention because of its ability to provoke a T-helper (Th)1 response. Many investigators have hypothesized that vaccination with BCG may offer protection from Th2-skewed diseases such as asthma, allergic rhinitis, and atopic dermatitis. Although this study reveals that immunization with BCG offers weak protection against asthma and allergic rhinitis in a homogeneous population, it is important to remember that these diseases are multifactorial, with genetic and environmental influences also impacting pathogenesis.

Hospitalization for RSV Bronchiolitis Before 12 Months of Age and Subsequent Asthma, Atopy and Wheeze: A Longitudinal Birth Cohort Study


PURPOSE OF THE STUDY. To compare asthma and atopy outcomes of children according to whether they had been admitted to a hospital in the first 12 months with respiratory syncytial virus (RSV)–proven bronchiolitis.

STUDY POPULATION. Data from a large, population-based, birth cohort (Avon Longitudinal Study of Parents and Children) were used.

METHODS. Outcomes considered were 12-month prevalence of wheeze at 2 ages (between 30–42 and 69–81 months), cumulative prevalence of doctor-diagnosed asthma at 91 months, and skin-prick test–defined atopy at 7 years. Multivariable logistic-regression models were used to calculate odds ratios for outcomes adjusted for potential confounders.

RESULTS. A total of 150 infants (1.1% of the cohort) were admitted to a hospital within 12 months of birth with RSV bronchiolitis. The prevalence of wheezing was 28.1% in the RSV group and 13.1% in controls at 30 to 42 months and 22.6% vs 9.6% at 69 to 81 months. The cumulative prevalence of asthma was 38.4% in the RSV group and 20.1% in the controls at 91 months. Atopy was found in 14.6% of those in the RSV group and in 20.7% of the controls at 7 years. RSV bronchiolitis was associated with subsequent wheezing between 30 to 42 months (odds ratio [OR]: 2.3; 95% confidence interval [CI]: 1.3–3.9) and 69 to 81 months (OR: 3.5; 95% CI: 1.8–6.6) and with the cumulative prevalence of asthma at 91 months (OR: 2.5; 95% CI: 1.4–4.3) but not with atopy (OR: 0.7; 95% CI: 0.2–1.7).

CONCLUSIONS. In a population-based birth cohort, RSV bronchiolitis was associated with subsequent wheezing and asthma but not with the development of atopy by 7 years of age.

REVIEWER COMMENTS. Because infants who have severe RSV infection have recurrent wheezing later in life, RSV has been suggested to be a risk factor for asthma. Some also postulate that early RSV infection may predispose children to atopy; however, this has been controversial. Henderson et al show in their large prospective cohort that severe RSV infection requiring hospitalization is associated with wheezing but not atopy. These results indicate that RSV infection may be a risk factor for nonallergic asthma.

Early Respiratory Infections, Asthma, and Allergy: 10-Year Follow-up of the Oslo Birth Cohort

PURPOSE OF THE STUDY. As one dimension of the hygiene hypothesis, early infections may protect against the development of atopic disease. However, there are few long-term follow-up studies of the influence of early respiratory infections. This study investigates associations between early respiratory infections and diagnosed asthma, allergic rhinitis, and skin-prick sensitization in children at 10 years of age.

STUDY POPULATION. A total of 2540 Norwegian children were followed prospectively from birth to the age of 10 years in the Oslo Birth Cohort.

METHODS. Information on child’s health and environmental exposures, including experiences with respiratory infections, was recorded at birth and at 6 and 12 months. Current symptoms and “ever” doctor-diagnosed asthma and allergic rhinitis were compared with these early life exposures. A subset of the cohort underwent skin-prick testing.

RESULTS. “Ever” diagnosis of asthma was positively associated with measures of early life infection. Current asthma was related to lower respiratory tract infection (adjusted odds ratio [aOR]: 2.1; 95% confidence interval [CI]: 1.3–3.0) and croup (aOR: 2.3; 95% CI: 1.3–4.2) in the first year. ORs for allergic rhinitis and skin-prick sensitization were smaller but “mainly positive.” Birth order and child care attendance at 1 year of age were not significantly associated with any of the studied outcomes.

CONCLUSIONS. Early respiratory infections did not protect against the development of atopic disease during the first 10 years of life. Rather, infections increased the risk for asthma at age 10.

REVIEWER COMMENTS. The hygiene hypothesis has been used to explain an inverse relation between early-life infection and allergic disease. Although a number of studies have described the relationship of early childhood infections and atopic disease, few have done so prospectively. This study, with its ORs near 1 with narrow CIs, shows a positive relationship of infections to atopy. Thus, it does not support the view of protection with increasing infection, bringing to light that this relationship is not as simple or direct as was first described. Additional prospective studies with long-term follow-up are required to further define this relationship. In addition, these results support previous conclusions that early childhood infection may be associated with an increased risk for future development of asthma. There continues to be many unanswered questions regarding the risks in susceptible hosts.

Exposure to Pets, and the Association With Hay Fever, Asthma, and Atopic Sensitization in Rural Children


PURPOSE OF THE STUDY. To evaluate the effect of exposure to animals on the development of hay fever, asthma, and atopy.

STUDY POPULATION. Cross-sectional study of 2618 families of Swiss, German, and Austrian decent, living in a rural location. Families were assigned to 1 of 2 categories: farming and nonfarming.

METHODS. Information was collected by standardized questionnaire and interview. Mattress dust was collected and measured for content of endotoxin and cat allergen. Specific immunoglobulin E levels to multiple common allergens and immunoglobulin G4 to cat were measured.

RESULTS. Complete data were available for 812 children. Among them, 319 were farmers’ children and 493 were nonfarmers’ children. In the entire group, early (<1-year-old) and current exposure to cats was associated with a reduced risk of wheezing and grass pollen sensitization. Current contact with dogs was inversely associated with hay fever, asthma, and sensitization to cat allergen and grass pollen. Early exposure to dog did not have any significant effects. When farm-animal contact was controlled for, most of these associations were weakened but were strongest in farmers’ children.

CONCLUSIONS. There was an inverse relationship between dog exposure and asthma, hay fever, and allergy. However, much of this protective effect was explained by exposure to farm animals.

REVIEWER COMMENTS. There are several studies that report pet exposure to be associated with a reduced risk for atopic disease. In this study, the primary outcome of decreased clinical manifestations of atopy was confounded by exposure to farm animals. Although the exposure to pets did not show an overall statistically significant association, the results approached significance, and a larger study population may have revealed significant differences. Also, the study ultimately found that animal exposure is most likely to provide a protective effect when the total level of exposure is highest (ie, those children exposed to pets and farm animals).
Early Childhood Environment Related to Microbial Exposure and the Occurrence of Atopic Disease at School Age


PURPOSE. There has been much interest in the effect of various microbial exposures early in life on the subsequent development of atopic disease. This study aimed to examine the effects of several exposure types on atopic sensitization.

STUDY POPULATION. This was a cross-sectional study of 4111 Dutch schoolchildren aged 8 to 13 years.

METHODS. A questionnaire evaluating day care attendance before age 4, cats or dogs in the home before age 2, siblings, history of doctor-treated airway disease before age 2, and current respiratory status was used. Atopic status was tested by either skin-prick testing or antigen-specific immunoglobulin E levels to multiple common antigens.

RESULTS. Complete data were available for 1555 of the participants. Atopic sensitization was less frequent in children who attended day care (adjusted odds ratio: 0.74; 95% CI: 0.56–0.99) or had a pet in the home (adjusted odds ratio: 0.78; 95% CI: 0.61–0.99). There was no statistically significant association between the presence of siblings or the occurrence of doctor-treated airway disease and atopy.

CONCLUSION. Day care attendance and having a pet in the home may provide a protective effect against atopic sensitization.

REVIEWER COMMENTS. This study attempts to help clarify factors that may be associated with the primary development of atopy, which has been an area of great interest, especially given the rising prevalence of allergic disease. The results are consistent with many other studies indicating that microbial exposure early in life may have a preventive effect. Additional studies, including prospective cohorts, are being performed to define these associations more clearly. With luck, one day we will be able to use this information to design effective preventive strategies.

Individual and Neighborhood-Level Factors in Predicting Asthma


PURPOSE OF THE STUDY. To investigate the association between asthma and neighborhood-level social and physical indicators. A secondary goal was to identify individual-level predictors for developing childhood asthma.

STUDY POPULATION. Cross-sectional study comprised of 2544 children, aged 5 to 18 years, from a network of 6 Midwestern urban primary care clinics (Indiana University Medical Group in Marion County, Indiana). A total of 1541 black children (947 females and 594 males) and 1003 white children (568 females and 435 males) were evaluated.

METHODS. A medical chart review was conducted to identify those with physician-diagnosed asthma and record demographic data to ascertain socioeconomic indicators. Other data for neighborhood factors such as median age of housing, family income, education, single-parent family, and language isolation were obtained through the Social Assets and Vulnerabilities Indicators Project. Medical chart data were used to compute age- and gender-adjusted BMI percentiles. Multiple logistic-regression models were used to analyze the data.

RESULTS. On the individual level, this study found that asthma prevalence for black children was 4% higher than for white children and that males had a 9% higher risk than females. BMI had different effects for males and females. Males who were normal weight and those at risk of being overweight had similar risks of asthma. However, males who were overweight had a higher risk of asthma than boys who were at risk of being overweight. In contrast, females who were overweight and those at risk of being overweight had similar risks of asthma, and the rates were substantially higher compared with those for females who were normal weight. On the neighborhood level, there was no trend in rising asthma rate with the rise in the median age of housing. Children from very-low-income-level neighborhoods had the same asthma rates as those children from moderate- or middle-income neighborhoods.

CONCLUSIONS. The authors concluded that in a predominantly urban population of children, the highest likelihood of having asthma is among young, black, overweight males and the lowest rate is among older, white, normal-weight females. There was no association between asthma and neighborhood characteristics or median family incomes.

REVIEWER COMMENTS. Although the data from this study did not support the hypothesis that lower neighborhood socioeconomic status and older age of homes were associated with childhood risk of asthma, other studies through the National Cooperative Inner-City Asthma Study suggest that other environmental factors may be involved in urban populations, such as higher cockroach, rat, and mouse allergen levels found in inner-city...
homes and sensitization to these allergens as a risk factor for developing asthma in urban neighborhoods. Asthma is the most common chronic childhood disease; thus, the findings from this study, that increased BMI is associated with increased risk of asthma, is additionally concerning because the rate of childhood obesity is increasing among our nation’s children.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900

Sally Joo Bailey, MD
New York, NY

The Canadian Childhood Asthma Primary Prevention Study: Outcomes at 7 Years of Age

PURPOSE OF THE STUDY. To evaluate the effects of a multifaceted intervention program involving high-risk infants on the development of asthma at 7 years of age.

STUDY POPULATION. Of the original 545 high-risk infants in the Canadian Childhood Asthma Primary Prevention Study, 380 were evaluated at 7 years of age. Infants at high risk for asthma development were defined as those with at least 1 first-degree relative with asthma or 2 first-degree relatives with other immunoglobulin E–mediated allergic diseases.

METHODS. The initial 545 high-risk infants were randomly assigned before birth to a multifaceted intervention group (n = 279) or the control group (n = 266). The multifaceted intervention program, which was implemented before birth and during the first year of life, included house dust mite–control measures, pet-avoidance measures, avoidance of environmental tobacco smoke, breastfeeding, and/or using partially hydrolyzed whey formula. This study describes the follow-up assessment of 380 subjects at 7 years of age who completed a questionnaire and were evaluated by a pediatric allergist for asthma. Allergy skin testing and methacholine challenge were also performed.

RESULTS. A significantly lower number of subjects had pediatric allergist–diagnosed asthma in the intervention group (14.9%) than in the control group (23.0%; adjusted relative risk [RR]: 0.44). The prevalence of asthma, defined as wheeze plus bronchial hyperreactivity (methacholine challenge), was also significantly lower in the intervention group when compared with the control group (12.9% vs 25%, respectively; adjusted RR: 0.39). There was no significant difference in the diagnosis of allergic rhinitis or atopic dermatitis, allergen skin-test reactivity, or bronchial hyperreactivity alone between the 2 groups. Symptoms of wheeze and wheeze apart from colds in the last 12 months were significantly lower in the intervention group compared with the control group. There were no significant differences in nocturnal symptoms, exercise-related symptoms, medication use, emergency visits for wheeze, nasal symptoms, or skin rash.

REVIEWER COMMENTS. Asthma and allergic diseases likely result from a combination of environmental and genetic factors. This study showed that the prevalence of asthma was decreased after an intervention program implemented early in life. Thus, recommending environmental controls as a safe method to decrease the risk of developing asthma in high-risk patients is reasonable. It is unclear from this study whether a specific environmental control or a combination of interventions is more effective. It is interesting that no difference was noted in the prevalence of allergic rhinitis or atopic dermatitis between the groups, which, theoretically, could also be affected by environmental controls.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900

Rajiv Arora, MD
Cecilia P. Mikita, MD
Washington, DC

The PREVASC Study: The Clinical Effect of a Multifaceted Educational Intervention to Prevent Childhood Asthma

PURPOSE OF THE STUDY. To evaluate the clinical effectiveness of a multifaceted education intervention to prevent childhood asthma.

STUDY POPULATION. General practitioners recruited 476 high-risk children during the prenatal period.

METHODS. These high-risk children were randomly assigned to either a control group, receiving usual care, or an intervention group, in which families received instruction from nurses on how to reduce exposure of newborns to dust mite, pet, and food allergens and passive smoking.

RESULTS. A total of 443 infants were followed up for 2 years. At 2 years of age, those in the intervention group (n = 222) had less asthma-like symptoms, including wheezing, shortness of breath, and nighttime cough, compared with those in the control group (n = 221). No significant differences in total and specific immunoglobulin E were found between the groups. During the first 2 years of life, the incidence of asthma-like symptoms was similar in both groups; however, subanalysis revealed a significant reduction in the females but not in the males in the intervention group.

CONCLUSIONS. The intervention used in this study was not effective in reducing asthma-like symptoms in high-risk
Asthma in Remission: Can Relapse in Early Adulthood Be Predicted at 18 Years of Age?

PURPOSE OF THE STUDY. To determine the frequency of asthma relapse in young adults in remission at 18 years over an 8-year follow-up period and to determine possible prognostic indicators of relapse.

STUDY POPULATION. A subset of 68 subjects in asthma remission at 18 years of age from of a cohort of 1037 subjects born in New Zealand from 1972 to 1973 followed from birth through the Dunedin Multidisciplinary Health and Development Study.

METHODS. The cohort was enrolled at 3 years old and followed every 2 years until age 15 and again at ages 18, 21, and 26. Subjects were given respiratory questionnaires and lung-function assessment by spirometry. Methacholine testing for bronchial hyperreactivity was performed at 9, 11, 13, 15, and 21 years of age in some. Atopy was assessed by skin tests at ages 13 and 21 years. Remission of asthma at 18 years was defined as no current symptoms with previous reported symptoms at ≥2 previous assessments.

RESULTS. At 18 years of age, there were 108 subjects with current asthma and 68 subjects with previous asthma in remission. Those in remission at age 18 had a later age of onset of asthma (6.4 ± 4.5 vs 4.7 ± 4 years for current asthma) and had better lung function. Those with current asthma at age 18 were more atopic at age 18, with higher skin-test reactivity for house dust mite and cat. They had higher bronchial hyperreactivity by methacholine at all age points between 9 and 18 than their counterparts in remission. Of the 68 subjects in remission at age 18, 44 remained in remission and 24 relapsed by age 26. Multiple logistic-regression analysis identified dust mite sensitization at age 13 (odds ratio [OR]: 2.63; 95% confidence interval [CI]: 1.23–5.61) and decreased forced expiratory volume in 1 second/forced vital capacity ratio at age 18 (OR: 0.9 per 1% higher ratio; 95% CI: 0.81–0.99). Those with better lung function had lower likelihood of asthma relapse by 16 years of age. Variables such as methacholine reactivity and tobacco smoking were not significant predictors.

CONCLUSIONS. Approximately one third of young adults with a history of asthma in childhood in remission at 18 years of age will relapse by 26 years of age. Most will have mild disease at relapse. There were weak associations with atopy and lower lung function at a young age as predictors of asthma relapse.

Adult Asthma Severity in Individuals With a History of Childhood Asthma

PURPOSE OF THE STUDY. Childhood asthma has a range of outcomes in adulthood. This study sought to identify clinical features and exposures associated with persistence and severity of childhood asthma in adulthood.

STUDY POPULATION. Subjects had been previously enrolled in the Childhood Asthma Study, a double-blind, randomized, placebo-controlled trial designed to study the role of immunotherapy as an adjunct treatment. The 121 original study members, aged 5 to 12 years at the time of randomization, had moderate-to-severe asthma and had been followed for at least 1 year before enrollment. Evaluations performed during the original study included daily medication-symptom diaries, home allergen analysis, allergy skin testing, and methacholine challenges. The cohort had varied socioeconomic status, genders, and ethnicities. For this study an attempt was made to enroll all original participants.
METHODS. Eighty-five of the original subjects participated in the adult evaluation, underwent spirometry and inhalant allergy skin testing, and completed questionnaires regarding their interim medical history, asthma symptoms, and medications. Asthma severity was classified by using a modified version of the 1997 National Asthma Education and Prevention Program algorithm. Postbronchodilator spirometry was used for severity categorization. Subjects were categorized in the most severe category for which they qualified.

RESULTS. Thirteen (15.3%) of these young adults, aged 17 to 30 years, were in remission. Another 19 (22%) had only mild intermittent asthma. There were 12 (14%) with mild persistent asthma, 25 (29%) with moderate persistent asthma, and 16 (19%) with severe persistent disease. Subjects in remission, compared with subjects with mild intermittent or persistent asthma, had lower serum immunoglobulin E in childhood (412 vs 1136 vs 968 ng/mL, respectively) and fewer positive allergy skin tests (7 vs 9 vs 10, respectively, from a panel of 18 allergens). Subjects in remission also had milder childhood asthma, indicated by lower average daily medication usage scores and lower percentage of days on inhaled corticosteroids (13.7% vs 24.7% vs 40.9%). There was no association found between current asthma severity and childhood immunotherapy.

CONCLUSIONS. The prognosis of childhood allergic asthma in adulthood is largely determined early in life. The degree of atopy seems to be a critical determinant of asthma persistence.

REVIEWER COMMENTS. The authors point out that numerous studies of the natural history of asthma have suggested associations between childhood atopy and disease severity with risk of asthma persistence and severity in later childhood and adulthood. It remains to be seen whether there is any sort of intervention at a very early phase in the disease that will more favorably alter the course of asthma. Thus far, there are no compelling candidates.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900R

Timothy Andrews, MD
James R. Banks, MD
Arnold, MD

ALLERGENS AND ENVIRONMENTAL EXPOSURES

Inner City Asthma Study: Relationships Among Sensitivity, Allergen Exposure, and Asthma Morbidity


PURPOSE OF THE STUDY. To describe the relationship between allergen sensitivities, allergen exposures, and asthma morbidity in children with moderate-to-severe asthma while also exploring geographic variations in indoor allergen levels.

STUDY POPULATION. Subjects were children aged 5 to 11 years (n = 937) from 7 inner-city and metropolitan areas across the United States participating in the Inner City Asthma Study.

METHODS. In a fully crossed factorial design, participants were randomly assigned to receive an allergen intervention, bimonthly feedback of the child’s health status to their primary care physicians, both interventions, or no intervention (control group, n = 234). At baseline, a clinical interview with the child’s primary caregiver (including demographics, asthma morbidity, home characteristics, and exposure to tobacco smoke) was conducted with skin-prick tests to aeroallergens. Morbidity was measured at 2-month intervals during a 24-month period. Home visits including a visual inspection and dust-sample collection (dust mite, cockroach, cat and dog dander) were conducted at baseline and every 6 months.

RESULTS. Of 1059 children tested, 94% had at least 1 positive skin test. Allergen sensitivities varied widely across the study sites, with cockroach (69%), dust mites (62%), and molds (50%) being the most predominant. Cockroach sensitivity was highest in The Bronx, New York, New York City, New York, and Dallas, Texas (81%, 79%, and 79%, respectively), whereas dust mite sensitivities were highest in Dallas and Seattle, Washington (84% and 78%, respectively). At least 30% of the subjects were allergic to cats at all sites. Cockroach levels were highest (>50% of homes) in Chicago, Illinois, New York City, The Bronx, and Dallas and were lower in Seattle and Tucson, Arizona (8% and 11% of homes, respectively). Dust mite levels were highest in Seattle and Dallas. Cockroach levels were higher in high-rise and low-rise apartments, whereas dust mite levels were higher in detached homes. No correlation was seen between animal dander and housing type.

CONCLUSIONS. There were significant differences between geographic study sites and the type of indoor allergen exposure and skin-test sensitivity in this study group. Cockroach predominated in the Northeast, whereas dust mite predominated in the South and Northwest. Although most children in the study were allergic to dust mite and/or cockroaches, only the children who were sensitive and exposed to cockroach had increased asthma morbidity.

REVIEWER COMMENTS. This study demonstrates the association of allergen sensitivities and exposures (particularly cockroach allergens) to increased asthma morbidity in children with moderate-to-severe asthma living in inner-city areas. Physicians can use this knowledge to identify significant risk factors in asthmatic patients, implement appropriate prevention measures (ie, environ-
Initial High-Dose Nasal Allergen Exposure Prevents Allergic Sensitization to a Neoantigen

PURPOSE OF THE STUDY. Epidemiologic studies have suggested that high-dose allergen exposure may protect against primary allergic sensitization—the formation of immunoglobulin E (IgE) after initial antigen exposure. This study uses a human nasal allergic sensitization model to evaluate the effect of the dose of the antigen on the rate of primary sensitization to a neoantigen, keyhole limpet hemocyanin (KLH).

STUDY POPULATION. Fifty-one healthy nonsmoking atopic subjects aged 18 to 55 years. Atopic status was defined by a positive skin-prick test to at least one aeroallergen; the subjects therefore had a propensity to mount an allergic (IgE) response to respiratory antigen exposure.

METHODS. Subjects underwent a 33-day sensitization protocol including initial exposure to 0.1-, 10-, 1000-, or 100 000-μg doses of intranasal KLH as well as later exposure to adjuvant intranasal diesel exhaust particles. At the conclusion of protocol, antigen-specific IgE, IgG, and IgG4 were measured in nasal lavage samples.

RESULTS. The rates of allergic sensitization, defined as detectable KLH-specific IgE, for the 0.1-, 10-, 1000-, or 100 000-μg dose groups were 0, 100, 57, and 11%, respectively. Furthermore, the mean KLH-specific IgE levels decreased with increasing doses of initial antigen exposure. Antigen-specific IgG and IgG4 were produced by all subjects, with the highest levels observed in the high-dose group.

CONCLUSIONS. Initial high levels of respiratory antigen exposure may prevent primary allergic sensitization through induction of an antigen-specific non-IgE humoral immune response.

REVIEWER COMMENTS. In children at high risk of allergic sensitization, a means of preventing primary sensitization and inducing durable allergic tolerance would be of great value. This study found that initial high-dose exposure to a neoantigen, KLH, results in a humoral immune response with high levels of antigen-specific IgG, including IgG4, and low levels of KLH-specific IgE. Whether these findings apply to other respiratory antigens remains unclear. The mechanism underlying this induction of tolerance remains unclear, and it is also not known whether this immune response represents durable allergic tolerance. Future studies investigating these issues are needed to move toward potential primary prevention therapy for allergic disease.

Michael Le Bras, DO
Stacie M. Jones, MD
Little Rock, AR

FOOD ALLERGY
The Natural History of Tree Nut Allergy

PURPOSE OF THE STUDY. To estimate the proportion of children who outgrow tree nut (TN) allergy and examine predictors of outgrowing it.

STUDY POPULATION. All children with TN allergy followed at the authors’ pediatric allergy clinic.

METHODS. Patients with TN allergy, defined as a history of reaction on ingestion and evidence of TN-specific immunoglobulin E (TN-IgE) or positive TN-specific IgE level but no history of ingestion, were evaluated. If all current TN-IgE levels were <10 kU/L of antibody (kU/L), double-blind, placebo-controlled food challenges were offered. Patients who had undergone open oral TN challenges as part of routine clinical care were also included.

RESULTS. Two hundred seventy-eight patients with TN allergy were identified. One hundred one (36%) had a history of acute reactions, 12 (12%) of whom had reactions to multiple TNs and 73 (63%) of whom had a history of moderate-to-severe reactions. Nine of 20 patients who had previously reacted to a TN passed challenges, so that 9 (8.9%; 95% confidence interval: 4%–16%) of 101 patients with a history of previous TN reactions outgrew TN allergy. Of 19 patients who had never ingested TNs but had detectable TN-specific IgE levels, 14 passed challenges. One hundred sixty-one did not meet the challenge criteria, and 78 met the criteria but declined challenges. Looking at specific TN-IgE values, 58% with TN-IgE levels of ≤5 kU/L and 63% with TN-IgE levels of ≤2 kU/L passed challenges.

CONCLUSIONS. Approximately 9% of patients outgrow TN allergy, including some who had previous severe reactions. Although ideal cutoffs for challenge cannot be firmly recommended on the basis of these data, patients aged 4 years or older with all TN-IgE levels of ≤5 kU/L should be considered for physician-supervised oral food challenges.

REVIEWER COMMENTS. This is the first study to comprehensively address the natural history of TN allergy. Although
Prevalence and Outcome of Allergic Colitis in Healthy Infants With Rectal Bleeding: A Prospective Cohort Study


**PURPOSE OF THE STUDY.** To determine the prevalence of allergic colitis (AC) in a cohort of healthy infants with rectal bleeding. A secondary purpose was to determine if bleeding would resolve in untreated infants with rectal bleeding without biopsy-proven AC.

**STUDY POPULATION.** There were 22 infants ≤6 months of age with rectal bleeding recruited from the referral area of Cincinnati Children’s Hospital Medical Center (Cincinnati, OH). All subjects had a negative history of bleeding disorders, negative stool cultures, positive hemoccult, and a negative history and physical examination for signs of infection, Hirschsprung disease, and inflammatory bowel disease.

**METHODS.** AC was defined histologically as colonic mucosa with ≥6 eosinophils per high-power field and/or eosinophils in the colonic crypts or muscularis mucosae. Formula or maternal diet was changed only for infants with histologic findings of AC. Formula-fed infants were switched to an extensively hydrolyzed formula and were rebiopsied at 3 weeks. If the biopsy was normal, they were continued on the formula and managed clinically. Those with continued histologic evidence of colitis were changed to an amino acid–based formula and were rebiopsied at 6 weeks. Breastfed infants continued breastfeeding while mothers followed a milk-protein–free diet. Those with resolution of bleeding and normal biopsies at 3 weeks continued with breastfeeding and a restricted maternal diet. Those with persistent histologic evidence of colitis were rebiopsied at 6 weeks with no further dietary change. Those with persistent bleeding were changed to hydrolysate and rebiopsied at 6 weeks. Those with persistent bleeding and histologic evidence of AC at 6 weeks were changed to an amino acid–based formula.

**RESULTS.** Of 22 subjects, 14 (63.6%) had histologic evidence of AC. Five had normal biopsies and 3 had nonspecific colitis. Seven of the 14 with AC were formula fed. Six of the 7 had resolution of bleeding, on average, in 1.8 weeks (range: 1–5 weeks). One of the 7 was changed to an amino acid formula at 3 weeks and had resolution of bleeding at 5 weeks. The remainder of the 14 were breastfed. Six were followed to completion of the study. One had a delayed diagnosis because of development of worsening rectal bleeding and an abnormal biopsy at week 3 despite a normal biopsy at the onset of the study. The infant failed to improve with hydrolyzed formula but had resolution of bleeding by week 8 after initiation of an amino acid formula. Of the remaining 5, 2 had normal histology at week 3 with maternal elimination of cow’s milk. Two had improvement by week 3, and 1 had no change. The average time for resolution in the breastfed group was 5.6 weeks (range: 2–8 weeks). For the 5 infants without histologic evidence of colitis, the average time for resolution of bleeding was 3.25 weeks. In those with nonspecific colitis, 2 had resolution by week 6, and the third was ultimately diagnosed with inflammatory bowel disease.

**CONCLUSIONS.** A significant proportion of infants with rectal bleeding may not have AC and may undergo unnecessary, expensive formula or maternal diet changes that may discourage breastfeeding.

**REVIEWER COMMENTS.** This small study provides important insights about the prevalence and natural course of protocolitis. A much larger prospective placebo-controlled study that compares treatment versus no treatment would be very helpful.
asthma symptoms was recorded on the basis of 3-month recall at baseline and at 3-month intervals for a period of 12 months. No information regarding food allergy diagnoses or reactions was obtained. Skin-prick testing to 13 environmental allergens was performed at enrollment in the National Cooperative Inner City-Asthma Study. The random serum samples were evaluated for specific immunoglobulin E (IgE) (UniCap System) to egg, milk, soy, peanut, wheat, and fish. On the basis of IgE levels, subjects were stratified into 4 groups: group 1, food-specific IgE levels that had >95% positive predictive value for food allergy; group 2, probable food allergy (IgE ≥ 0.7 kU/L); group 3, any sensitization (IgE ≥ 0.35 kU/L); and group 4, no evidence of food allergy (IgE < 0.35 kU/L).

RESULTS. There was a significant correlation between sensitization to foods and sensitization to aeroallergens, with sensitization to the highest number of aeroallergens correlating with sensitization to soy, wheat, and peanut. Forty-five percent of study patients were sensitized to at least one food (groups 1–3): 4% of the participants were categorized to group 1, 26% to group 2, and 14% to group 3. Fifty-five percent were not sensitized to any of the 6 foods (group 4). Food allergy to egg and peanut were associated with the highest specific IgE levels. Patients who were sensitized to at least one food had higher rates of hospitalization and steroid medication use. The food-sensitized groups required more medications in general, but this difference was not significant. Most group 1 children (96%) demonstrated sensitization to >1 food, with 25% of the patients sensitized to all 6 foods tested. Most group 2 patients (75%) and 19% of group 3 patients were sensitized to multiple foods. There was a significant increase in hospitalizations for asthma in children sensitized to >1 food. When specific foods were examined, a correlation between higher asthma morbidity and sensitization to fish or soy was noted.

CONCLUSIONS. Food sensitization correlated with increased asthma severity in the study population. The prevalence of food allergy was not determined because of the nature of the study (anonymous serum samples and lack of blinded food challenges); however, on the basis of the study results, the authors predicted that inner-city children with asthma were more likely than the general population to have food allergy. The association of increased asthma morbidity with at least 1 food sensitization, and findings that patients with sensitization to multiple foods had significantly more asthma morbidity than those with single-food sensitization, suggest that food sensitization is a marker for increased asthma severity.

REVIEWER COMMENTS. This study suggests that the prevalence of food sensitization, and possibly food allergy, is increased in patients with asthma and may be a useful marker for increased asthma severity. Health care providers should consider screening for food sensitization in patients with severe or poorly controlled asthma.

Risk of Celiac Disease Autoimmunity and Timing of Gluten Introduction in the Diet of Infants at Increased Risk of Disease

PURPOSE OF THE STUDY. Patients with HLA-DR3 or DR4 alleles are at increased risk for the development of celiac disease. However, not all genetically susceptible individuals develop celiac disease. The objective of this study was to investigate whether there was an association between the timing of exposure to gluten and subsequent development of celiac disease autoimmunity (CDA) in children with a genetic predisposition for celiac disease.

STUDY POPULATION. Children (n = 1560) were identified in the Denver, Colorado, metropolitan area with an increased risk for celiac disease (or type 1 diabetes), defined as having either a first-degree relative with type 1 diabetes or positive cord blood screening for HLA-DR3 or DR4 alleles. This study was conducted over 10 years with a mean follow-up of 4.8 years.

METHODS. This was a prospective, observational study. Infant diet data were collected during telephone or face-to-face interviews at 3, 6, 9, 12, and 15 months of age. No dietary advice was given to the families. Children had blood drawn at 9, 15, and 24 months and annually thereafter for the measurement of the celiac disease autoantigen, and tissue transglutaminase (tTG). After 1 or 2 positive tTG autoantibody results, small-bowel biopsy was offered to the families, although not all had this procedure performed. The primary outcome of the study was the time to development of CDA defined as the presence of tTG autoantibodies on 2 consecutive results or a positive small-bowel biopsy after a single tTG-positive test.

RESULTS. Fifty-one children developed CDA. Children exposed to foods containing wheat, barley, or rye in the first 3 months of life had a 5 times increased odds ratio (P = .02) of CDA as compared with children first exposed to gluten at 4 to 6 months of age. Twenty-five of the CDA-positive children had biopsy-proven celiac disease. In these children, exposure to gluten in the first 3 months of life had a 23 times increased risk (P = .001) of CDA. In the biopsy-proven cohort, children not exposed to gluten until >7 months of age also had a significantly increased risk of CDA (odds ratio: 4; P = .04). There was
no association between the development of CDA and the timing of introduction of oats or rice. No protective effect of breastfeeding was found with the development of CDA. Although all children in the cohort were exposed to gluten by 12 months of age, the first positive tTG autoantibody test did not occur until 2 years of age, with a mean age of positive conversion of 4.7 years.

CONCLUSIONS. In children at increased risk of developing celiac disease, timing of gluten exposure in the diet is associated with the appearance of CDA. Exposure to gluten in the first 3 months of life is thought to be associated with increased risk because of immature or incomplete intestinal barrier function. The authors speculate that late gluten exposure may have been associated with CDA because of greater amounts introduced in the older infants.

REVIEWER COMMENTS. It is important to understand that this study population was specific children with genetic and family history characteristics at increased risk for the development of celiac disease and may not be generalizable to the entire population. Mean follow-up of this population was just under 5 years, and long-term follow-up of these patients is needed to determine if earlier exposure to gluten simply leads to earlier appearance of CDA and that many (if not all) exposed at-risk children would eventually develop CDA. This study also does not address the relationship between CDA and celiac disease.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900X

A National Prospective Study on Childhood Celiac Disease in the Netherlands 1993–2000: An Increasing Recognition and a Changing Clinical Picture


PURPOSE OF THE STUDY. To investigate whether the incidence of diagnosed celiac disease (CD) is increasing in the Netherlands and whether the clinical presentation is changing.

STUDY POPULATION. Children between the ages of 0 and 14 years with newly diagnosed cases of CD from 1993–2000.

METHODS. Diagnosis of CD was based on biopsy of the small intestine. The following data were collected: age, gender, weight, height, and aspects of the presenting clinical picture.

RESULTS. The overall crude incidence rate for CD from 1993–2000 was 0.81 per 1000 live births. There was a significant linear increase of the crude incidence from 1993–2000. During the period of 1993–2000 there was a significant increase in the diagnosis of CD with partial villous atrophy of the small-bowel mucosa and a relative decrease in the diagnosis with subtotal villous atrophy. Fewer children are presenting with abdominal distention, chronic diarrhea, and failure to thrive, and more children are presenting with weight <10th percentile, abdominal pain, and lassitude.

CONCLUSIONS. The increase in newly diagnosed cases of CD seems to represent greater awareness of the disease and the availability of serologic tests. The increase in the number of children with CD diagnosed with small-bowel biopsy specimens showing partial villous atrophy suggests increased recognition of milder cases.

REVIEWER COMMENTS. In the United States, CD now seems to affect ~0.5 to 1.0% of the population (10 times higher than previous estimates). In the past, diagnosis of CD has taken an average of 10 years. Serologic screening (eg, tissue transglutaminase immunoglobulin A antibodies) should be considered for children with symptoms of diarrhea, abdominal cramping, pain, and distention as well as short stature and delayed puberty; individuals with Down syndrome or type 1 diabetes mellitus; and first-degree relatives of patients with biopsy-proven CD. Positive serologic tests should be followed up by small-bowel biopsy. Increased awareness of CD allows earlier diagnosis and institution of a gluten-free diet.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900Y

ATOPIC DERMATITIS

Long-term Treatment of Atopic Dermatitis With Pimecrolimus Cream 1% in Infants Does Not Interfere With the Development of Protective Antibodies After Vaccination


PURPOSE OF THE STUDY. To examine if pimecrolimus 1% cream in the treatment of atopic dermatitis would have any effect on vaccinations.

STUDY POPULATION. A total of 91 children with mild-to-severe atopic dermatitis (AD), aged 3 to 23 months at enrollment.

METHODS. Children were enrolled in a 1-year double-blind study (76 children received pimecrolimus, and 15 children received placebo). All 91 children were enrolled in a 1-year open-label extension study of pimecrolimus 1% cream. Patients were treated with either pimecrolimus
1% cream or placebo for initial symptoms, and more potent topical corticosteroids were used for flares not prevented by pimecrolimus 1% cream. Patients were vaccinated at normal scheduled times (4 doses of tetanus and diphtheria and 1 or 2 doses of measles and rubella). Response was evaluated at months 18 and 24 of the 2-year period.

RESULTS. The seropositivity rates of 93.6% for tetanus, 88.6% for diphtheria, 88.5% for measles, and 84.4% for rubella were comparable with those reported in the literature. Seropositivity was not significantly affected by the use of pimecrolimus at the time of vaccinations (±28 days). These seropositivity rates were within the ranges of 87% to 100% for tetanus, 83.3% to 99.3 for diphtheria, 60.5% to 97.1% for measles, and 55.6% to 88.1% for rubella, similar to those reported in age-matched pediatric populations.

CONCLUSION. Topical pimecrolimus in the treatment of atopic dermatitis had no effect on the response to routine childhood vaccination.

REVIEWER COMMENTS. Topical pimecrolimus, similar to topical tacrolimus (J Am Acad Dermatol. 2005;53[2 suppl 2]:S206–S213), had no effect on routine childhood vaccination. These topical calcineurin inhibitors did not affect basic B-cell function as measured by postvaccination titers.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900Z

Jonathan M. Spergel, MD, PhD
Philadelphia, PA

Efficacy and Safety of Tacrolimus Ointment Treatment for up to 4 Years in Patients With Atopic Dermatitis

PURPOSE OF THE STUDY. To determine the efficacy and tolerability of topical pimecrolimus and tacrolimus compared with other treatments for atopic dermatitis.

METHODS. Randomized, controlled trials of topical pimecrolimus or tacrolimus reporting efficacy outcomes or tolerability from the Cochrane Library, Medline, and Embase were identified. Eligible trials were evaluated for efficacy, identified as investigators’ global assessment of response; patients’ global assessment of response; proportions of patients with flares of atopic dermatitis; and improvements in quality of life. Trials were also evaluated for tolerability, identified as overall rates of withdrawal, withdrawal resulting from adverse events, and proportions of patients with burning of the skin and skin infections.

RESULTS. A total of 4186 of 6897 participants in 25 randomized, controlled trials received pimecrolimus or tacrolimus. Both drugs were significantly more effective than a vehicle control. Tacrolimus 0.1% was as effective as potent topical steroids at 3 weeks and more effective than combined treatment with hydrocortisone butyrate 0.1% plus hydrocortisone acetate 1% at 12 weeks (num-
ber needed to treat [NNT]: 6). Tacrolimus 0.1% was also more effective than hydrocortisone acetate 1% (NNT: 4). In comparison, tacrolimus 0.03% was more effective than hydrocortisone acetate 1% (NNT: 5) but less effective than hydrocortisone butyrate 0.1% (NNT: 8). Direct comparisons of tacrolimus 0.03% and tacrolimus 0.1% consistently favored the higher strength formulation. Pimecrolimus was far less effective than betamethasone valerate 0.1% (NNT: 3 at 3 weeks).

CONCLUSIONS. Both topical pimecrolimus and topical tacrolimus are more effective than placebo treatments for atopic dermatitis, but in the absence of studies that show long-term safety gains, any advantage over topical corticosteroids is unclear. Topical tacrolimus is similar to potent topical corticosteroids and may have a place for long-term use in patients with resistant atopic dermatitis on sites at which adverse effects from topical corticosteroids might develop quickly. In the absence of key comparisons with mild corticosteroids, the clinical need for topical pimecrolimus is unclear. The usefulness of either treatment in patients whose conditions have failed to respond adequately to topical corticosteroids is also unclear.

REVIEWER COMMENTS. With the recent worry of “black-box” warnings on these medications, it is useful to see a meta-analysis of controlled trials on pimecrolimus and tacrolimus as an alternative to steroids in the treatment of atopic dermatitis. The results of this study suggest that the usefulness of either treatment in patients whose conditions have failed to respond to topical corticosteroids is unclear but that they may provide an alternative to steroids in certain clinical scenarios. One should keep in mind the risk/benefit ratio of all immunosuppressive medications in the treatment of atopic dermatitis.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-090088
Wanda Phipatanakul, MD, MS
Boston, MA

Effects of Probiotics on Atopic Dermatitis: A Randomised Controlled Trial

PURPOSE OF THE STUDY. To examine the effects of probiotics on moderate-to-severe atopic dermatitis (AD) in young children.

STUDY POPULATION. Fifty-six children (aged 6–18 months) with moderate-to-severe AD (a modified scoring AD [SCORAD] index of ≥25). Patients were excluded if they had previous exposure to probiotics, were currently taking antibiotics, or had other major medical problems.

METHODS. Study participants were randomly assigned to receive probiotics (1 × 10⁸ colony forming units Lactobacillus fermentum) or placebo twice daily for 8 weeks. Patients were stratified and block-randomized by SCORAD index, topical corticosteroid potency, and age. Participants were evaluated at baseline and weeks 2, 4, and 8 of the intervention period, with a final postintervention evaluation at week 16. The primary outcome measure was change in AD extent and severity as assessed by the modified SCORAD index. Secondary outcome measures included (1) change in family quality of life, (2) change in topical corticosteroid use, and (3) parental impression of the intervention.

RESULTS. The SCORAD index of the children in the intervention group was significantly reduced over time compared with those in the placebo group, and the effect continued 2 months after the intervention was completed. Statistically significant improvement over baseline was seen in 92% of the intervention participants compared with 63% of children in the placebo group. Secondary outcome measures were not significantly different between groups. There were significantly fewer reported lower respiratory tract infections in the intervention group and no clinically significant adverse events recorded in either group.

CONCLUSIONS. Probiotics are beneficial in decreasing severity and extent of moderate-to-severe AD among children <2 years old.

REVIEWER COMMENTS. This is the first study to examination the effects of probiotics among young children with moderate-to-severe AD (mean SCORAD index: 41); previous studies examined children with milder disease (mean SCORAD index: 16). Similar to previous reports, the current study found significant improvements in objective signs of disease in terms of severity and extent. However, there were no significant differences in parental subjective observations or topical steroid use. The chronic nature of AD makes it difficult to assess subtle changes in quality of life or parental perceptions of disease in such a short period of time. It is possible that improvements in subjective findings and medication use would have been more evident if the study period was longer. There was a considerable placebo effect, and although statistically insignificant, more than half of the participants receiving placebo showed improvement at the end of the study period. This effect was likely, in part, because of improved adherence with medications as a result of being in the study. Future long-term studies should be conducted in this population to further assess long-term efficacy, changes in quality of life, medication use, and effects on development of other atopic diseases such as allergic rhinitis and asthma.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900CC
Tamara T. Perry, MD
Little Rock, AR
ANAPHYLAXIS

Allergic Reactions in the Community: A Questionnaire Survey of Members of the Anaphylaxis Campaign

PURPOSE OF THE STUDY. To investigate the circumstances and clinical characteristics of food allergies in adults and children in the community.

STUDY POPULATION. Six thousand of the United Kingdom Anaphylaxis Campaign members, both children and adults. The Anaphylaxis Campaign is the major British patient resource group for people who have suffered severe allergic reactions.

METHODS. The Anaphylaxis Campaign members were asked via a newsletter to report any food reactions during the 6-month period.

RESULTS. One hundred nine respondents reported 126 reactions during the study period; 75 were children (<16 years old; median: 6 years old at the time of reaction). More boys than girls were reported to have had reactions, but more women reported reactions than men (P < .05). Specific foods were identified in 112 (89%) of the reports; peanut and tree nuts were responsible for most reactions in both children and adults. Children with asthma reported more severe reactions than those without asthma (P = .008), although frequency or severity of recent asthma symptoms was not associated with severity of allergic reaction reported. One fifth of the children reported a reaction in school or day care. Self-injectable epinephrine was used in 35% of the severe reactions and 13% of the nonsevere reactions (P = .01). One quarter of the adults (3 of 12) who received a dose of epinephrine also received a second dose, whereas only 10% of the children (one of 10) required a second dose of epinephrine.

CONCLUSIONS. The allergens implicated in this report reflect previous data from similar patient groups in North America. Asthmatic children suffer more severe reactions than nonasthmatic children. Even when it is prescribed and available, self-injectable adrenaline seems underused in severe reactions. The incidence of severe but nonfatal allergic reactions in the United Kingdom may have been underestimated in the past.

REVIEWER COMMENTS. Limited data are available regarding details of treatment of food allergic reactions in the community, but published experience consistently demonstrates underuse of epinephrine for treatment of food anaphylaxis. This underscores the need to continually educate food-allergic patients on the indications for epinephrine administration. In addition, although the availability of the second dose of self-injectable epinephrine should be recommended to all food-allergic patients, children seem to be at lower risk for having severe reactions requiring treatment with multiple doses of epinephrine.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900DD

Anna Nowak-Wegrzyn, MD
New York, NY

Parental Use of EpiPen for Children With Food Allergies

PURPOSE OF THE STUDY. Food allergy affects up to 6% of children, and adverse reactions can be fatal. Appropriate emergency treatment consists of early administration of injectable epinephrine. Previous studies have revealed deficiencies in parental knowledge surrounding indications for self-injection, deficiencies in the method of EpiPen administration, and underuse in children experiencing anaphylaxis. This study explores whether underuse of EpiPen may be attributed to parental discomfort with administration, as measured by a lack of parental empowerment and knowledge of proper administration.

STUDY POPULATION. Parents of children with physician-diagnosed food allergy who had been prescribed an EpiPen.

METHODS. A self-administered survey was mailed to parents of children with food allergy, recruited through a food-allergy support group and a pediatric allergist’s practice. The questionnaire collected demographic information, medical history, history of previous “life-threatening allergic reaction(s),” past experience with EpiPen use, and knowledge of EpiPen indications. Knowledge was assessed with a series of multiple-choice and true/false queries. Perceived parental comfort with EpiPen administration was measured with a 10-cm analog scale, anchored with “uncomfortable” versus “very comfortable” at either end. Empowerment was measured with a 16-item instrument, including statements directly from or modified from the previously validated Family Empowerment Scale.

RESULTS. Of 360 mailed surveys, 165 eligible surveys were included in the study (46%). The majority of respondents were married white mothers with college or advanced degrees. The children of respondents ranged in age from 1 to 19 years. Previous anaphylaxis was reported in 70 responses (42%). Fourteen parents (8%) had administered the EpiPen to their child. Factors correlating with parental comfort with EpiPen administration included previous administration of EpiPen, EpiPen training, and high empowerment scores. Neither a history of previous anaphylaxis nor parental knowledge correlated with an increased level of reported comfort with EpiPen administration.
CONCLUSIONS. Increased empowerment scores directly correlated with increased parental comfort with EpiPen use. Although increased knowledge scores did not prove to be a significant contributor to parental comfort, training on EpiPen use is an important component in improving parental comfort. The authors question the impact of other psychological factors, such as fear, that may contribute to underuse of the EpiPen.

REVIEWER COMMENTS. Previous studies of parental EpiPen administration have reported incorrect use of autoinjectors despite training at the time of prescription. This study suggests that factors beyond parental knowledge are critical for proper administration of this potentially life-saving medication. The importance of hands-on training to increase caregiver comfort is underscored by this study. Demonstration units and training videos are available free of charge through the manufacturers for EpiPen and the Twinject, another epinephrine self-injection unit not discussed in this study.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900EE

Karla L. Davis, MD
Cecilia P. Mikita, MD
Washington, DC

Recognition, Evaluation, and Treatment of Anaphylaxis in the Child Care Setting

PURPOSE OF THE STUDY. Although many young children with a history of allergic reactions or anaphylaxis spend considerable time in child care centers, little is known about the centers’ knowledge of, experience with, and capacity to treat anaphylaxis. The purpose of this study was to evaluate the ability of child care centers to recognize, evaluate, and treat anaphylaxis episodes.

STUDY POPULATION. Children aged 1 to 6 who attended child care center in the suburbs of Chicago, Illinois.

METHODS. Eighty-five independent child care centers in suburbs of Chicago were selected randomly. They were contacted by telephone and asked to join the study by completing an initial questionnaire about allergic reactions and anaphylaxis. The center directors and teachers were then offered an allergy seminar on anaphylaxis avoidance, recognition, evaluation, and treatment. After the seminar, center directors were given a posttest that included some of the questions from the original questionnaire.

RESULTS. Of the 85 centers, 44 agreed to participate. Forty-two centers completed the surveys before the seminar and 39 after the seminar. On average, each center had up to 7 children with an identifiable food allergy. The most commonly reported source of education concerning allergies was information provided by the parents.

Before the seminar, 24% of child care centers would administer intramuscular epinephrine for a severe allergic reaction. After the seminar, 77% of centers stated they would administer intramuscular epinephrine (P < .001). In addition, center staff significantly improved their knowledge of symptoms of allergic reactions and the correct methods of intramuscular epinephrine administration.

CONCLUSIONS. There is a knowledge deficit in anaphylaxis education at child care centers for children 1 to 6 years old. Intervention with individual education seminars can significantly increase the ability of child care center staff to recognize, evaluate, and treat anaphylaxis.

REVIEWER COMMENTS. Although it is encouraging that the staffs at child care centers seem to be able to learn how to recognize and treat allergic reactions and anaphylaxis, it is at the same time discouraging that such a small percentage would have done so correctly before the seminar. Most child care centers receive their education from discussions with parents. However, studies have shown that only 50% of parents could identify all the critical steps for proper usage of epinephrine. Therefore, I agree with the authors that it is critical that health care professionals become more involved in the education of parents and the staffs of child care centers. In addition, detailed treatment plans should be written to help guide centers in the proper care of allergic reactions.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900FF

Helen Skolnick, MD
Princeton, NJ

Differences in Race, Ethnicity, and Socioeconomic Status in Schoolchildren Dispensed Injectable Epinephrine in 3 Massachusetts School Districts

PURPOSE OF THE STUDY. To analyze the demographic characteristics of schoolchildren dispensed injectable epinephrine in 3 school districts with widely diverse socioeconomic, racial, and ethnic populations.

STUDY POPULATION. Students (prekindergarten to grade 12) from 3 school districts in Massachusetts (n = 21 875) were evaluated. Two of the school districts were affluent, suburban towns outside of Boston (5855 students). The third district (16 020 students) was also a Boston suburb but with a very low per-capita income, with 23% of the school-age population living below the poverty line. The 2 suburban districts were 92% and 95% white, respectively, and the third district was 60% nonwhite.

METHODS. All school districts in Massachusetts are required to report the number of students using daily or as-needed prescription medications to the Department of
Public Health. Data were taken from reports filed by school nurses monthly for all students from the 2003–2004 school year for these 3 school districts.

RESULTS. A total of 181 schoolchildren (0.83%) in the 3 districts were dispensed injectable epinephrine during the school year studied. Diagnoses listed for the prescription of epinephrine included peanut/tree nut allergy (65%), stinging-insect allergy (19%), seafood allergy (6%), and egg or dairy allergy (3%). A miscellaneous group (7%) included diagnoses for latex, chocolate, pollen, fruit, cold air, and ibuprofen allergy. Males were more likely to be dispensed epinephrine than females (odds ratio [OR]: 1.44; \( P < .02 \)). White students were nearly 5 times more likely to have been dispensed epinephrine for peanut and tree nut allergy (OR: 4.5; \( P < .001 \)) and almost 9 times more likely for stinging-insect allergy (OR: 8.7; \( P < .001 \)). Seventy-five percent of students dispensed epinephrine for peanut or tree nut allergy were enrolled in prekindergarten through grade 5.

CONCLUSIONS. Significant racial and socioeconomic differences for prescribing self-injectable epinephrine was seen in 3 school districts in Massachusetts.

REVIEWER COMMENTS. This study describes the racial and socioeconomic demographics of children prescribed injectable epinephrine but does not address the reasons for the disparity between affluent and nonaffluent or white and nonwhite populations. This study suggests that minority, socioeconomically disadvantaged students are being either underdiagnosed or undertreated for potential anaphylactic reactions that require epinephrine. Other studies have not shown racial differences in the incidence of food allergies, suggesting that other factors are involved in the lower rate of epinephrine dispensed to disadvantaged minority students.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900GG

Alan B. Goldsobel, MD
San Jose, CA

DRUG ALLERGY

Immediate Allergic Reactions to Cephalosporins and Penicillins and Their Cross-Reactivity in Children

PURPOSE OF THE STUDY. To evaluate the frequency of anaphylactic reactions to cephalosporins and penicillins and their cross-reactivity in a pediatric population.

STUDY POPULATION. A prospective survey was conducted in a group of 1170 children with suspected immediate allergic reactions to cephalosporins and/or penicillins, which were examined during a period of 8 years.

METHODS. In vivo (skin tests and challenges) and in vitro tests (for specific immunoglobulin E) were performed with a standard concentration of penicillins and cephalosporins.

RESULTS. When 1170 children with a clinical history of allergy to penicillins and/or cephalosporins were tested in vivo for immediate hypersensitivity to \( \beta \)-lactams, 58.3% of cases overall were found to be skin- or challenge-test–positive. Among them, 94.4% of patients were positive to penicillins and 35.3% to cephalosporins. The frequency of positive reactions in the in vivo testing was in the range of 36.4% to 88.1% for penicillins and from 0.3% to 29.2% for cephalosporins. However, 31.5% of the penicillin-allergic children cross-reacted to some cephalosporin. If a child was allergic to a cephalosporin, the frequency of positive reactions to penicillin was 84.2%. The cross-reactivity between cephalosporins and penicillins varied between 0.3% and 23.9%. The cross-reactivity among different generations of cephalosporins varied between 0% and 68.8%, being the highest for first- and second-generation cephalosporins and 0% for third-generation cephalosporins.

CONCLUSIONS. The frequency of immediate allergic reactions to cephalosporins is considerably lower compared with penicillins, and the degree of cross-reactivity between cephalosporins and penicillins depends on the generation of cephalosporins, being higher with earlier-generation cephalosporins. The cross-reactivity among cephalosporins is lower compared with cross-reactivity between penicillins and cephalosporins.

REVIEWER COMMENTS. Penicillins and cephalosporins are common antibiotics inducing immunoglobulin E–mediated reactions in children. This large pediatric prospective study revealed that more than half of the children with a history of drug reaction to penicillin and/or cephalosporins were skin- or challenge-test–positive, unlike adults in whom the majority of those with a history of penicillin allergy are found to be skin test–negative. Almost one third of penicillin-allergic children are sensitized to cephalosporins. However, this sensitization was only to first- and second-generation cephalosporins; there was no cross-reactivity seen with third-generation cephalosporins. Interestingly, there was less cross-reactivity among the different cephalosporins. The results of this study can help guide antibiotic choices for penicillin-allergic children.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900HH

Julie Wang, MD
New York, NY

Hypersensitivity Reactions to Paracetamol in Children: A Study of 25 Cases

S20
PURPOSE OF THE STUDY. Reports of paracetamol (acetaminophen) allergic and nonallergic hypersensitivity reactions are rare. However, urticaria, angioedema, dyspnea, and allergic and nonallergic anaphylactic reactions have been reported in both children and adults in association with paracetamol administration. Most reactions to paracetamol occur in patients with a nonallergic hypersensitivity to nonsteroidal antiinflammatory drugs (NSAIDs). Alternatively, reactions may result from an allergic hypersensitivity to paracetamol, with tolerance of NSAIDs. This study reports an investigation of 25 children with suspected paracetamol hypersensitivity.

STUDY POPULATION. Twenty-five children, aged 8 months to 15 years, with a history of adverse reactions associated with paracetamol administration. In 12 of the 25 children studied, paracetamol adverse reactions were associated with concurrent administration of other medications or biological agents.

METHODS. Diagnosis of paracetamol hypersensitivity was based on either clinical history or the results of an oral challenge test. Reported reactions included urticaria, angioedema, conjunctivitis, dyspnea, and a maculopapular rash. Oral challenge tests with paracetamol were performed in the hospital setting. Paracetamol dosing was initiated at 1 mg and gradually increased until the appropriate cumulative dose for age and weight was achieved. An oral challenge with acetylsalicylic acid was performed in 1 child with a history highly suggestive of paracetamol hypersensitivity.

RESULTS. Paracetamol hypersensitivity was diagnosed in 1 patient (4%) on the basis of clinical history. The child reported accelerated reactions on 2 occasions, including facial angioedema, conjunctivitis, and dyspnea with wheezing, after isolated intake of paracetamol. Oral challenge to acetylsalicylic acid in this patient induced urticaria and angioedema. Oral challenges to paracetamol in the 24 other children studied were tolerated.

CONCLUSIONS. Results of this study of 25 children with suspected paracetamol hypersensitivity concur with those of previous reports: paracetamol hypersensitivity is rare and is associated with hypersensitivity reactions to anti-inflammatory medications.

REVIEWER COMMENTS. Adverse reactions temporally associated with paracetamol may result from reactions to other medications or the underlying conditions for which these medications have been prescribed. Diagnostic evaluation of suspected paracetamol hypersensitivity is complicated further by the lack of validated, available skin or in vitro testing. Adverse reactions to paracetamol can be both allergic and nonallergic in nature. The results of this study underscore the need for careful evaluation for both paracetamol and NSAID hypersensitivity in children with a history suggestive of adverse reactions to paracetamol.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900II

Karla L. Davis, MD
Cecilia P. Mikita, MD
Washington, DC

A Review of Evidence Supporting the American Academy of Pediatrics Recommendation for Prescribing Cephalosporin Antibiotics for Penicillin-Allergic Patients

PURPOSE OF THE STUDY. The American Academy of Pediatrics, in their evidence-based guidelines for treatment of otitis media and sinusitis, endorse the use of cephalosporin antibiotics for patients with reported allergies to penicillin. Many physicians, however, remain reluctant to prescribe such agents. This article reviews evidence in support of the American Academy of Pediatrics recommendations for administration of cephalosporins to penicillin-allergic children.

STUDY POPULATION AND METHODS. The author reviewed data from published studies related to penicillin and cephalosporin allergies in children and adults and in animal models.

RESULTS. Included in this review is an examination of the types and incidence of reactions to penicillins and cephalosporins, the frequency of cross-reactivity between these 2 groups of agents, and a thorough discussion of the clinical guidelines related to penicillin and cephalosporin allergy. Experimental and clinical studies that suggest that side chain–specific antibodies predominate in the immune response to cephalosporins, thereby explaining the lack of cross-sensitivity between most cephalosporins and penicillins. Specific recommendations for the treatment of patients on the basis of their responses to previously prescribed agents are summarized.

CONCLUSIONS. The author concludes that there is a low but measurable (0.5%) attributable risk associated with administration of a first-generation or selected second-generation cephalosporin to a patient with penicillin allergy. This increased risk is not present for third- or fourth-generation cephalosporins or for second-generation molecules with non–cross-reactive side chains.

REVIEWER COMMENTS. This is a very careful, comprehensive, and clinically useful review article. I recommend this article to physicians who would like to understand the evidence base and immunologic concepts underlying the use of cephalosporins in penicillin-allergic individuals.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900IU

James E. Gern, MD
Madison, WI
The Upper Airway

A Prospective, Randomized, Double-blind, Placebo-Controlled Multi-centre Study on the Efficacy and Safety of Sublingual Immunotherapy (SLIT) in Children With Seasonal Allergic Rhinoconjunctivitis to Grass Pollen


PURPOSE OF THE STUDY. Subcutaneous immunotherapy (SCIT) for seasonal allergic rhinitis is a well-established, effective, and potentially curative therapy. This study evaluated an alternate route for immunotherapy: the oral mucosa and gastrointestinal tract.

STUDY POPULATION. Ninety-seven children, aged 3 to 14 years, with seasonal allergic rhinitis and proven sensitivity to grass pollen were studied.

METHODS. Sensitivity to grass pollen was confirmed by positive skin-prick test, grass pollen-specific immunoglobulin E, and conjunctival provocation test. Patients were enrolled in a prospective, double-blind trial comparing sublingual immunotherapy (SLIT) to placebo. The treatment duration was 32 months. The primary outcome measure was the change in a multiple-symptom/medication score (which measured eye, nasal, and lung symptoms and rescue-medication use) after treatment. Data collected included patient-reported symptom scores and medication use, total and antigen-specific immunoglobulin E, skin-prick test, conjunctival provocation test, nasal provocation test, spirometry, exhaled nitric-oxide concentration, atopic dermatitis score, and eosinophilic cationic protein in nasal lavage fluid.

RESULTS. The multiple-symptom/medication score was significantly reduced by SLIT to 77.3% of the placebo group (P = .049). This overall score was affected mainly by a large reduction in rescue-medication usage among those in the treatment group (67% of placebo; P = .0025). There was no significant difference in any individual-symptom score.

CONCLUSION. SLIT had a positive effect on rescue-medication usage but no significant effect on symptoms alone.

REVIEWER COMMENTS. SLIT represents an alternative therapy with multiple potential advantages to SCIT, including the elimination of injections and improved safety profile. Several studies in adults and children have found improvement in symptom scores as well as reductions in medication use to the point where this is now being used in clinical practice in place of SCIT in many European countries. Additional studies, including investigation of optimal dosing and the potential to use multiple allergens, are needed to further define the future role of SLIT in the United States.

The Safety of Sublingual-Swallow Immunotherapy: An Analysis of Published Studies


PURPOSE OF THE STUDY. To perform a meta-analysis of all published controlled studies concerning sublingual-swallow immunotherapy (SLIT) to determine rates of adverse events (AEs).

STUDY POPULATION. Subjects were from 25 published studies (primarily European) aged 5 to 60 years (6 studies only enrolled children, 9 only adults, and the remainder a mix of both).

METHODS. A systematic Medline review from 1986 to May 2004 was performed. Twenty-five published double-blind, placebo-controlled studies using SLIT that included efficacy and safety data were analyzed. Twelve studies used a high allergen dose (defined as 50–500 times the standard subcutaneous dose), and 13 used a low allergen dose (defined as 1–50 times the subcutaneous dose). AEs were defined as local or systemic: local included oral itching and/or swelling and gastrointestinal complaints, and systemic reactions included skin reactions and ocular, nasal, and chest symptoms. The rates of AEs were compared between the groups. The allergens used in the studies included mites, grasses, trees, and ragweed (single-allergen treatments).

RESULTS. Combining the studies, there were a total of 445 subjects (405 placebo) in the high-allergen-dose group and 302 subjects (285 placebo) in the low-allergen-dose group. Children accounted for 103 total active-dose subjects. A total of 904 AEs were reported in the 198 553 active-allergen doses given, with 694 local reactions and 210 systemic reactions, with a rate of 0.15 to 0.2 reactions per patient. There were no reports of anaphylaxis. Overall, subjects in the low-allergen-dose group had significantly more local reactions than those in the high-dose group. However, there was no significant difference in the number of patients with AEs between the high- and low-allergen-dose groups when compared as a ratio of the number of SLIT doses received.

CONCLUSIONS. This analysis found that local reactions were common with SLIT but were mild and self-resolved. Systemic reactions occurred rarely and were not dose...
The Efficacy and Safety of Heat-Killed Lactobacillus paracasei for Treatment of Perennial Allergic Rhinitis Induced by House-Dust Mite


PURPOSE OF THE STUDY. Live Lactobacillus paracasei 33 (LP33) may effectively improve the quality of life for patients with perennial allergic rhinitis. It has been demonstrated that heat-killed lactic acid bacteria suppress specific immunoglobulin E synthesis and stimulate interleukin-12 production in animals. The aim of this study, therefore, was to evaluate the efficacy of heat-killed LP33 in the treatment of allergic rhinitis induced by house-dust mite in human subjects.

STUDY POPULATION. A total of 90 patients older than 5 years with perennial allergic rhinitis characterized by intermittent or continuous nasal symptoms for >1 year were enrolled in a randomized, double-blind, placebo-controlled trial and assigned to 3 treatment groups.

METHODS. Patients in groups A and B received 2 capsules per day of live or heat-killed lactic acid bacteria (5 × 10⁹ colony-forming units per capsule), respectively, over a period of 30 days, whereas those in group C received placebo capsules. A modified questionnaire on pediatric rhinoconjunctivitis-related quality of life was administered to all subjects or their parents during each clinical visit.

RESULTS. The overall quality-of-life score decreased for groups A and B compared with the placebo group in terms of both frequency (9.47 ± 2.89, 6.30 ± 2.19, and −3.47 ± 1.53, respectively; P < .0001) and level of bother (5.91 ± 3.21, 6.04 ± 2.44, and −2.80 ± 1.64, respectively; P = .004) after the 30-day treatment. The efficacy of the heat-killed LP33 was not inferior to the live variant. No obvious adverse effects were reported for either active-treatment group during the study period.

CONCLUSIONS. The results suggest that heat-killed LP33 can effectively improve the overall quality of life for patients with allergic rhinitis and that it may be efficacious as an alternative treatment.

REVIEWER COMMENTS. The hygiene hypothesis suggests that lack of early exposure to microorganisms is a factor in the recent rise in allergic disorders. Studies have shown the certain gut flora, including Lactobacillus, may have immunomodulatory effects that may be beneficial in regulating allergic responses. Concerns over safety of administering live bacteria as a therapeutic agent led Peng and Hsu to investigate the effectiveness of heat-killed lactobacillus in the treatment of allergic rhinitis. The authors demonstrate that the heat-killed version is effective in improving the quality of life of patients suffering from allergic rhinitis.

Surgical Management of Chronic Sinusitis in Children

Ramadan HH. Laryngoscope. 2004;114:2103–2109

PURPOSE OF THE STUDY. To compare the outcomes of children treated for refractory chronic sinusitis with adenoidectomy, endoscopic sinus surgery (ESS), or adenoidectomy with ESS.

STUDY POPULATION. Children, 2 to 13 years old, with sinusitis that persisted after 6 months of medical treatment (eg, antibiotics, nasal steroids, decongestants, reflex medications). These children had surgery (adenoidectomy, ESS, or both) over the 10-year study period.

METHODS. This was a nonrandomized study in which children were followed prospectively every 3 months after the surgical approaches. Each child was evaluated preoperatively for allergy, immunodeficiency, and cystic fibrosis and had a sinus computed tomography (CT) scan to assess disease severity. Parents filled out a questionnaire to assess improvement every 6 months for 1 year. Improvement based on questionnaire reports and need for more surgery were the principal outcome measures.

RESULTS. A total of 222 children had surgery for sinusitis during the study period (11% of children referred for evaluation of sinusitis), and 183 had adequate follow-up. The 3 surgical groups were similar with regard to gender, asthma, allergy, smoke exposure, and day care attendance. The children who had adenoidectomy alone were younger and had less severe sinus disease on CT scan than those in the other groups. Children who had adenoidectomy/ESS showed the greatest rate of improvement (87%) and lowest need for more surgery.
Seventy-five percent of children after ESS alone were improved, and 13% of the children in this group needed revision surgery. The adenoidectomy group had improvement in 52% of its subjects, and more surgery was needed for 25%. Younger children (aged \leq 6) had lower rates of improvement and needed revision surgery more than older children, with no difference in results between surgical groups. Children older than 6 years had the greatest improvement rate with adenoidectomy/ESS (96%). Children with asthma had lower rates of surgical success than those without (62% vs 80%); there was no difference in surgical success in children with and without allergies. For patients with asthma, adenoidectomy/ESS was superior. When CT scans showed mild disease, no differences were seen in the 3 surgical groups. With more severe disease on CT scan, adenoidectomy/ESS improved more patients (87%) than did ESS (72%) or adenoidectomy (46%) alone.

CONCLUSIONS. Surgery is recommended for children with chronic sinusitis refractory to medical therapy, and improvement is seen in most children. Adenoidectomy alone is recommended for children who are 6 years old or younger with mild sinus disease on CT scan. Adenoidectomy/ESS should be considered for older children, those with severe sinusitis, and those with asthma. 

REVIEWER COMMENTS. Children with chronic sinusitis usually do not need surgery. For those whose conditions fail medical treatment, the choice of initial surgery (adenoidectomy, ESS, or both) remains problematic. This comparison of postsurgical results has several limitations. The patients were not randomly assigned to the groups, which was most evident in the adenoidectomy group: the children in this group were younger and had less severe disease than those in the other 2 groups. It is not surprising that the children in the adenoidectomy group would have a higher rate of additional surgery, because the threshold to perform ESS in a child after adenoidectomy alone failed is certainly lower than that of performing additional surgery on one in whom ESS failed. The postoperative survey was not validated, and objective measures of improvement (school days missed, number of antibiotic courses, etc) were not included. A comparable group treated without surgery was not studied. Despite these shortcomings, this study provides clinical indicators to assign appropriate surgery for the child with refractory sinusitis.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900NN

Stacey Ishman, MD
David Tunkel, MD
Baltimore, MD
Asthma

PATHOPHYSIOLOGY

**Asthmatic Bronchial Epithelial Cells Have a Deficient Innate Immune Response to Infection With Rhinovirus**


**PURPOSE OF THE STUDY.** To determine if bronchial epithelial cells (BECs) from asthma patients have abnormal innate responses to rhinovirus infection.

**STUDY POPULATION.** BECs from 14 subjects with moderate persistent asthma treated with inhaled corticosteroids (ICSs), 10 subjects with mild intermittent asthma who were never treated with ICSs, and 10 healthy controls.

**METHODS.** BECs were cultured from bronchial brushings obtained by bronchoscopy. BECs were studied prerhinovirus infection, postinfection, and post–inactivated rhinovirus-16 exposure. Cytokines and chemokines were measured. Viable cell numbers, numbers of apoptotic cells, and cell lysate caspase activity were used to measure apoptotic activity. Apoptotic activity inhibition using the caspase-3 inhibitor, ZMD-fmk, was used to verify the presence of apoptosis. Rhinovirus-infection induction of interferon-β (IFN-β) was measured. Influence of IFN-β on apoptosis induction was evaluated by prerhinovirus and postrhinovirus infection treatment of BECs with exogenous IFN-β. The effect of IFN-β was also measured on virus titer preinfection and postinfection.

**RESULTS.** Rhinovirus-16 infection induced ICAM-1 (intercellular adhesion molecule-1), IL-6 (interleukin-6), and RANTES (regulated upon activation, normal T cells expressed and secreted) expression equally in BECs from asthmatic and healthy subjects. Viral RNA expression, lactate dehydrogenase activity, and virus titers all significantly increased in asthmatic versus healthy subjects’ BECs. The percentage of viable cells was 63% in asthmatic versus 80% in healthy subjects’ BECs, whereas apoptosis increased 1.4-fold in asthmatic and 2.2-fold in control subjects’ BECs (P = .02). Caspase activity increased significantly more in the control versus asthmatic subjects’ BECs postinfection. Induction of apoptosis in the healthy controls was inhibited by treatment of BECs with ZVD-fmk, and in a similar experiment, viral titers increased in the control BECs posttreatment and closely approximated the titers seen in infected asthmatic subjects’ BECs. Induction of IFN-β messenger RNA and IFN-β production were both significantly greater in the control versus the asthmatic subjects’ BECs. The effect of IFN-β on induction of apoptosis was evaluated: although apoptosis increased with posttreatment, there was significantly greater (P = .02) induction of apoptosis with pretreatment. Likewise, viral titers in the supernatant of infected asthmatic subjects’ BECs were inhibited by postinfection treatment with IFN-β but were most inhibited by pretreatment with IFN-β. Responses were similar between ICS-treated and ICS-naive asthmatic subjects.

**CONCLUSIONS.** Examination of early innate immune responses revealed profound impairment of virus-induced IFN-β messenger RNA expression and IFN-β production from BECs of subjects with asthma. A novel use for type I interferons in the treatment or prevention of virus-induced asthma exacerbations is proposed.

**REVIEWER COMMENTS.** How a rhinovirus infection induces an asthma exacerbation remains largely speculative. Differences between the innate immune response to rhinovirus infection of asthmatic and healthy subjects are demonstrated by using this novel approach. Very interesting is the lack of difference seen in ICS-naive and ICS-treated asthmatic subjects, which may explain why controversy remains regarding the role of ICSs in prevention of viral-induced asthma exacerbations. These data suggest that impairment in IFN-β production may be important in the induction of immune responses resulting in an asthma exacerbation. The authors’ proposal that type I interferon use may treat or prevent viral-induced asthma exacerbations is intriguing.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-090000

Mark H. Moss, MD
Madison, WI

IL-19 Induced Th2 Cytokines and Was Upregulated in Asthma Patients


**PURPOSE OF THE STUDY.** Interleukin-10 (IL-10) has been shown to inhibit allergen-induced airway hyperresponsiveness and inflammation. This study evaluates whether IL-19, a member of the IL-10 family, is associated with asthma.

**STUDY POPULATION.** The authors investigated IL-19 levels in 100 asthmatic patients, aged 3 to 12 years, as well as 50 healthy adults and 50 age-matched children. A dust mite–induced mouse model of asthma was also used to study the association of IL-19 with asthma.

**METHODS.** Cytokine levels were quantified by enzyme-linked immunosorbent assay. IL-19 levels were measured in all study subjects, but among asthmatic patients, the levels of IL-4 and IL-13 were analyzed in the 27 patients with the highest and 25 patients with the lowest IL-19 levels. By using a dust mite–sensitized murine...
asthma model, IL-19 levels were measured in asthmatic and control mice. To test whether IL-19 upregulates T-helper 2 (Th2) cytokines, IL-19 complementary DNA was injected into healthy mice using intramuscular electroporation, and serum levels of IL-4, IL-5, IL-10, and IL-13 were later monitored. After injection of IL-19 into asthmatic mice, IL-13 and immunoglobulin E (IgE) levels were measured. To determine if IL-19 could induce Th2 cytokine production in vitro, IL-19 was incubated with CD4+ T cells and IL-4, IL-5, IL-10, and IL-13 levels were quantified in the cell-culture supernatant.

RESULTS. Among asthmatic patients, the serum level of IL-19 was twice that of healthy controls, and those with a high level of IL-19 also had high levels of IL-4 and IL-13. In the murine asthma model, asthmatic mice also had IL-19 levels twice that of healthy control mice. Injection of the IL-19 gene into healthy mice induced production of IL-4, IL-5, and IL-10 but not IL-13. IL-19 upregulated IL-13 in asthmatic mice and also upregulated IgE production. In vitro, IL-19 was associated with increased IL-4, IL-5, IL-10, and IL-13 production by activated cells.

CONCLUSIONS. IL-19 upregulates production of Th2 cytokines in activated T cells and may be an important molecule in the pathogenesis of asthma.

REVIEWER COMMENTS. The Th2 cytokines upregulated by IL-19 play crucial roles in the pathogenesis of asthma. IL-13 regulates airway hypersensitivity and mucus hypersecretion; IL-4 is critical for IgE antibody switching; and IL-5 plays a key role in eosinophil maturation. The findings from this study suggest that IL-19 is another potentially important molecule in asthma pathogenesis and may be responsible, at least in part, for upregulation of Th2 cytokines that are critical to the development of allergic disease.

Inflammatory Basis of Exercise-Induced Bronchoconstriction

PURPOSE OF THE STUDY. To establish whether epithelial cell and mast cell activation with release of inflammatory mediators occurs during exercise-induced bronchoconstriction (EIB) and how histamine and cysteinyl leukotriene antagonists alter the airway events occurring during EIB.

STUDY POPULATION. There were 25 patients aged 14 to 55 whose asthma was being treated only with a short-acting β2 agonist as needed and who experienced a fall in FEV1 of ≥15% after an exercise challenge.

METHODS. Induced sputum was obtained at baseline and 30 minutes after exercise challenge. In a randomized, double-blind crossover study, the cysteinyl leukotriene antagonist montelukast and antihistamine loratadine, or 2 matched placebos, were administered for 2 doses before exercise challenge.

RESULTS. The percentage of columnar epithelial cells in induced sputum at baseline was associated with the severity of EIB. After exercise challenge, histamine, tryptase, and cysteinyl leukotrienes significantly increased in the airways, and there was an increase in columnar epithelial cells in the sputum. The concentration of columnar epithelial cells was associated with the levels of histamine and cysteinyl leukotrienes. Treatment with montelukast and loratadine inhibited the release of cysteinyl leukotrienes and histamine but did not inhibit the release of columnar epithelial cells.

CONCLUSION. Epithelial cells, mast cell mediators, and eicosanoids are released into the airways during EIB, supporting an inflammatory basis for EIB.

REVIEWER COMMENTS. “Exercise-induced asthma” (EIA) is not a disease unto itself. As the authors point out, “[EIB] is a highly prevalent condition present in approximately half of patients with asthma.” Most such patients, if questioned carefully, will admit to symptoms under circumstances other than exercise, such as with upper respiratory infections or irritant or allergen exposures. It is better to consider EIB a very common phenomenon among patients with asthma. There are 2 competing hypotheses of the mechanism of EIB: (1) loss of heat leads to vascular engorgement as the airways rewarm after exercise, initiating bronchoconstriction; and (2) loss of water leads to a change in airway osmolarity that initiates epithelial cell and mast cell activation, leading to the release of inflammatory mediators in the airways that cause bronchoconstriction. These 2 theories are not necessarily mutually exclusive, and the former theory may apply more to the minority of patients who complain of symptoms only after they finish exercising (ie, when they stop breathing through an open mouth). If the number of desquamated epithelial cells before exercise is taken as an indication of the level of ongoing airway inflammation, this study would suggest that patients with worse baseline inflammation would have worse EIB. Also of note is that the combination of the cysteinyl leukotriene antagonist and antihistamine did not inhibit the desquamation. For patients in whom a short-acting β2 agonist does not prevent EIB or who have any abnormality on baseline spirometry, a truly and broadly antiinflammatory medication (ie, inhaled...
Induction and Inhibition of the Th2 Phenotype Spread: Implications for Childhood Asthma


PURPOSE OF THE STUDY. T-helper 2 (Th2) phenotype spread refers to the concept that an established antigen-specific Th2 immune response may promote a Th2 response to a neoantigen. This study used a mouse model to investigate the requirements for induction and inhibition of phenotype spread to ragweed, a clinically relevant allergen.

METHODS. To induce and characterize phenotype spread, BALB/c mice were first immunized by a series of subcutaneous injections of egg ovalbumin and then challenged intranasally with ovalbumin, ragweed, or both simultaneously. Mice were finally challenged intranasally with ragweed alone to assess allergic response (Th2-mediated lung inflammation, ragweed-specific immunoglobulin E). To study the effect of time interval between the first and second antigens, the above-described experiment was repeated with ragweed being given either simultaneously with ovalbumin or 8, 24, or 48 hours after ovalbumin challenge. To investigate the role of activated Th2 cells in the induction of phenotype spread, severe combined immunodeficient (SCID) mice received ovalbumin-specific Th2 cells and naive CD4+ T cells intravenously and were initially challenged with ovalbumin and ragweed and then challenged later with ragweed and assessed for allergic response. To evaluate whether trafficking of naive CD4+ T cells to bronchial lymph nodes is required for the induction of phenotype spread, these cells were labeled and treated with an inhibitor of chemotaxis before the adoptive transfer experiments in the SCID mice. The effect on phenotype spread of immunostimulatory sequence-oligodeoxynucleotide (ISS-ODN), a Toll-like receptor 9 (TLR9) agonist, was first assessed in BALB/c mice by using the protocol described above, with injection of ISS-ODN before intranasal ovalbumin and ragweed challenge. ISS-ODN was also tested in the SCID adoptive-transfer model to study its effect on trafficking to regional lymph nodes.

RESULTS. The experiments yielded the following results: (1) Th2 phenotype spread to the neoallergen (ragweed) was induced only within the first 8 hours after bronchial challenge with the first antigen (ovalbumin); (2) the differentiation of naive CD4+ T cells to Th2 cells required trafficking of naive CD4+ T cells to bronchial lymph nodes and required interleukin-4 produced by ovalbumin-activated Th2 cells; and (3) a TLR9 agonist inhibited phenotype spread and experimental asthma by decreasing the production of chemokines involved in the trafficking of activated Th2 and naive CD4+ T cells to regional lymph nodes.

CONCLUSIONS. Th2 phenotype spread is the mechanism by which allergic sensitization to inhaled allergens is expanded in an already Th2-primed host. It occurs in regional lymph nodes and is mediated by interleukin-4 produced by activated Th2 cells.

Self-Organized Patchiness in Asthma as a Prelude to Catastrophic Shifts


PURPOSE OF THE STUDY. To reveal self-organized small airway constriction contributing to large ventilation defects in asthmatics.

STUDY POPULATION. Mild and moderate asthmatics.

METHODS. Ventilation defects in asthmatics were studied during methacholine bronchoprovocation by using serial dynamic positron emission tomography with a positron-emitter nitrogen-13 tracer and a single terminal-airway model.

RESULTS. Heterogeneity of ventilation defects in asthmatics was demonstrated. In this model, constriction of terminal bronchioles was the main feature of bronchoconstriction, contributing to nonuniform ventilation defects. Consequently, on the basis of the mechanical independence in expansion between airways and surrounding parenchyma, clusters of constricted terminal bronchioles fed by a common tree branch developed and led to large ventilation defects.
CONCLUSION. Clustered groups of self-organized terminal bronchiolar constriction, not large airways obstruction, contribute to large ventilation defects in acute asthma.

REVIEWER COMMENTS. The nature of functional changes of both small and large airways affecting ventilation during acute asthma attacks has been unclear. Previously, MRIs of asthmatic lungs during bronchoprovocation suggested large-airway obstruction as a major cause of large ventilation defects (eg, *J Allergy Clin Immunol*. 2003;111:1205–1211). In this study, Venegas et al demonstrated the role of clustered terminal bronchiolar constriction resulting in ventilation defects in acute asthma. On the basis of this model, inhaled bronchodilators could be ineffective because the inhaled form might reach only well-ventilated regions and could further impede lung expansion of problematic regions and exacerbate regional ventilation defects. The concept of catastrophic shifts might account for sudden, unexplained, and severe asthma attacks in some patients. Systemic bronchodilators may be needed in some asthmatics to bypass this problem. This line of investigation is further elucidated elsewhere (*J Appl Physiol*. 2005;99:2388–2397).

**The Bronchial Lavage of Pediatric Patients With Asthma Contains Infectious *Chlamydia***


**PURPOSE OF THE STUDY.** To examine the frequency of *Chlamydia pneumoniae* infections in pediatric patients with asthma.

**STUDY POPULATION.** Seventy pediatric patients undergoing flexible fiber-optic bronchoscopy as a part of their ongoing clinical care.

**METHODS.** Bronchoaveolar lavage (BAL) fluid and blood were examined for the presence of *C pneumoniae* by smear examination and culture. The BAL and blood samples were cultured on human or mouse macrophages to determine infectivity. Polymerase chain reaction (PCR) amplification of BAL samples was performed to confirm specificity of the culture technique. Blood was examined for total immunoglobulin E (IgE). Blood samples from 70 matched, nonrespiratory control patients were cultured for *Chlamydia*.

**RESULTS.** Forty-two patients undergoing bronchoscopy had asthma and 28 had various other respiratory diseases. Thirty-eight (54%) BAL samples were positive for *Chlamydia* by PCR and 22 (31%) samples were positive for *Chlamydia* by culture. Of the positive BAL samples, 28 (74%) of 38 PCR-positive and 14 (64%) of 22 culture-positive samples were from children with asthma. Culture-positive blood samples were found in 24 (34%) of 70 respiratory patients and 8 (11%) of 70 nonrespiratory controls. In the blood culture–positive respiratory group, 17 (71%) of 24 were from children with asthma. Elevated total serum IgE was associated with BAL culture–positive results, and this relationship was stronger than total IgE and asthma diagnosis.

**CONCLUSIONS.** Viable *C pneumoniae* organisms are frequently present in the lung lavage in a cohort of predominately asthmatic pediatric patients.

**REVIEWER COMMENTS.** Results from this study suggest that infectious *C pneumoniae* may be common in BAL fluid of children with asthma. Historically, *C pneumoniae* has been associated with exacerbation and increased incidence of respiratory conditions in adults, but studies to examine similar associations in children have not been performed. This is the first investigation to report viable and infectious *C pneumoniae* in the BAL fluid of children with asthma. These findings are intriguing and should encourage investigators to examine the clinical implications of *Chlamydia* infection among pediatric patients with asthma.

**Repeat Exercise Normalizes the Gas-Exchange Impairment Induced by a Previous Exercise Bout in Asthmatic Subjects***


**PURPOSE OF THE STUDY.** To determine the effects of a second exercise bout on the gas-exchange impairment caused by an initial exercise-induced bronchospasm (EIB) response in asthmatic subjects.

**STUDY POPULATION.** Twenty-one subjects with a known history of asthma participated after meeting at least 1 inclusion criteria: (1) 12% increase in forced expiratory volume in 1 second (FEV1) after β-agonist inhalation, (2) 10% decrease in FEV1 after exercise test to exhaustion, or (3) a provocative concentration ≤4.0 mg/mL of methacholine causing a 20% decrease in FEV1.

**METHODS.** The subjects performed 2 submaximal workloads for 3 minutes. After 3 minutes of rest, constant work-rate exercise was performed until exhaustion at 90% of maximal O2 uptake (EX1). Arterial blood and expired gases were collected at 3 (early recovery) and 35 (late recovery) minutes after EX1. Subjects then per-
formed a second bout of exercise to exhaustion at 100% of maximal O2 uptake (EX2). Pulmonary-function tests were repeated at 5-minute intervals after EX1 and EX2.

RESULTS. Subjects classified as EIB+ (>10% FEV1 decrease 5–10 minutes after EX1) and EIB− had similar baseline lung function. In the EIB+ group, the inspiratory pulmonary resistance (RLi) peaked at 4.2 ± 3.2 cm H2O/L per second above baseline (P < .05) 4 minutes after EX1 and dropped back to baseline during EX2. The RLi did not change significantly in the EIB− group. After EX1, the EIB+ group showed a sustained decrease in FEV1 (2.8 ± 0.66 L versus baseline, 3.97 ± 0.47 L; P < .05), whereas the EIB− group did not (3.60 ± 0.56 L versus baseline, 3.72 ± 0.53 L). In the EIB+ group, the alveolar-to-arterial Po2 difference (A-aDo2) remained greater than baseline during early recovery after EX1 and widened to 14.1 mm Hg above baseline (P < .001) during late recovery. In the EIB− group, the A-aDo2 returned to baseline during early recovery and increased to 18.1 ± 9.1 mm Hg above baseline during late recovery. In both groups, the RLi, FEV1, and A-aDo2 were similar during EX1 and EX2. In the EIB+ group, sputum histamine increased after exercise (61.2 ± 42.0 ng/mL versus baseline 34.6 ± 25.9 ng/mL; P < .05) and was correlated with the A-aDo2 (r = 0.68; P = .02) during EX1.

CONCLUSIONS. In asthmatic patients, late gas-exchange disturbance after exercise occurs independently of decreased FEV1 or increased pulmonary resistance. Gas exchange normalizes with a second bout of exercise, likely because of bronchodilation.

REVIEWER COMMENTS. A new finding from this study is the gas-exchange impairment seen after exercise in asthmatic patients without measurable disturbance in FEV1 or pulmonary resistance after exercise; this late-recovery impairment of gas exchange may be a result of peripheral airway abnormalities that take time to develop. As expected, sputum inflammatory mediators were increased in patients with EIB. One of the goals of asthma management is to avoid restrictions on activity and exercise, and the normalization of lung function and gas exchange seen in most subjects with a second bout of exercise offers some reassurance to asthmatic patients involved in repetitive, intense physical activity.

Elinor Simons, MD
Albany, NY

An Immunoepidemiological Approach to Asthma: Identification of in-Vitro T-Cell Response Patterns Associated With Different Wheezing Phenotypes in Children

PURPOSE OF THE STUDY. To determine if variations in clinical asthma phenotypes are the result of differences in underlying T-cell immune responses to inhalant allergens.

STUDY POPULATION. One hundred forty-seven children (aged 8.6–13.5 years) and 25 of their siblings (aged 7.4–17.4 years) were recruited from 194 members of a birth cohort studied prospectively for asthma development.

METHODS. Wheeze and asthma were defined by parental questionnaire. Atopy was defined as at least 1 positive skin-prick test for environmental or food allergens. Increased bronchial hyperreactivity (BHR) was defined as a ≥20% drop in forced expiratory volume in 1 second after inhaled histamine up to 7.8 μmol/L. T-cell responses to allergens and mitogens, blood eosinophils, and immunoglobulin E (IgE) were measured and compared with clinical phenotypes.

RESULTS. Ninety-five (55.2%) of the children were atopic, sensitized predominantly to house dust mite (42.4%). Asthma was present in 26 (15.1%) children, of whom 22 (85%) were atopic; BHR was present in 62 (35.9%) children, of whom 45 (73%) were atopic. Atopy was associated with T-helper 2 (Th2) cytokine responses (interleukin-4 [IL-4], IL-5, IL-9, IL-13), whereas Th1 responses (IL-10, interferon-γ [IFN-γ], tumor necrosis factor-α [TNF]) occurred in all children. Skin-prick test wheal size was positively associated with house dust mite allergen-induced IL-5 (P < .0001) and IFN-γ (P = .003) and negatively associated with IL-10. Asthma was associated with eosinophilia and elevated house dust mite–specific IL-5, IL-9, IL-13, and IgE. BHR was associated with eosinophilia, elevated allergen-specific IL-5 and IgE, increased total IgE, and a polyclonal cytokine response (IL-5, IL-13, IFN-γ, and TNF-α). In atopics, current asthma or wheeze was associated with house dust mite allergen-specific IL-5 and IL-13. BHR was associated with IL-5 and IgE. In nonatopics, BHR was associated with increased house dust mite allergen-specific and polyclonal IL-10 and polyclonal IFN-γ and TNF-α.

CONCLUSIONS. In atopic and nonatopic children, distinctive immune-response patterns were identified for asthma and BHR. Immunologic Th1 and Th2 hyperresponsiveness was identified as a hallmark of BHR.

REVIEWER COMMENTS. Modification of T-cell responses has become an increasingly important focus in the investigation of treatments for atopic disease. Although this study further highlights the prominence of Th2-driven responses in atopic individuals, the results also demonstrate allergen-specific and polyclonal Th1 responses associated with BHR in atopic and nonatopic children. These findings suggest a nonantagonistic interaction between Th1 and Th2 pathways in the production of asthma symptoms. Further understanding of the associ-
Wheeze Phenotypes and Lung Function in Preschool Children

PURPOSE OF THE STUDY. To determine the relationship between wheeze phenotypes in childhood and lung function at age 3 and 5 years and determine if lung function at 3 years of age predicts the development or persistence of wheeze.

STUDY POPULATION. A population-based cohort of 874 children from the Manchester Asthma and Allergy Study. Subjects were recruited prenatally and followed up at 3 and 5 years of age.

METHODS. Subjects were assigned to categories on the basis of parental report of wheezing: “no wheezing” was defined as no wheezing by age 5; “transient early wheezing” was defined as wheezing before age 3 but none in the year before the 5-year follow-up; “late-onset wheezing” was defined as no wheezing before age 3 but wheezing in the 12 months before the 5-year follow-up; and “persistent wheezing” was defined as wheezing before age 3 and in the year before the 5-year follow-up. Specific airway resistance (sRAW) was measured at age 3 and 5 by body plethysmography when subjects were symptom-free. Postbronchodilator lung function was measured as sRAW after albuterol inhalation.

RESULTS. The 530 (60.6%) subjects successfully performing sRAW at age 3 were distributed as: 248 never wheezed, 115 had transient early wheeze, 22 had late-onset wheezing, and 78 had persistent wheezing. The 730 children successfully performing sRAW at 5 years old were distributed as: 384 never wheezed, 162 had transient early wheeze, 40 had late-onset wheeze, 104 had persistent wheeze, and 40 were not classifiable. At 3 years of age, the only significant differences in sRAW between groups was an increased resistance in those with persistent wheeze compared with children with late-onset wheeze (P = .04) and those who never wheezed (P < .001). At 5 years of age, sRAW was elevated in children with persistent wheeze compared with those with transient early wheeze (P = .02) and those who never wheezed (P < .001). Also, sRAW was significantly higher in those with transient-early wheezing compared with those who never wheezed (P = .01), but there was no significant difference between those who never wheezed and those with late-onset wheezing (P = .43). Among the subgroup of children who had wheezed by age 3, the risk of persistent wheeze increased markedly with increasing sRAW values.

CONCLUSIONS. Children with persistent wheeze have reduced lung function at 3 and 5 years compared with other wheeze phenotypes. In children who wheezed during the first 3 years of life, reduced lung function at age 3 predicted persistent wheezing. However, reduced lung function at age 3 did not predict late-onset wheeze in those who had not wheezed previously.

REVIEWER COMMENTS. It would be useful to be able to predict whether wheeze early in life will be transient or persistent. This study augments the findings of the similarly sized, longitudinal, Tucson Children’s Respiratory Study by suggesting that: (1) poor lung function at age 3 is a predictor of persistent symptoms in those with a history of early wheezing, but for individuals the measurement has limited predictive value; (2) children with transient early wheeze have increased airflow resistance at age 5 compared with those who never wheezed; and (3) those with persistent wheeze and transient early wheeze both have airflow obstruction compared with the group who never wheezed. At age 5, the group with persistent wheeze also had lower postbronchodilator lung function than the group with no wheeze, indicating that factors other than smooth muscle contraction are present early in life. Additional studies are needed to determine the factors contributing to poor lung function early in life and to identify measures that would predict persistent wheezing in individuals.

Asthma Phenotypes, Risk Factors, and Measures of Severity in a National Sample of US Children

PURPOSE OF THE STUDY. To determine if there are differences in risk factors and measures of severity between children with different asthma phenotypes.

STUDY POPULATION. The authors reviewed data from children aged 6 to 16 years derived from the Third National Health and Nutrition Examination Survey.

METHODS. The authors used questionnaire and skin-prick-testing data to separate children into the following categories: atopic asthma, nonatopic asthma, resolved asthma,
frequent respiratory symptoms with no asthma diagnosis, and normal. Multivariate regression was used to determine if demographic or potential risk factors varied between phenotypes and whether measures of severity varied by phenotype.

RESULTS. A total of 4.8% of children had atopic asthma, 1.9% had nonatopic asthma, 3.4% had resolved asthma, and 4.3% had frequent respiratory symptoms. Mean BMI was higher among children with nonatopic asthma, whereas prenatal maternal smoking was a risk factor for resolved asthma. Atopic and nonatopic asthma were similar for most measures of asthma severity (eg, medication use and lung function), and relatively few children in either group were receiving inhaled corticosteroids (5%–10%). Patients with resolved asthma had fewer symptoms but lung-function impairment similar to that seen with current asthma, whereas children with frequent respiratory symptoms but no asthma diagnosis had normal lung function.

CONCLUSIONS. The authors conclude that asthma risk factors and measures of severity vary between children with different asthma phenotypes.

REVIEWER COMMENTS. Studies of children and adults have identified several unique phenotypes of asthma that share the feature of chronic and/or recurrent airflow obstruction. Accurate categorization is crucial in efforts to define genetic and environmental risk factors for asthma, and this work uses a very large national database to help establish environmental correlates to asthma subgroups in children. Notably, resolved asthma was linked to prenatal exposure to tobacco smoke and also to persistent impairment in lung function. Because environmental and lifestyle factors are almost certainly behind the rise in asthma prevalence, this line of research is clearly valuable from a public health perspective.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900XX

James E. Gern, MD
Madison, WI

DIAGNOSIS AND MANAGEMENT

Bacterial Contamination of Spacer Devices Used by Asthmatic Children

PURPOSE OF THE STUDY. To investigate bacterial contamination in spacer devices used by asthmatic children and the device-maintenance procedures practiced by parents.

STUDY POPULATION. The study group consisted of 62 consecutive children (aged 2–5 years) attending a clinic. All were enrolled in the study during an acute asthma attack.

METHODS. Spacer devices used by 62 asthmatic children were examined. Swabs taken from the inner surface of the reservoirs and face masks were cultured. Parents were interviewed regarding their spacer-cleaning and -disinfection routines.

RESULTS. Bacterial contamination was noted in 22 reservoirs (35.5%) and 16 masks (25.8%). Pseudomonas aeruginosa was isolated from 21.0% of the reservoirs and 14.5% of the face masks, Klebsiella pneumoniae from 6.5% and 4.8%, and Staphylococcus aureus from 9.7% and 8.1%, respectively. Only 34 parents (54.8%) reported that they received cleaning and maintenance instructions from the medical staff at initiation of spacer use by their child, and only 38 (61.8%) cleaned the device after each use.

CONCLUSIONS. Bacterial contamination is common in spacer devices. This study demonstrates that contamination rates are significantly lower when parents clean and actually dry (preferably with an air blower) spacer devices after each use. Spacer device maintenance should be emphasized in education programs for managing asthma.

REVIEWER COMMENTS. This study underscores the need for pediatricians and families to be educated about the proper care of spacer devices and the potential risks associated with improper cleaning. In particular, simple cleansing techniques can lessen or eliminate the number of nosocomial infections introduced by poor care of these devices. The benefit of metered-dose inhalers used with spacers and a face mask is high, and it is worthwhile to ensure that patients and health care workers use these devices properly and to their best advantage.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900YY

Troy Leo, MD
Harvey L. Leo, MD
Ann Arbor, MI

Clinical Use of Noninvasive Measurements of Airway Inflammation in Steroid Reduction in Children

PURPOSE OF THE STUDY. To examine the clinical utility of noninvasive measures of airway inflammation as predictors for successful inhaled corticosteroid (ICS) dose reduction in children with asthma.

STUDY POPULATION. Forty children (aged 6–17 years) with stable asthma on a constant ICS dose and eligible for steroid dose reduction.
METHODS. Children were followed prospectively every 8 weeks with noninvasive measures of airway inflammation including exhaled nitric oxide (eNO), sputum induction with bronchial hyperreactivity testing, and exhaled breath condensate. Physicians who were unaware of the results of inflammatory measures made reductions in the steroid dose on the basis of clinical assessment and spirometry. Multiple logistic-regression models were used to determine the usefulness of noninvasive inflammatory markers in predicting successful steroid reduction.

RESULTS. Seventy-five percent of patients tolerated a reduction in steroid dose for at least 2 months; however, 15 (38%) of the 40 patients’ conditions subsequently failed ICS dose reduction and experienced an asthma exacerbation. All children with absence of sputum eosinophils successfully tolerated dose reduction. Increased eNO ≥ 22 ppb (odds ratio: 6.3; 95% confidence interval: 3.75–10.58) and increased sputum eosinophils ≥ 3% (odds ratio: 1.38; 95% confidence interval: 1.06–1.81) were significant predictors of failed ICS dose reduction.

CONCLUSIONS. Noninvasive measures of airway inflammation may be useful tools in optimizing treatment of children with asthma.

REVIEWER COMMENTS. These findings suggest that noninvasive measures of airway inflammation are potential adjunctive tools that can be used in pediatric patients who appear clinically stable. However, their clinical usefulness may be limited by several factors. Sputum induction was not successfully performed in 25% of the children, and some measures including bronchial hyperreactivity and breath condensate did not prove to be useful predictors in this study. In addition, criteria for predicting failure were met in 6 (21%) of 28 and 19 (39%) of 49 occasions for sputum eosinophil and eNO cutoffs, respectively, when the child was successfully weaned on the basis of clinical judgment. Conversely, use of noninvasive markers would have prevented an attempt to wean steroids on > 70% of occasions when patients subsequently experienced an exacerbation. Inflammatory markers as sole predictors of success or failure will likely result in both significant undertreatment and overtreatment with ICSs. Treatment algorithms that include noninvasive airway inflammatory markers in conjunction with clinical markers are likely the best approach to optimize therapy in children who appear clinically stable.

The Influence of Pulmonary Function Testing on the Management of Asthma in Children

PURPOSE OF THE STUDY. Seventy-five percent of the asthma care in the United States is provided by primary care generalists. The National Asthma Education and Prevention Program guidelines recommend spirometry to assess management once the peak flow has stabilized. The purpose of this study was to assess how pulmonary function tests (PFTs) performed during a patient encounter influence management decisions beyond the history and physical examination alone.

STUDY POPULATION. A total of 367 asthmatic patients were enrolled during their visit to a pediatric pulmonary clinic. The patients were 4 to 18 years old (mean: 10.4 years), and 60% were male. Patients were excluded if PFTs could not be performed on them, if they had a pulmonary diagnosis other than asthma, or if they had used albuterol within 4 hours.

METHODS. History of asthma symptoms was obtained, and a physical examination was performed. Spirometry was performed before the provider assessment. Peak expiratory flow rate (PEF) was also obtained. The results of the PFTs were not known to the provider at the time of the assessment and initial decision-making. The provider then reviewed the spirometry results and revised the initial recommendations if necessary. Changes in management were analyzed with respect to demographic data and spirometry. The diagnostic accuracy of PEF to detect abnormal lung function was determined.

RESULTS. Eight percent of the patients had mild intermittent asthma, 21% mild persistent asthma, 57% moderate persistent asthma, and 14% severe persistent asthma. Spirometry results were normal in 55% of the visits. Abnormal spirometry occurred equally in boys and girls. Sixty percent of the abnormal results were new compared with previous baseline measurements. The likelihood of an abnormal PFT increased with increasing severity classification. Ten percent of those in the group with mild intermittent asthma had abnormal PFTs, compared with 74% of those with severe persistent asthma. PFT results changed management in 15% of the visits. When spirometry did not change the treatment, the providers were more likely to have already decided to maintain therapy (58%). When spirometry did change treatment, providers were more likely to increase medications (75%). PEF was moderately inaccurate in detecting abnormal spirometry.

CONCLUSIONS. In a clinical setting, even asthma care experts tended to overestimate the degree of asthma control as
measured by airway obstruction. Spirometry results in this study were just as likely to be abnormal in patients with a normal history and physical examination.

REVIEWER COMMENTS. The next logical question is: Does decision-making enhanced by spirometry result in better outcomes such as decreased symptoms, improved functioning and sleep, fewer exacerbations requiring steroid rescue, and less use of urgent asthma care services? When assessing asthma control, one should always consider comorbidities and adherence issues before stepping up therapy.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900AAA

Michael S. Kaplan, MD
Los Angeles, CA

Titrating Steroids on Exhaled Nitric Oxide in Children With Asthma: A Randomized, Controlled Trial

PURPOSE OF THE STUDY. To evaluate whether titrating inhaled corticosteroids (ICSs) on the fraction of nitric oxide in exhaled air (FeNO) improves asthma management in children.

STUDY POPULATION. A total of 85 children (aged 6–18 years) with asthma who had been using ICSs at a constant dose for at least 3 months.

METHODS. Children were randomly allocated to 1 of 2 groups stratified for baseline FeNO and dose of ICSs. In one group, ICS doses were determined by FeNO and symptoms according to an algorithm; in the other group, only symptoms influenced ICS dosing. The study duration was 12 months, with 5 visits at 3-month intervals. FeNO was measured at each visit, and the ICS dose was then adapted to FeNO and/or symptom scores that were recorded during the previous 2 weeks.

RESULTS. The cumulative ICS dose was not different between groups. Within the FeNO group, no significant change in FeNO was found, whereas in the symptom group there was a significant increase in FeNO (P = .035). In the FeNO group, hyperresponsiveness improved more than in the symptom group (2.5 vs 1.1 methacholine doubling dose; P = .04). Eight prednisone courses were prescribed for 7 patients in the FeNO group versus 18 courses in 10 patients in the symptom group, but this difference was not statistically significant (P = .60). There was no difference between groups in forced expiratory volume in 1 second (FEV1) or symptom scores.

CONCLUSION. In children with asthma, 1 year of steroid titration on FeNO did not result in higher steroid doses and did improve airway hyperresponsiveness and inflammation.

REVIEWER COMMENTS. I am still not sure what to make of eNO. If monitoring FeNO and making treatment decisions on the basis of the values leads to better asthma outcomes, then it would be a useful tool. Because the FeNO group did not end up receiving a higher cumulative ICS dose, we have to assume that they got more when they needed it and less when they did not. However, the clinical results seem inconsistent. I suppose it is a good thing to have a higher methacholine PD20 (the dose provoking a 20% fall in FEV1) and a lower FeNO, but I would have been happier to see a difference in FEV1 and symptom scores, or if the difference in the number of episodes requiring prednisone courses had been statistically significant. Although I am not sure that I can share the authors’ conclusion that “the time has come to introduce FeNO in to the routine assessment of children with asthma,” I believe we should pay attention to future studies on FeNO monitoring and clinical asthma outcomes.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900BBB

John M. Kelso, MD
San Diego, CA

Use of Exhaled Nitric Oxide Measurements to Guide Treatment in Chronic Asthma

PURPOSE OF THE STUDY. To determine if measurement of exhaled nitric oxide (FeNO) adds to guideline-driven asthma management for patients with chronic asthma.

STUDY POPULATION. A total of 110 patients (aged 12–75 years) with chronic asthma on inhaled corticosteroids (ICSs) for at least 6 months using stable doses for 6 weeks were initially evaluated. Exclusion criteria included ≥4 courses of oral prednisone in the previous 12 months, admission to the hospital because of asthma in the previous 6 months, ICU admission at any time in the past, or >10 pack-years (an average of 1 pack of cigarettes smoked per day for >10 years) of cigarette smoking.

METHODS. This was a single-blind, placebo-controlled study. In phase 1 the ICS dose was adjusted on the basis of FeNO or guidelines-based algorithms. When the optimal dose was determined, patients were managed for 12 months.

RESULTS. There were 46 patients in the FeNO group and 48 patients in the guideline group who completed the
study. The final ICS dose for fluticasone was 370 µg/day (95% confidence interval [CI]: 263–477 µg) in the FeNO group and 641 µg/day (95% CI: 526–756 µg; \(P = .003\)) in the guideline group. The rate of exacerbations per patient per year was 0.49 (95% CI: 0.31–1.49) in the FeNO group, compared with 0.9 (95% CI: 0.31–1.49; \(P = .27\)) in the guideline group. There was no difference in the number, frequency, or time of first exacerbation between groups. There was no significant difference in nighttime awakenings, bronchodilator use, percent symptom-free days, or number of oral corticosteroid courses. There also was no difference in percent sputum eosinophils or pulmonary-function tests.

CONCLUSIONS. With the use of FeNO, control of asthma can be obtained with a lower ICS dose.

REVIEWER COMMENTS. The values for FeNO differ from other studies because a flow rate of 250 mL/second was used instead of 50 mL/second. The control group had downward titration of dose on the basis of symptoms, which was achieved only in a minority of patients. This may have magnified the observed difference in the ICS dose. This and subsequent studies suggest that markers of airway inflammation are becoming accepted as important surrogate markers of asthma control.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900CCC

Bradley E. Chippo, MD
Sacramento, CA

The Prevalence of Ibuprofen-Sensitive Asthma in Children: A Randomized Controlled Bronchoprovocation Challenge Study

PURPOSE OF THE STUDY. To determine the prevalence of ibuprofen-sensitive asthma in school-aged children with mild or moderate persistent asthma.

STUDY POPULATION. Children (\(n = 100\)) between the ages of 6 and 18 years with a 2-year history of asthma.

METHODS. Ibuprofen (10 mg/kg) was administered via a randomized, double-blind, placebo-controlled crossover trial. At 0.5, 1, 2, and 4 hours postingestion, spirometry and physical examinations were performed. Children taking leukotriene receptor antagonists or with a known sensitivity to aspirin or ibuprofen sensitivity were excluded.

RESULTS. Two subjects (2%) had bronchospasm after administration of ibuprofen, with decreases in the forced expiratory volume in 1 second (FEV\(_1\)) of 35% and 25%, respectively. The maximal drop in FEV\(_1\) occurred 1 hour after ibuprofen administration in both subjects. Clinical manifestations of shortness of breath and wheezing on auscultation were noted in both patients. Resolution of symptoms and pulmonary-function values occurred after administration of albuterol. Neither patient had a decrease in FEV\(_1\) after placebo. Neither patient had a history of ibuprofen use before study enrollment. Two additional patients had a decrease in FEV\(_1\), of 15% (with no change after placebo) but remained asymptomatic with normal physical examinations.

CONCLUSIONS. In this study of children ages 6 to 18 years with mild or moderate persistent asthma, the prevalence of ibuprofen-induced bronchospasm was 2%. This is much lower than previous estimates (9%–28%) of aspirin-sensitive asthma in children.

REVIEWER COMMENTS. Use of inhaled corticosteroids by 70% of study subjects and exclusion of patients with severe asthma and those using leukotriene receptor antagonists may have resulted in an underestimate of the prevalence of ibuprofen-sensitive asthma. However, given the widespread use of ibuprofen as an over-the-counter analgesic and antipyretic, pediatricians should be aware of the possibility of ibuprofen-induced asthma exacerbations.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900DDD

John E. Duplantier, MD
Indianapolis, IN

Patterns of Quick-Relief and Long-term Controller Medication Use in Pediatric Asthma

PURPOSE OF THE STUDY. To simultaneously examine adherence to long-term controller and quick-relief medications and to contrast patterns of medication use in children with asthma.

STUDY POPULATION. There were 75 children aged 8 to 16 years diagnosed with persistent asthma and prescribed quick-relief and long-term medications by metered-dose inhaler. Participants were a subsample of a larger adherence study.

METHODS. This was a cross-sectional, 1-month follow-up study. The primary outcome measure was adherence to both medications as measured by electronic monitoring devices. A classification framework for contrasting adherence patterns between medication classes was developed to identify cases for individual analysis.

RESULTS. High levels of nonadherence to long-term controller medications (median: 46% of prescribed doses taken) and variable patterns of quick-relief medication use (range: 0–251 doses over the month) were documented, but consistent relationships between patterns of medication use across both classes were not found. Individual cases identified by the classification scheme il-
Asthma as a Risk Factor for Invasive Pneumococcal Disease


PURPOSE OF THE STUDY. To determine if asthma is a risk factor for invasive pneumococcal disease.

STUDY POPULATION. Patients 2 to 49 years of age in a Tennessee Medicaid program (TennCare) with >1 year of continuous enrollment during the study period (1995–2002). For each patient with invasive pneumococcal disease, 10 age-matched controls were chosen. A total of 11 counties in Tennessee with a population of 2.8 million participated in the study. Asthma was defined as ≥1 inpatient diagnoses (admission or emergency department visit), ≥2 outpatient diagnoses, or use of asthma-related medications. High-risk asthma was defined as an admission for asthma, an emergency department visit, long-term use of oral steroid, or use of ≥3 short-acting β agonists per year.

METHODS. Invasive pneumococcal disease was defined as isolation of strep pneumonia from a normally sterile site (eg, blood, cerebrospinal fluid, pleural fluid, surgical aspirate, joint fluid, and/or bone). The organisms were serotyped.

RESULTS. A total of 635 patients with invasive pneumococcal disease and 6350 controls were identified. A total of 18% (114 patients) with asthma had an invasive infection compared with 8.1% (516 patients) in the control group. Patients with asthma had increased risk of invasive disease (odds ratio: 2.4; 95% confidence interval: 1.9–3.1). In patients with high-risk asthma, the annual risk for invasive disease was 4.2 of 10 000 compared with 2.3 of 10 000 in the low-risk asthma group and 1.2 of 10 000 in the control group.

CONCLUSIONS. Asthma is an independent risk factor for invasive pneumococcal disease.

REVIEWER COMMENTS. The risk of invasive disease did not depend on comorbid conditions or advancing age. This is the first study to show the association and, if upheld with further data, will significantly affect our recommended immunization strategy for patients with asthma.

Exercise-Induced Dyspnea in Children and Adolescents: If Not Asthma Then What?


PURPOSE OF THE STUDY. Exercise-induced asthma (EIA) is the most commonly recognized cause of exercise-induced dyspnea (EID) in children and adolescents. However, EID in otherwise healthy children and adolescents may have other causes besides asthma. The purpose of this study is to report the outcome of evaluations for EID when other signs and symptoms of asthma were absent or there was no response to previous use of an inhaled β2 agonist.

STUDY POPULATION. One hundred forty-two patients, 6 to 21 years old (mean: 14 years), with EID were studied.

METHODS. In this retrospective study, investigators reviewed the results of all exercise tests performed in otherwise healthy patients with EID between 1996 and 2003. Physiologic measures assessed included preexer-
cise and postexercise spirometry with the addition of oxygen uptake, carbon dioxide production, continuous oximetry, and electrocardiogram monitoring during most tests. EIA was diagnosed if treadmill exercise resulted in reproduction of symptoms in association with a decrease in forced expiratory volume in 1 second of at least 15%. Endoscopy was performed if stridor and/or decreased maximal inspiratory flow were present. Criteria were established for restrictive abnormalities, physical conditioning, exercise-induced hyperventilation, and normal physiologic limitation.

RESULTS. EID was present in the subjects for an average of 30.2 months (range: <1 to 192 months) before evaluation, and in 98 patients the symptoms were attributed to asthma. Symptoms of EID were reproduced during exercise testing in 117 patients. EIA was identified as the cause of EID in only 11 of the 117. Seventy-four demonstrated only normal physiologic exercise limitation; 48 of the 74 had normal-to-high cardiovascular conditioning, and 26 had poor conditioning. Other diagnoses for reproducible EID included restrictive abnormalities in 15, vocal cord dysfunction in 13, laryngomalacia in 2, primary hyperventilation in 1, and supraventricular tachycardia in 1.

CONCLUSIONS. The diagnoses of EIA should be questioned as the etiology of EID in children and adolescents who do not have other symptoms of asthma and who do not respond to pretreatment with a β2 agonist.

REVIEWER COMMENTS. Although asthma is the most common cause of EID, this article demonstrates the important point that not all EID is caused by asthma. Patients who experience EID but not other signs or symptoms of asthma or who do not benefit from pretreatment with an inhaled β2 agonist clearly can benefit from a treadmill test with cardiac and respiratory physiologic monitoring. A large portion of these patients demonstrated normal physiologic limitation associated with reproduction of symptoms. Routine treatment of EID as asthma can lead to both unnecessary medication and frustration on the part of the patients and their families.

Helen Skolnick, MD
Princeton, NJ

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900GGG

Use of Asthma Guidelines by Primary Care Providers to Reduce Hospitalizations and Emergency Department Visits in Poor, Minority, Urban Children

PURPOSE OF THE STUDY. To determine if a standardized city-wide asthma management program delivered by pri-
mary care providers (PCPs) would increase adherence with the National Asthma Education and Prevention Program guidelines and whether this would improve medical service utilization.

STUDY POPULATION. Children between 6 months and 18 years of age (n = 8324) who presented for care at any of 6 primary care clinics in Hartford, Connecticut, between 1998 and 2002 and had enrolled in either Medicaid or the State Children’s Health Insurance Plan (SCHIP).

METHODS. Enrollment in the Easy Breathing asthma management program for PCPs included completing a survey regarding the child’s clinical history, provider assessment of asthma severity, and a written asthma treatment plan for the caregiver. Providers underwent training in the Easy Breathing curriculum. Data regarding demographics for enrolled patients were obtained from the survey and compared with all resident children in Hartford. Claims data were obtained. Utilization of medical services and prescriptions was examined. Children were continuously enrolled in the program during the 4-year analysis period. Relative rates of utilization (in event/child-months) were compared for the same children before and after enrollment.

RESULTS. Of the 1799 children with persistent asthma, only 38% were treated with antiinflammatory therapy before Easy Breathing; after enrollment, this improved to 96%, with 85% of those treated specifically with an inhaled corticosteroid. After enrollment in Easy Breathing, the rate of hospitalization for all children with asthma decreased 35% (P < .006), and the decrease was sustained over 3 years. There was a 27% overall decrease in emergency department (ED) visits for asthma (P < .01) and less seasonal variation in hospitalizations. Adjusted relative rates for total and asthma-specific ED and hospital visits decreased significantly for children with persistent asthma. Decreases in adjusted rates of outpatient visits after enrollment were also found for children overall (19%; P < .0001). This was true for children with intermittent asthma (22%; P < .001) and persistent asthma (18%; P < .001).

CONCLUSIONS. Adherence to National Asthma Education and Prevention Program guidelines by PCPs managing asthma for low-income minority children decreased their total number of hospitalizations and asthma-specific ED visits and outpatient visits. The authors believe that contributors to the success of the program include the standardized approach to therapy, including inhaled corticosteroids when indicated, as well as the development of a written, individualized asthma treatment plan. The benefits of the program continued through the 3 years.

REVIEWER COMMENTS. Despite a few limitations (nonrandomized, use of claims data), this study strongly reinforces the idea that improving asthma management relies not only on patient adherence but also physician review and faithful implementation of the current guidelines. PCPs managing asthma in low-income, urban, minority children would benefit the community by participating in such standardized programs that are focused on diagnosis and treatment. This not only decreases the morbidity related to asthma in these children but also alleviates the financial burden involved in excessive utilization of medical services.

A Multisite Randomized Trial of the Effects of Physician Education and Organizational Change in Chronic Asthma Care: Cost-effectiveness Analysis of the Pediatric Asthma Care Patient Outcomes Research Team II (PAC-PORT II)


PURPOSE OF THE STUDY. To estimate the cost-effectiveness of 2 different asthma care interventions: a peer leader–based physician behavior-change intervention (PLE) and a practice-based redesign called the planned asthma care intervention (PACI).

STUDY POPULATION. Participants were 638 children (aged 3–17 years) with mild-to-moderate asthma. More than half of the subjects were on maintenance medication.

METHODS. This was a 3-arm cluster-randomized trial conducted in 42 primary care practices. These practices were randomly assigned to PLE (n = 226), PACI (n = 213), or usual care (n = 199). The PLE strategy involved training a pediatrician at each of the practice sites as an asthma expert and champion. This leader provided support, education, and feedback to the other members of the practice with regard to asthma management. The PACI strategy included all the components of the PLE arm and also included scheduled asthma care visits with an asthma nurse, who provided standardized assessments, care planning, coordination with the primary care physician, and self-management tools. Practices in the usual-care arm received copies of the National Asthma Education and Prevention Program Expert Panel Report 2 and patient-information handouts 12 months into the study. The subjects were followed for 2 years. The primary outcome was symptom-free days (SFDs). Costs included asthma-related health care utilization and intervention.

RESULTS. Patients in the usual-care arm of the study had an increase in SFDs of 14.8 per year. Patients in the PLE and
Paci arms had an additional gain of 6.5 and 13.3 SFDs per year, respectively, compared with the usual-care arm. When the costs of development were excluded, the cost for SFDs gained compared with usual care was $18 for PLE and $68 for PACI.

CONCLUSIONS. It is possible to increase SFDs in children and to move organizations toward guideline recommendations for asthma management. However, the improvements were associated with an increase in the costs associated with asthma care.

REVIEWER COMMENTS. This trial was designed to provide cost analyses to both health care providers and health maintenance organizations. It is difficult, however, to establish a threshold for cost-effectiveness. The authors cite other trials to provide a context for this question. For example, the cost-effectiveness of inhaled corticosteroids in the treatment of children ranges from $7 to $12 per SFD gained. A social worker–based intervention had a cost-effectiveness ratio of $9 per SFD gained. What is it worth to patients, their families, and their health care providers to have an extra SFD?

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900JJJ

Brian A. Smart, MD
Glen Ellyn, IL

A Randomized Trial of Primary Care Provider Prompting to Enhance Preventive Asthma Therapy

PURPOSE OF THE STUDY. To determine if systematic school-based asthma screening, coupled with primary care provider notification of asthma severity, would prompt providers to prescribe a new preventive medication or change a current dose.

STUDY POPULATION. The study included 151 children (aged 3–7 years) with mild persistent to severe asthma living in an urban setting.

METHODS. A routine school health-and-development form was sent to parents of schoolchildren. When asthma was indicated on this form, the parents were contacted by telephone. To be eligible for the trial, the child’s parent needed to report that a physician had diagnosed their child as having asthma, and the child’s symptoms needed to be consistent with mild persistent asthma or worse according to National Heart, Lung, and Blood Institute guidelines. The intervention arm of the study involved notification of the primary care providers via fax of the child’s symptoms and recommendations for action on the basis of national criteria. Confirmation of receipt was received from 90% of providers. In the control arm of the study, primary care providers were not contacted. Interviewers then contacted the parents 3 to 6 months later to determine if preventive actions were taken.

RESULTS. Children in the provider-notification group were not more likely to receive a preventive medication action than children in the control group (21.9% vs 26%). Additional preventive measures such as encouraging compliance with medications, recommending environmental modifications, and referrals to specialty care also did not differ between the 2 groups. The only factors that significantly predicted the occurrence of a preventive action were acute visits for asthma and baseline use of preventive medications. At the end of the study, 52.4% of children in both groups with no medications change were still experiencing symptoms.

CONCLUSIONS. School-based asthma screening identified many symptomatic children in need of medication modification, but notification of their primary care providers did not improve preventive care.

REVIEWER COMMENTS. Asthma is a complex disease, and there are many barriers to effective care. These barriers include steroid phobia, cost of medication, denial of the presence or severity of the disease, access to health care, exposure to asthma triggers, and poor adherence to treatment. It is concerning that another barrier to effective care of asthma, as illustrated by this study, is a poor response of health care providers to supportive education, such as treatment guidelines. In an effort to better understand this deficit, the authors queried the providers: “Was the information in the original notification helpful?” Only 27 of 73 providers responded: 10 said the information was helpful (7 changed medications); 9 replied that their patients had mild, intermittent asthma and did not need changes; 4 replied that their patients already were on preventive medications; and 4 replied that they were unable to contact their patients for follow-up.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900KKK

Brian A. Smart, MD
Glen Ellyn, IL

Asthma-Related Health Care Resource Use Among Asthmatic Children With and Without Concomitant Allergic Rhinitis

PURPOSE OF THE STUDY. To determine the incremental effect of allergic rhinitis on health care resource use in children with asthma.
STUDY POPULATION. Children (aged 6–15 years) with asthma and >1 asthma-related encounter with a general practitioner (GP) during a 12-month follow-up period were included from the United Kingdom medical plus general-practice database, including 2 million office patient visits per year to >500 GPs.

METHODS. This was a population-based historical cohort investigation. Asthma and allergic rhinitis were determined by diagnosis codes and drug codes for appropriate medications.

RESULTS. Of 9522 children with asthma, 1879 (19.7%) had allergic rhinitis recorded in the GP medical charts. Compared with children with asthma alone, children with comorbid allergic rhinitis experienced more GP visits (4.4 vs 3.4) and more of them were hospitalized for asthma (1.4% vs 0.5%) during the 12-month follow-up period. In multivariable regression analyses, comorbid allergic rhinitis was an independent predictor of hospitalization for asthma (odds ratio: 2.34; 95% confidence interval [CI]: 1.41–3.91) and was associated with increases in the number of asthma-related GP visits (mean increase: 0.53; 95% CI: 0.52–0.54) and asthma drug costs (mean increase [British pounds]: £6.7; 95% CI: £6.5–£7.0). The association between allergic rhinitis and higher costs of prescriptions for asthma drugs was independent of asthma severity, measured indirectly by the intensity of use of asthma drugs.

CONCLUSIONS. Children with comorbid allergic rhinitis incurred greater prescription drug costs and experienced more physician visits and hospitalizations for asthma than did children with asthma alone. A unified treatment strategy for asthma and allergic rhinitis, as recommended by the Allergic Rhinitis and Its Impact on Asthma initiative, might reduce the costs of treating these conditions.

REVIEWER COMMENTS. This is a useful study emphasizing the importance of understanding the impact of allergic rhinitis on asthma, with implications for better therapeutic approaches. The study may have actually underestimated the impact of allergic rhinitis, because the data are retrospective and diagnosed allergic rhinitis was estimated at only 19.7%, compared with rates as high as 50% among children with asthma in other studies.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900LLL

Christopher Randolph, MD
Waterbury, CT

Racial and Ethnic Differences in Asthma Diagnosis Among Children Who Wheeze


PURPOSE OF THE STUDY. To determine if racial and ethnic differences in documented pediatric asthma prevalence relate to true prevalence differences or a different probability of receiving the diagnosis.

STUDY POPULATION. The study population was 3- to 17-year-old children of non-Hispanic white, non-Hispanic black, Puerto Rican, and Mexican ethnicity taken from a con-
Screening for Children’s Exposure to Environmental Tobacco Smoke in a Pediatric Primary Care Setting

PURPOSE OF THE STUDY. To develop a brief screening tool to accurately predict environmental tobacco smoke (ETS) exposure.

RESULTS. A total of 7 subjects (2%) had hair cotinine levels of <0.01 ng/mg, 99 subjects (34%) had levels of <0.3 mg/ng, 68 (23%) had midrange levels of 0.3–0.7 mg/mg, and 124 (43%) had levels of >0.7 mg/ng. Factors associated with higher cotinine levels included maternal smoking, the presence of other smokers in the home, and where persons other than the mothers smoke (ie, in the home or outside the home). Interestingly, the reported location of mothers’ smoking (indoors versus outdoors) was not associated with cotinine levels in the hair. The investigators used this information to create a model questionnaire to predict ETS exposure. Three questions were selected: does the mother smoke, do others in the home smoke, do others who smoke remain inside the home or go outside. Using this model, children of mothers who smoke and are also exposed to others who smoke inside the home have an 81% chance of having high exposure to ETS. In contrast, children of mothers who do not smoke and are not exposed to others who smoke have a 64% chance of low exposure to ETS.

CONCLUSIONS. It was possible to derive a simple and valid screening tool to identify children at risk for ETS exposure, but this tool still needs to be tested prospectively.

REVIEWER COMMENTS. We all struggle with our patients’ exposure to ETS in the home. Part of the struggle has to do with obtaining accurate information about exposures. The screening tool described in this study needs to be tested prospectively, but it may prove to be highly useful. Of interest is the finding that it did not matter, in terms of levels of cotinine in children’s hair, whether their mothers smoked indoors or reported that they limited themselves to outdoor smoking. We may speculate that this finding has to do with inaccurate reporting (shame about smoking indoors) or to the large amount of particulate residue that remains on smokers after they smoke.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900OOO

Christopher Randolph, MD
Waterbury, CT

Brain A. Smart, MD
Glen Ellyn, IL
Daily Versus As-Needed Corticosteroids for Mild Persistent Asthma


PURPOSE OF THE STUDY. To determine the effectiveness of as-needed versus regular controller therapy in adults with mild persistent asthma.

STUDY POPULATION. A total of 225 adults with symptom criteria for mild persistent asthma and forced expiratory volume in 1 second (FEV1) >70% predicted with >12% reversibility or PC20 (provocative concentration causing a 20% decrease in FEV1) methacholine at ≤16 mg/mL.

METHODS. Patients were assigned to 1 of 3 treatment groups: budesonide DPI 200 μg twice daily (BUD), oral zafirlukast 20 mg twice daily (ZAF), or placebo. The study was double-blind, double-dummy. At the beginning and the end of the study, all patients were treated with 0.5 mg/kg per day of prednisone, 800 μg twice a day of budesonide, and 20 mg twice a day of zafirlukast plus as-needed albuterol. Evaluation was accomplished by assessing asthma symptoms followed by pulmonary-function testing and gathering information on, albuterol use and exacerbations over the 1-year study.

RESULTS. For both of the primary efficacy outcomes, morning peak expiratory flow rate and exacerbations, there were no differences between the groups. Several outcomes were superior for the BUD group, including prebronchodilator FEV1, bronchial reactivity, symptom scores, exhaled nitric oxide, asthma control score, and symptom-free days (26 more). Postbronchodilator FEV1 and quality of life were not different between the groups. The as-needed group took budesonide, on average, for only one-half week during the study.

CONCLUSIONS. Adults with mild persistent asthma can be managed with high-dose budesonide on an intermittent basis. However, greater improvement in markers of airway inflammation and more symptom-free days (26 per year) occurred with regular use of low-dose budesonide.

REVIEWER COMMENTS. This is an adult study that focused on short-term outcomes, which may not translate to children. It is not known if similar results would be seen with a longer-term study.

Safety of Budesonide Inhalation Suspension in Infants Aged Six to Twelve Months With Mild to Moderate Persistent Asthma or Recurrent Wheeze


PURPOSE OF THE STUDY. To compare the safety of budesonide inhalation suspension (BIS) with placebo.

STUDY POPULATION. Infants (aged 6–12 months) with mild-to-moderate persistent asthma or recurrent wheeze.

METHODS. A multicenter, randomized, double-blinded, parallel-group, placebo-controlled study, in which 141 infants received 0.5 mg of BIS (n = 48), 1.0 mg of BIS (n = 44), or placebo (n = 49) once daily for 12 weeks. The primary variable was adrenal function, which was based on cosyntropin-stimulated plasma cortisol levels. Spontaneous adverse events and clinical laboratory findings were monitored.

RESULTS. Overall, the types and frequencies of adverse events reported during the study were comparable across treatment groups. The response to cosyntropin stimulation was similar across treatment groups, with no significant difference between BIS treatment and placebo.

CONCLUSIONS. The safety profile of BIS was similar to that of placebo, with no suppressive effect on adrenal function in patients 6 to 12 months of age with mild-to-moderate persistent asthma or recurrent wheeze.

REVIEWER COMMENTS. Inhaled corticosteroids remain the preferred choice for the long-term management of persistent asthma in pediatric patients. In addition, because BIS has become available for clinical use, more and more infants and young children with persistent asthma and/or recurrent episodes of wheezing have been managed with this inhaled antiinflammatory medication. In turn, appropriate questions have arisen from caregivers and providers about the overall safety of this therapy in these very young patients. Although the safety and efficacy of nebulized BIS have been confirmed in well-designed investigations in patients 6 months to 8 years of age, controlled clinical studies addressing the safety and efficacy of inhaled corticosteroids exclusively in the infant age range have been lacking. This current investigation provides very useful safety data for BIS in this understudied infant population. The data demonstrate that once-daily administration of BIS, 0.5 or 1.0 mg, was not associated with a decrease in adrenal function, which was based on cosyntropin-stimulated plasma cortisol levels. This information should be very useful to health care providers who prescribe this medication for...
Long-term Safety of Once-Daily Budesonide in Patients With Early-Onset Mild Persistent Asthma: Results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) Study


PURPOSE OF THE STUDY. Inhaled corticosteroids are the recommended treatment for all patients with persistent asthma. The aim of this study was to evaluate the safety and tolerability of long-term treatment of patients with mild persistent asthma with once-daily budesonide.

STUDY POPULATION. Seven thousand two hundred twenty-two patients (aged 5–66 years) with mild persistent asthma diagnosed within 2 years of study entry, with wheeze, cough, dyspnea, or chest tightness weekly and demonstration of reversible airway obstruction, were enrolled into the study.

METHODS. This was a prospective, double-blind, placebo-controlled study. Patients were divided into 2 groups according to age. Those patients younger than 11 years received 200 μg of budesonide via a dry-powder inhaler or placebo, and patients 11 years and older received 400 μg of budesonide via dry-powder inhaler or placebo. All treatments were administered for 3 years and in addition to the patients’ usual asthma therapy.

RESULTS. Overall, 21,520 adverse events were reported (10,850 in the budesonide group and 10,670 in the placebo group). The most commonly reported events were respiratory infections such as rhinitis, pharyngitis, bronchitis, viral infections, and sinusitis. Oral candidiasis was more common in the budesonide group (1.2%) than in the placebo group (0.5%); the frequencies of other adverse effects previously reported to be associated with inhaled corticosteroids (skin disorders, psychiatric disorders, and allergic reactions) were similar between the 2 groups. The number of deaths and serious adverse events were similar for children and adults in both treatment groups.

CONCLUSIONS. Three-year treatment with budesonide (200 or 400 μg) is safe and well tolerated in both children and adults who have recent onset of mild persistent asthma.

REVIEWER COMMENTS. This study shows not only that budesonide has very little risk of causing any significant adverse events. One of the most difficult, yet very important tasks as a physician is to educate the patient that inhaled corticosteroids are not the enemy, but rather that the patient’s health is at greater risk from asthma itself. Clearly, early intervention is safe and effective. This study provides valuable information and should help patients and their families to feel comfortable with long-term inhaled corticosteroids use in asthma.

Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma


PURPOSE OF THE STUDY. Previous studies have shown that the combination of inhaled corticosteroids (ICSs) with long-acting β2 agonists improves asthma control and reduces exacerbations. The authors hypothesized that in patients already receiving daily budesonide/formoterol (B/F), replacing conventional short-acting β2 agonist (SABA) rescue with the B/F combination drug would increase anti-inflammatory therapy while simultaneously giving rapid relief of symptoms. The investigators reasoned that using the B/F combination drug in this manner might reduce asthma exacerbations and improve asthma control compared with other possible regimens.

STUDY POPULATION. Subjects were 2760 patients with asthma (aged 4–80 years), all previously on ICSs.

METHODS. A double-blind parallel-group study was performed with subjects randomly assigned to 3 groups: B/F (80 mg/4.5 μg) twice daily for maintenance and also for rescue; B/F (80 mg/4.5 μg) twice daily with terbutaline 0.4 mg for rescue; or budesonide 320 μg twice daily with terbutaline 0.4 mg for rescue. Pediatric patients (11%–13% of each group) received half of the above-stated doses for maintenance. The primary outcome was time to first severe exacerbation, defined as asthma symptoms requiring an emergency department visit or hospitalization; an increase in ICS dose; use of oral steroids; or a morning peak expiratory flow rate ≤70% of baseline on 2 consecutive days.

RESULTS. Multiple positive outcomes were seen in the group using B/F for maintenance and rescue: a significant increase in the time to the first severe and mild exacerbations (P < .001); a 45% to 50% decrease in the number of severe exacerbations; significant decreases in the use of rescue medication, nighttime symptom score,
and the number of nighttime awakenings; and fewer courses of oral steroids per year. The average daily dose of ICS received per patient was lower in the 2 B/F groups. All of the medications were well tolerated. Pediatric subjects receiving B/F demonstrated greater linear growth than those on higher-dose budesonide.

CONCLUSIONS. Use of B/F for both maintenance and rescue is associated with a lower asthma-exacerbation rate and an improvement in several other indicators of asthma control. In addition, subjects using B/F in this manner have a decreased exposure to oral steroids and require less use of rescue medication. The authors suggest that the timing of the increase in ICS use for asthma exacerbations, rather than the total ICS dose administered, provides the greater improvement in efficacy.

REVIEWER COMMENTS. The rapid onset of action of the \( \beta_2 \)-agonist formoterol suggests that it could be used as a rescue medication, although this is not a licensed indication. Use of the B/F combination as controller and rescue presents an attractive option because of the decrease in asthma morbidity compared with either B/F and SABA or ICS and SABA. Even with the use of B/F for rescue, the mean dose of ICS received was lower than in the ICS-and-SABA group (240 vs 640 \( \mu \)g/day in the adults) and only slightly higher than in the B/F-and-SABA group (240 vs 160 \( \mu \)g/day in the adults). This combination product is not yet licensed in the United States, but if approved, B/F used in this fashion will offer a novel treatment alternative for asthmatic patients. In addition, B/F maintenance and rescue therapy may provide a significant benefit for patients for whom adherence to 2 separate drugs may present serious difficulties or confusion.

Characterization of Within-Subject Responses to Fluticasone and Montelukast in Childhood Asthma


PURPOSE OF THE STUDY. Asthmatic individuals vary in their responses to inhaled corticosteroids (ICSs) and leukotriene antagonists (LTRAs). The authors of this study sought to determine if responses are concordant for both types of drugs and sought markers for responses.

STUDY POPULATION. Children (aged 6–17 years) with mild-to-moderate asthma. They had asthma symptoms or bronchodilator use on average at least 3 days/week over the preceding 4 weeks and improvement in forced expiratory volume in 1 second (FEV\(_1\)) of \( \geq 12% \) after maximal bronchodilation or methacholine PC\(_{20}\) (provocative concentration causing a 20% decrease in FEV\(_1\)) of \( \leq 12.5 \) mg/mL. Children with severe asthma were excluded, as were those with recent use of corticosteroid or LTRA.

METHODS. After a 5- to 10-day characterization phase, participants were randomly assigned to 1 of 2 crossover treatment sequences with 8-week periods of either active ICS (fluticasone 100 \( \mu \)g twice daily) or an age-appropriate dose of montelukast. During the active-treatment period for one drug, the participant received a placebo for the alternative drug. Baseline-only characterization included various asthma biomarkers. The primary outcome measure was percentage change in pre-bronchodilator FEV\(_1\) from baseline to the end of the treatment period. “Response” was defined as improvement in FEV\(_1\) of at least 7.5%.

RESULTS. Fifty-five percent of the 126 participants showed no response to either drug, whereas 23% responded to fluticasone alone, 17% responded to both, and 5% responded to montelukast alone. Compared with those who responded to neither drug, those who responded to fluticasone alone had higher exhaled nitric oxide, serum immunoglobulin E, serum eosinophilic cationic protein, and total eosinophil count, along with lower methacholine PC\(_{20}\) and lower pulmonary function. Favorable response to montelukast alone was associated with younger age and shorter disease duration. Greater differential response to fluticasone over montelukast was associated with higher bronchodilator use and response, along with higher exhaled nitric oxide and serum eosinophilic cationic protein levels and lower methacholine PC\(_{20}\) and pulmonary function.

CONCLUSIONS. Responses to fluticasone and montelukast vary. Children with low pulmonary function or high levels of biomarkers should start with ICSs. In children with less severe disease, it would be reasonable to start with either ICSs or LTRAs. Asthma therapy might soon move from the current approach, which is based on mean responses in populations, to one predicated on a given person’s asthma phenotype and genotype.

REVIEWER COMMENTS. The vast majority of asthmatic patients in a primary care practice can maintain excellent control with one or the other of the above-mentioned drugs as simple monotherapy. History is paramount in assessing asthma severity, especially because the above-described biomarkers are largely unavailable to the pediatrician. It is tantalizing to consider a time when we will be able to more accurately target successful treatment in advance.
Comparative Efficacy and Safety of Low-Dose Fluticasone Propionate and Montelukast in Children With Persistent Asthma


PURPOSE OF THE STUDY. To evaluate efficacy, safety, health outcomes, and cost-effectiveness of fluticasone propionate (FP) versus montelukast in children with asthma

STUDY POPULATION. Children aged 6 to 12 years with persistent asthma.

METHODS. Multicenter, randomized, double-blind, double-dummy, parallel-group study of 342 children with persistent asthma. Children received either FP 50 μg twice daily via Diskus or montelukast 5 mg once daily for 12 weeks. The primary efficacy variable was percent change in morning predose forced expiratory volume in 1 second at the end point.

RESULTS. Compared with montelukast, children treated with FP experienced a significantly greater increase in mean percent forced expiratory volume in 1 second, mean morning peak expiratory flow rate, and mean evening peak expiratory flow rate. Children treated with FP also experienced significantly greater reductions in total supplemental albuterol use, mean nighttime albuterol use, and mean nighttime symptom scores compared with children treated with montelukast. There were no significant differences between the groups for daytime asthma symptom scores, daytime albuterol use, percent symptom-free days, or adverse events. Parent and physician satisfaction ratings were significantly higher for FP treatment. The daily total asthma-related cost per patient in the FP group was approximately one third of the cost in the montelukast group.

CONCLUSIONS. FP was significantly more effective than montelukast in improving pulmonary function, asthma symptoms, and rescue albuterol use. Both therapies had similar safety profiles.

REVIEWER COMMENTS. Comparative studies in adults and adolescents have previously shown greater efficacy with inhaled corticosteroids versus leukotriene receptor antagonists. This 12-week study reports similar findings for children 6 to 12 years of age with persistent asthma. Based on efficacy, cost, and safety profiles, low-dose inhaled corticosteroids should be considered first-line therapy in this age group.

Montelukast, Compared With Fluticasone, for Control of Asthma Among 6- to 14-Year-Old Patients With Mild Asthma: The Mosaic Study


PURPOSE OF THE STUDY. Per current asthma guidelines, montelukast is considered a suitable alternative to inhaled corticosteroids (ICSs) for the treatment of mild persistent asthma, and this study was conducted to evaluate the use of oral montelukast compared with inhaled fluticasone in children with mild asthma.

STUDY POPULATION. Children (aged 6–14 years) with mild persistent asthma participating in the Montelukast Study of Asthma in Children (MOSAIC) study.

METHODS. In this 12-month, multicenter, randomized, double-blind, noninferiority comparison study, patients were randomly assigned to receive oral montelukast 5 mg once a day (n = 495) or inhaled fluticasone 100 μg twice a day (n = 499) after an appropriate run-in period. After baseline evaluations, patients were evaluated at 4-month intervals with spirometry and review of an asthma diary card. The primary end point, the percentage of asthma rescue-free days (RFDs), included days with no rescue-medication use and no asthma-related primary care or urgent care visits or hospitalizations. Secondary end points included forced expiratory volume in 1 second (FEV1), use of additional asthma medications, asthma attacks, β-agonist use, and peripheral blood eosinophil levels.

RESULTS. The mean percentage of RFDs was 84% in the montelukast group compared with 86.7% in the fluticasone group. The least-squares means difference was −2.8% (95% confidence interval: −4.7% to −0.9%), which represents a difference of ≤1 day/month. Both montelukast and fluticasone were associated with improvement in FEV1 (percent predicted) from baseline as well as reduction in the percentage of days with β-agonist use, reduction in blood eosinophils, and improvement in patient-perceived asthma control and asthma quality-of-life scores; however, fluticasone was significantly favored in terms of FEV1, β-agonist use, asthma control, and quality of life.

Montelukast was associated with the increased use of systemic corticosteroids (17.8% vs 10.5%; P < .001) and a higher percentage of patients with an asthma attack (32.2% vs 25.6%) compared with fluticasone.
CONCLUSIONS. Montelukast was not inferior to fluticasone in terms of asthma RFDs; however, the use of montelukast was associated with more asthma attacks and more systemic steroid use. FEV$_1$, β-agonist use, and quality of life improved significantly better for those in the fluticasone group.

REVIEWER COMMENTS. This study represents the first direct comparison between montelukast and an ICS measuring differences in multiple parameters of asthma control in children with mild persistent asthma. This study establishes the noninferiority of montelukast compared with fluticasone in terms of RFDs; however, in terms of FEV$_1$, systemic corticosteroid use, number of asthma attacks and β-agonist use, fluticasone was significantly superior to montelukast. This study underscores the fact that asthma control cannot be determined with just one measure and confirms the role of montelukast as an alternative to ICSs as suggested by the current guidelines. The role of montelukast in future asthma guidelines is currently under investigation. Future studies are needed for evidence-based clinical application.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900WV

Jeremy D. Bufford, MD
Mark H. Moss, MD
Madison, WI

Montelukast Reduces Asthma Exacerbations in 2- to 5-Year-Old Children With Intermittent Asthma

PURPOSE OF THE STUDY. To evaluate the role of montelukast in prevention of viral-induced asthma exacerbations among 2- to 5-year-old children with a history of intermittent asthma.

STUDY POPULATION. A total of 549 children aged 2 to 5 years (from 68 sites in 23 countries) with a history of intermittent wheezing associated with upper respiratory infections.

METHODS. This was a multicenter, double-blind, parallel-group randomized trial comparing once-daily oral montelukast (4- or 5-mg chewable tablets) with placebo for 12 months. Subjects were required to have been free of symptoms and β-agonist use in a typical week over the 3 months before enrollment. An asthma exacerbation was defined as any 3 consecutive days with daytime symptoms and at least 2 β-agonist treatments per day; rescue use of oral/inhaled corticosteroids during ≥1 days; or a hospitalization because of asthma. The primary efficacy end point was number of exacerbation episodes over 1 year. Numerous secondary outcomes were also measured.

RESULTS. Patients in the montelukast group experienced a mean of 1.60 asthma-exacerbation episodes, compared with 2.34 in the placebo group, for a 31.9% rate reduction (P ≤ .001). Other end points with significant differences favoring the montelukast group included time to first exacerbation (median: 206 vs 147 days; P = .0024), rate of inhaled corticosteroid use (39.8% rate reduction; P = .027), and proportion of patients with asthma episodes (45% vs 56%; P = .008). There were no statistically significant differences in rates of oral corticosteroid use, average duration and severity of exacerbations, or proportion of patients who missed time from day care or school. Both groups experienced more exacerbations in the fall and fewer in the summer. Montelukast was well tolerated, and no patient discontinued therapy because of a drug-related adverse event.

CONCLUSIONS. The authors concluded that once-daily montelukast significantly reduces asthma exacerbations secondary to respiratory tract infections compared with placebo among 2- to 5-year-old children with intermittent asthma and also reduces time to first exacerbation and need for β-agonist or inhaled corticosteroid therapy. There was no difference in severity or duration of episodes, although the authors argue that the study was not specifically designed to detect differences in these end points.

REVIEWER COMMENTS. This study attempts to address the question of whether a controller medication may be useful in young children who wheeze with colds but are otherwise categorized as mild intermittent or even symptom-free. Asthma guidelines do not endorse use of preventive medications for such children, yet this study suggests that daily montelukast during the respiratory viral season may be useful to reduce exacerbations (although it did not reduce oral steroid use or severity of exacerbations). Montelukast during specified times might be a good option for many young children with intermittent asthma, but the cost/benefit ratio of chronic use is unclear, because the number of wheezing episodes per child was low even in the placebo group. Investigation of episodic use of montelukast with upper respiratory infections would be of interest.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900WWW

Todd D. Green, MD
Larry W. Williams, MD
Durham, NC

A Meta-analysis on Intravenous Magnesium Sulphate for Treating Acute Asthma

PURPOSE OF THE STUDY. To evaluate the effectiveness of intravenous magnesium sulfate in the treatment of acute asthmatic attacks in children.
STUDY POPULATION. Pediatric patients \( n = 182 \) with moderate-to-severe asthmatic attacks in the emergency department in 5 randomized, placebo-controlled trials comparing intravenous magnesium sulfate to placebo, with co-therapies of inhaled \( \beta_2 \) agonists and systemic steroids.

METHODS. Meta-analysis that evaluated outcomes of hospitalization, short-term pulmonary-function tests, and symptom scores.

RESULTS. Magnesium sulfate was effective in preventing hospitalization (odds ratio: 0.29; 95% confidence interval: 0.143–0.589). The number needed to treat was 4 (95% confidence interval: 3–8). Secondary outcomes of short-term pulmonary-function tests and clinical symptom scores also showed significant improvement. The therapy was well tolerated with only minor adverse effects reported.

CONCLUSION. Intravenous magnesium sulfate probably provides additional benefit in moderate-to-severe acute asthma in children treated with bronchodilators and steroids.

REVIEWER COMMENTS. Meta-analyses are useful when multiple previous studies have shown inconsistent results. They may not, however, be the final answer, because subsequent large trials can alter the conclusion of a meta-analysis. Nonetheless, the data to date considered in this meta-analysis seem quite convincing. Also, the treatment is inexpensive and well tolerated, and the number needed to treat is small (you would need to give this therapy to only 4 children to keep 1 out of the hospital).

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900XXX

John M. Kelso, MD
San Diego, CA
Immunodeficiency

PRIMARY IMMUNODEFICIENCY

Development of Population-Based Newborn Screening for Severe Combined Immunodeficiency

PURPOSE OF THE STUDY. To evaluate analysis of T-cell development as a potential population-screening method for severe combined immunodeficiency (SCID).

STUDY POPULATION. Twenty-three infants with SCID, 2 patients without SCID, 245 randomly selected infants, and several healthy adults.

METHODS. DNA was extracted from dried blood spots on standard newborn screening (Guthrie) cards. The DNA was subjected to polymerase chain reaction (PCR) to amplify and quantitate the number of T-cell receptor excision circles (TRECs), a marker of T-cell development in the thymus. For comparison, the β-actin gene was also amplified by PCR.

RESULTS. None of the SCID patients’ blood spots contained detectable TRECs, whereas the infants without SCID had normal TRECs. Healthy adults had normal TRECs, and intentional depletion of T cells led to the disappearance of TRECs in simulated blood spots. Approximately 3% of randomly collected blood spots did not contain measurable TRECs but did contain β-actin.

CONCLUSIONS. Measurement of TRECs by PCR can accurately identify infants with SCID. The relatively high percentage (3%) of screened spots having the SCID profile indicates the need for further refinement of the method before a larger population study.

REVIEWER COMMENTS. Newborn screening for SCID is desirable because of the rapidly fatal nature of this disease and because of the good outcomes that may be obtained with the earliest possible diagnosis. The minimum estimate of the incidence of SCID is >1 per 100,000 births, comparable to other diseases that are already part of newborn screening programs. Almost all patients with SCID lack detectable TRECs. The ability to accurately measure them in dried blood spots represents a tremendous advance toward the possibility of effective newborn screening for this genetically very heterogeneous group of disorders. If the specificity of the analysis can be improved, this may soon be implemented in newborn screening programs.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900

Francisco A. Bonilla, MD, PhD
Boston, MA

Presenting Phenotype in 100 Children With the 22q11 Deletion Syndrome

PURPOSE OF THE STUDY. To describe the clinical presentations of individuals having deletion of the 22q11 region.

STUDY POPULATION. The first 100 individuals <20 years old presenting to the Queen Sylvia Children’s Hospital (Gothenburg, Sweden) and found to have 22q11 deletion (from 1993–2002).

METHODS. All diagnoses were confirmed by fluorescence in situ hybridization. Clinical data collected at diagnosis included age and clinical findings in 8 categories (1, cardiac defects; 2, thymus size, infection history, auto-immune disease; 3, hypocalcemia; 4, feeding difficulties; 5, cleft lip/palate, speech/language impairment; 6, developmental delay, learning difficulties, behavioral abnormalities; 7, other malformations/deformities; 8, dysmorphic features). Those features that led (in particular) to the consideration of the diagnosis were distinguished.

RESULTS. The largest number was diagnosed by cardiologists (39) at a median age of 0.5 years old, with cleft palate or speech pathology specialists second (22) at a median age of 8 years, and neurologists or psychiatrists third (19) at a median age of 11.2. Note that 68 of the 74 children diagnosed after age 2 were born before the fluorescence in situ hybridization test was routinely available. The main findings are summarized in Table 1.

CONCLUSIONS. The authors offer diagnostic guidelines for testing for 22q11 deletion (for infants: any typical cardiac defect or 2 of the features in categories 2 through 5, 7, or 8; for preschool-aged children and adolescents: any 2 of the 8 categories either present currently or in the past medical history).

REVIEWER COMMENTS. 22q11 deletion leads to a spectrum of phenotypes most commonly called velocardiofacial syndrome and/or DiGeorge syndrome. Occurring in ~1 in 3000 to 4000 live births, it is among the most common syndromes associated with primary immunodeficiency. Serious infection occurs but is relatively rare. Early diagnosis is most desirable to prevent or mitigate morbidity arising from developmental and psychiatric complications in childhood and adolescence. Of the major clinical manifestations, the symptoms arising from velopharyngeal insufficiency (poor suck, nasal reflux) and various associated malformations seem to be significantly overlooked. The fact that all patients had subtle characteristic dysmorphisms that did not contribute very much to diagnosis shows how much our vision improves with the aid of molecular genetic glasses.
Mutations in TNFRSF13B Encoding TACI Are Associated With Common Variable Immunodeficiency in Humans

PURPOSE OF THE STUDIES. To search for mutations of TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor; also TNFRSF13B) in patients with common variable immunodeficiency (CVID) and immunoglobulin A deficiency (IGAD).

STUDY POPULATIONS. Salzer et al screened 162 unrelated individuals with CVID. Castigli et al studied 19 unrelated individuals with CVID and 16 with IGAD. Healthy individuals (100 and 50, respectively) served as controls.

METHODS. Genomic DNA from patients was subjected to reverse transcription and polymerase chain reaction sequencing analysis of the 5 exons of the gene encoding TACI. Binding of mutant TACI to ligands and stimulation of immunoglobulin production in vitro with TACI agonists in patients was also studied.

RESULTS. Salzer et al identified 13 individuals with CVID who had mutations in TACI. Castigli et al identified 4 individuals with CVID and 1 with IGAD and TACI mutations. None of the 150 controls studied had any of the identified TACI mutations. Interestingly, TACI mutations could cause disease in both the heterozygous and homozygous conditions. Patients’ cells had diminished binding to TACI ligands and showed diminished responses (immunoglobulin production) to TACI agonists in vitro. The clinical characteristics of the patients included hypogammaglobulinemia and impaired antibody responses, recurrent bacterial sinopulmonary infections, autoimmune disease (anemia, thyroiditis, positive antinuclear antibody), lymphoproliferative disease, and malignancy (B-cell lymphoma, gastric carcinoma).

CONCLUSIONS. Approximately 8% to 20% of patients with severe combined immunodeficiency or IGAD may have heterozygous or homozygous mutation in TACI. This genetic alteration should be sought in patients with these disorders.

REVIEWER COMMENTS. CVID and IGAD are among the most prevalent humoral immunodeficiencies at all ages. These studies represent important descriptions of defined mutations in patients with CVID and IGAD occurring in a significant fraction of these patients in 2 relatively genetically disparate populations. The ability to clearly define the underlying cause of disease in these patients will immediately lead to greater accuracy and confidence in diagnosis, earlier and more aggressive therapy, and, hopefully, improved outcomes.
nodeficiency (SCID-X1) in patients without an HLA-matched donor for bone marrow transplant.

STUDY POPULATION. All 4 children with SCID-X1 resulting from a γ-c chain mutation and without an HLA-identical sibling referred to Great Ormond Street Hospital (London, United Kingdom) between July 2001 and December 2002 were offered and consented to receive gene therapy.

METHODS. The complete coding region of human γ-c was cloned into a pMFG gammaretroviral vector and transfected into bone marrow CD34+ stem cells for reinfusion into the patients. T-cell function was assessed by responses to mitogens, Candida antigen, and mixed lymphocyte reactions. T-cell receptor (TCR) repertoires were assessed by direct immunofluorescence with fluorochrome-conjugated antibodies to TCRV-δ. Somatic hypermutation was expressed as the fraction of κ light-chain polymerase chain reaction product with mutations preventing cleavage by Fnu4HI.

RESULTS. At reinfusion, 27% to 58% of cells were CD34-positive and γ-c-positive. In all patients, natural killer cells appeared 2 to 4 weeks postinfusion and remained at low-normal levels. Naive CD45RO−, CD27+ T cells appeared at 10 to 30 weeks. Two patients developed normal numbers of CD3, CD4, and CD8 cells, allowing discontinuation of prophylactic medications. One of these patients developed a maculopapular rash on the palms and soles after CD4 T-cell recovery. Another patient had gastrointestinal bleeding resulting from rejection of engrafted maternal cells. The eldest patient, who received gene therapy at 33 months of age, had slower lymphocyte recovery. All patients developed normal T-cell–proliferative responses to mitogens, antigens, and mixed lymphocyte reactions. One year after treatment, all patients showed normal TCRV-β usage and polyclonality within individual V-β families. Two patients maintained normal immunoglobulin levels after discontinuing replacement, and normal serologic responses to vaccines were documented in 1 patient. Somatic mutation demonstrated by mutated V-k A27 transcripts increased from <2.0% to 5.3% to 23.3% by 1 to 2 years after gene therapy. No pathologic clonal expansions or insertions near the T-cell protooncogene LMO-2 were detected.

CONCLUSION. After somatic gene therapy, all 4 patients with SCID-X1 had significant improvement in clinical and immunologic function without serious adverse events.

REVIEWER COMMENTS. Morbidity and mortality are high in patients with SCID-X1 for whom an HLA-matched family donor is not available. This small study suggests that substantial, prolonged immunologic recovery is possible with somatic gene therapy; however, recovery of thymopoiesis may be compromised in older patients. Previous studies have shown more serious adverse events, including enhancer-mediated activation of the T-cell protooncogene LMO-2. Additional longitudinal studies will help to determine the duration of reconstitution and quantify the risk of adverse events.
and in ~40% of the cases, it has been associated with acute leukemia. As opposed to the vast majority of adult HES cases, no pediatric case with the FIP1L1-PDGFR fusion gene has been reported.

CONCLUSION. There are several distinct features of pediatric, compared with adult, HES.

REVIEWER COMMENTS. Most of the published information on the HES has focused on adult patients. This report compares a pediatric case report of HES and a review of published pediatric cases of this condition to adult patients with this syndrome. This is an insightful clinical report that should be useful in the overall workup of pediatric patients who present with dramatic eosinophilia (>1500/mm³) for >6 months’ duration without other known causes of eosinophilia and who have evidence of organ involvement that might be attributable to HES.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900CCCC

John James, MD
Fort Collins, CO

HUMAN IMMUNODEFICIENCY VIRUS

HIV-Infected Individuals Receiving Effective Antiviral Therapy for Extended Periods of Time Continually Replenish Their Viral Reservoir


PURPOSE OF THE STUDY. Latently infected, resting CD4+ T cells provide a reservoir for HIV, and the persistence of these cells prevents the eradication of HIV even in patients who have received highly active antiretroviral therapy (HAART) for prolonged periods. The purpose of this study was to examine the underlying mechanisms by which HIV persists in CD4+ T cells in individuals treated effectively for up to 9 years.

METHODS. Eleven HIV-infected subjects were studied. These individuals had received effective therapy for an average of 8 years (range: 7.16–9.1 years). None of the patients had experienced detectable plasma viremia after initial suppression. Peripheral blood cells were obtained sequentially on all individuals and studied for the presence of replication-competent virus.

RESULTS. All infected subjects carried replication-competent HIV in their CD4+ T cells despite having received prolonged, effectively suppressive antiviral therapy. Contrary to current thinking, substantial higher levels of HIV proviral DNA were found in circulating activated CD4+ T cells when compared with the resting subset. Sequence analysis revealed evidence for cross infection between the resting and activated T-cell compartments, indicating that ongoing reactivation of latently infected, resting CD4+ T cells may occur in these patients.

CONCLUSIONS. Continual replenishment of the CD4+ T-cell reservoir occurs despite prolonged periods of plasma aviremia.

REVIEWER COMMENTS. It is only with the elimination of viral reservoirs that HIV infection can be “cured.” Resting T cells harboring proviral DNA do not live forever. However, the rate of viral replenishment in this cell compartment at least equals the natural decline in their numbers. Eliminating this cell reservoir will be a daunting task.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900DDDD

Joseph A. Church, MD
Los Angeles, CA

Emergence of Drug Resistant HIV-1 After Intrapartum Administration of Single-Dose Nevirapine Is Substantially Underestimated


PURPOSE OF THE STUDY. An inexpensive, effective regimen to prevent perinatal HIV transmission in the developing world is highly desirable. Nevirapine, a nonnucleoside reverse transcriptase inhibitor, seems to provide such an intervention. However, drug-resistance mutations have been identified in up to 40% of women shortly after they received a single intrapartum nevirapine dose as part of a transmission-prevention strategy. This study was undertaken to reexamine the incidence of drug-resistant HIV-1 after single-dose nevirapine.

STUDY POPULATION. Fifty South African women infected with HIV subtype C.

METHODS. Sensitive, real-time polymerase chain reaction assays were sequentially performed for nonnucleoside reverse transcriptase inhibitor–resistance mutation, K103N and Y181C.

RESULTS. Resistance mutations emerged in 65% of women after a single dose of nevirapine.

CONCLUSIONS. Single-dose nevirapine as used in the developing world for prevention of perinatal HIV transmission results in the development of resistance mutations in a very high percentage of women who receive this intervention.

REVIEWER COMMENTS. Although single-dose nevirapine has been successfully implemented as a strategy to prevent perinatal HIV transmission, it is increasingly apparent that the women who are treated with this regimen more often than not develop resistance mutations to nevirapine. The clinical implications are clear: Will nevirapine...
work for future perinatal interventions for individual women with drug-resistance mutations? Will women with these drug-resistance mutations fail to respond to nevirapine as part of a highly active antiretroviral therapy intervention when they need treatment for their own HIV disease? In the same issue of The Journal of Infectious Diseases, Flys et al (J Infect Dis. 2005;192:24–29) demonstrated that drug-resistance variants of HIV may persist for >1 year in this situation. In addition, Lee et al (J Infect Dis. 2005;192:1260–1264) showed that women who developed drug-resistant HIV after exposure to single-dose nevirapine shed drug-resistant HIV in their breast milk. This increases the risk of transmission of resistant virus to uninfected infants. Together, these studies demonstrate that single-dose nevirapine, although an effective strategy for reducing maternal-child transmission of HIV, also predisposes treated women to the development of drug-resistant virus as well as the potential for transmitting drug-resistant virus to their infants via breastfeeding.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900

Joseph A. Church, MD
Los Angeles, CA

Depletion of Latent HIV-1 Infection in Vivo: A Proof-of-Concept Study

PURPOSE OF THE STUDY. Resting CD4+ T cells are a primary reservoir for HIV. In these cells the HIV is in a latent form and not a target of current antiviral agents. The chromatin-remodeling enzyme histone deacetylase 1 (HDAC1) maintains latency of integrated HIV. This study tested the hypothesis that an inhibitor of HDAC1, valproic acid, would result in depletion of latently infected resting CD4+ T cells.

STUDY POPULATION. Four human volunteers with HIV receiving highly active antiretroviral therapy.

METHODS. The individual subjects’ antiretroviral therapies were intensified with enfuvirtide, a fusion inhibitor, to minimize the spread of HIV during potential release from latency. The subjects then were treated with oral valproic acid, 500 to 750 mg twice daily, in addition to their antiretroviral therapy, and they were followed for 3 months. Latently infected resting T cells were quantified before and after augmentation of treatment with limiting-dilution culture of resting cells after ex vivo activation.

RESULTS. The frequency of resting CD4+ T-cell infection was stable before the addition of enfuvirtide and valproic acid but declined thereafter. This decline was significant in 3 or 4 patients, with a mean reduction of 75% in circulating HIV-infected resting CD4+ T cells. There were no complications of the additional treatments except for the expected injection-site reactions to enfuvirtide.

CONCLUSIONS. Combination therapy with an HDAC inhibitor and very potent antiretroviral therapy accelerated the reduction in HIV-infected resting T cells. This suggests a new approach to the management of HIV that eventually may result in clearance of HIV from infected individuals.

REVIEWER COMMENTS. This study received a fair amount of media coverage at the time it was published. It begs the question, can HIV be cured? A 75% reduction in the resting T-cell reservoir seems impressive. However, this was a very short-term study, and the kinetics and degree to which the resting T-cell reservoir was replenished after discontinuation of valproic acid was not reported. In addition, valproic acid, a widely used anticonvulsant, is potentially highly toxic and has “black-box” warnings for hepatotoxicity, teratogenicity, and pancreatitis. Despite the authors’ optimistic conclusions, “this finding, though not definitive, suggests that new approaches will allow the cure of HIV in the future,” use of the “C word” is likely premature.

Paradoxical CD4+ T-Cell Decline in HIV-Infected Patients With Complete Virus Suppression Taking Tenofovir and Didanosine

PURPOSE OF THE STUDY. Tenofovir and didanosine are adenosine analogs commonly used in highly active antiretroviral therapy combinations. Although virologically effective, this combination is theoretically associated with pharmacokinetic interactions and increased risks of pancreatitis and hyperglycemia. The study examined the CD4+ T-cell effects of the use of these 2 drugs as part of a highly active antiretroviral therapy regimen.

METHODS. Data from 570 individuals were analyzed retrospectively according to the nucleoside analog “backbone” of protease inhibitor–containing regimens: tenofovir + didanosine in 298 subjects, didanosine in 88, tenofovir in 44, and neither didanosine nor tenofovir in 140.

RESULTS. Significant CD4+ T-cell declines were noted in patients taking the combination of tenofovir + didanosine relative to all other nucleoside analog combinations including didanosine or tenofovir only. Patients exposed to higher didanosine doses showed a more pro-
nounced CD4⁺ T-cell decline, and plasma levels of didanosine correlated with the extent of T-cell loss.

CONCLUSIONS. Although patients receiving tenofovir + didanosine–based combinations generally achieved excellent viral suppression, their CD4⁺ T cells often paradoxically declined. This effect generally progressed over time. It is hypothesized that the use of these 2 agents together results in a condition that metabolically resembles purine nucleoside phosphorylase deficiency, a rare but well-described primary immunodeficiency syndrome.

REVIEWER COMMENTS. Tenofovir and didanosine frequently are the only nucleoside analog agents available to patients with drug-resistant virus. This combination with either a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor is often effective in suppressing virus in patients with limited options. However, the paradoxical decline in T-cell numbers is of great concern. Patients on this regimen must be monitored carefully for this potential complication.

Massive Infection and Loss of Memory CD4⁺ T Cells in Multiple Tissues During Acute SIV Infection


PURPOSE OF THE STUDY. It was recently established that both acute HIV and its simian counterpart, simian immunodeficiency virus (SIV), are accompanied by dramatic and selective loss of memory CD4⁺ T cells. This loss has been shown to primarily occur in mucosal tissues. The extent and mechanisms underlying this depletion have not been defined. The purpose of this study was to investigate these questions in a simian model.

METHODS. Eight rhesus macaque monkeys were infected with a pathogenic strain of SIV. Plasma and tissue samples were collected at various time points by biopsy and necropsy. Lymphocyte subsets were analyzed with standard flow cytometry, and T-cell–associated viral DNA was measured by a highly sensitive quantitative polymerase chain reaction assay.

RESULTS. This study demonstrated that in this monkey model, memory CD4⁺ T cells are depleted in multiple tissues during acute SIV infection. In addition, the loss of these cells is explained by a massive infection of these cells by the virus. Specifically, ~50% of these cells throughout the body are infected by SIV at the peak of infection, and most of the infected cells disappear within several days. Alternative mechanisms are not required. This depletion occurs to a similar extent in all tissues.

CONCLUSIONS. Acute immunodeficiency virus infection results in the loss of ~50% of all memory T cells within days of infection. This and other studies strongly suggest that this loss, at least in adult animals and humans, is irreversible.

REVIEWER COMMENTS. This study confirms and extends previous findings demonstrating massive memory T-cell loss during acute HIV or SIV infection. The extent to which this loss is recoverable is likely to be very limited. Most interesting is that these authors also noted that naive T cells are highly resistant to SIV infection. These observations are particularly important for infants infected with HIV. Young infants have fewer memory CD4⁺ T cells, and, therefore, their loss may not be as critical in newborns. In addition, the thymus in young children may be more capable of reconstituting memory T-cell functions if HIV is completely suppressed early. Similar studies should be performed on infant laboratory animals to determine the extent to which recovery is likely in infected children.
Infectious Disease

Missed Opportunities for Influenza Vaccination in Children With Chronic Medical Conditions

PURPOSE OF THE STUDY. To assess the frequency and characteristics of missed opportunities for influenza immunization in children with chronic medical conditions, and among unimmunized children in that group, to explore parent-reported reasons for not vaccinating their child.

STUDY POPULATION. A cohort of 926 children (aged 6 to 72 months) who were identified from October 1, 2002, through January 31, 2003, as having ≥1 high-risk conditions (HRCs). A total of 594 (64%) were male, and 734 (79%) were between 24 and 72 months of age. The children were insured privately (84%) or publicly (12%) or uninsured (3%). Diagnoses included asthma only (89%), cardiac conditions (3%), immunosuppressive conditions or therapies (2%), chronic nonasthma pulmonary conditions (2%), and other HRCs (2%).

METHODS. Data were obtained from shared billing and immunization registry databases of 4 private pediatric practices in metropolitan Denver, Colorado, during the 2002–2003 influenza season. Study sites had 5 to 8 pediatricians and 2 to 6 nonphysician providers per practice. The method of HRC identification through billing data using set diagnostic codes was documented to have a sensitivity of 72%, specificity of 95%, and an overall accuracy of 90% compared with medical charts. The billing system contained data for individual patient demographics, diagnostic codes, procedural codes for immunizations, and type of visit distinguished as well-child care (WCC) visit or not (non-WCC visit). Telephone surveys of randomly selected parents of children not given influenza vaccine were conducted in April to May 2003.

RESULTS. In children with asthma only (820), of all vaccine-eligible visits (881), 78% resulted in missed opportunities. Missed opportunities occurred at 62% of WCC visits and 86% of non-WCC visits (difference of 24%; 95% confidence interval: 16%–31%). The rate of influenza immunization was 43% among subjects with vaccine-eligible WCC visits compared with 18% for those without a vaccine-eligible WCC visit. In children with other HRCs (106), the rates of missed opportunities were similar to those children with asthma only. The rate of influenza immunization was also similar at 40% with vaccine-eligible WCC visits; however, the rate of immunization for those without a vaccine-eligible WCC visit was higher at 28%. If the subjects were immunized at their first opportunity, similar rates of immunization (61% for those with asthma vs 62% for those with other HRCs) would have been achieved. Telephone interviews with parents revealed lack of physician recommendation, low perceived susceptibility to influenza, and misconception of the risks of vaccination as the primary reasons.

CONCLUSIONS. Missed opportunities for influenza immunization are common among children with asthma and other HRCs, particularly at non-WCC visits and later in the influenza season, and contribute to the persistently low influenza-immunization rate in this population.

REVIEWER COMMENTS. As illustrated in this study, parents often rely on their child’s health care provider to advise them about preventive health care measures. Therefore, it is important for providers to identify the patients at risk (existence of HRC), recognize the indications for influenza immunization, and discuss the pros and cons of influenza immunization with the parents and patients.

Identification of a Universal Group B Streptococcus Vaccine by Multiple Genome Screen

PURPOSE OF THE STUDY. To apply comparative genomic techniques for the development of a universally protective group B Streptococcus (GBS) vaccine.

METHODS. The genome sequences of 8 GBS strains were compared to identify shared and strain-restricted genes. Computer algorithms were used to identify putative surface or secreted proteins. Candidates were cloned and expressed recombinantly in Escherichia coli. Purified proteins initially alone and then in combination were used to immunize groups of female mice. Immunized animals were then mated, and resulting offspring were challenged at <48 hours of age with virulent GBS. Protection was also correlated with specific antibody binding.

RESULTS. Genomic analysis identified 1811 shared genes representing ~80% of the genome of each strain. Of these, 589 proteins were predicted to be surface or secreted proteins (396 shared, 193 variable), and 312 of them were successfully expressed as soluble fusion proteins from E coli. Systemic screening of all 312 of these proteins revealed that 4 were capable of significant protection of GBS-challenged offspring of immunized mothers. One of these 4, Sip, was a previously described shared gene, whereas 3 were variably present in the genomes from different strains. As expected, in experiments with single-antigen vaccination, there was no
CONCLUSIONS. Multistrain genome analysis and screening represents an effective new approach for the identification of vaccine candidates that single-strain analysis would miss.

REVIEWER COMMENTS. Vaccine strategies taking into account the enormous variability at the genomic and proteomic levels that many pathogens have evolved are the best hedge against a mere “arms race” in which temporary vaccine efficacy gives way to the emergence of antigenic variants. This is a novel application of such a rational strategy. However, the extent of the challenge is underscored by the identification of only 4 targets despite a comprehensive approach. Furthermore, 3 of 4 are not part of the “core” conserved genome and are, therefore, likely to be nonessential. It remains unproven whether targeting of so few surface proteins of an encapsulated organism would prove to be a good long-term strategy. Nevertheless, this approach seems likely to be at least complementary to efforts directed to polysaccharides for encapsulated organisms.

Wayne G. Shreffler, MD, PhD New York, NY

Passive Immunization During Pregnancy for Congenital Cytomegalovirus Infection

PURPOSE OF THE STUDY. To investigate the effectiveness of cytomegalovirus (CMV)-specific hyperimmune globulin for primary CMV infection during pregnancy as a preventive therapy for lethal CMV infection.

STUDY POPULATION. One hundred fifty-seven pregnant women from 8 Italian cities with a primary CMV infection diagnosed via serologic testing.

METHODS. Women were placed in 1 of 2 groups. The therapy group comprised women who underwent amniocentesis and whose amniotic fluid contained either CMV antigen detected by culture or CMV DNA detected by polymerase chain reaction. The group was offered intravenous CMV-specific hyperimmune globulin at a dose of 200 U per kg of maternal weight. Additional intravenous, intrapartum, trumbilical-cord, or intra-amniotic doses were administered if evidence of persistent fetal involvement was present on ultrasound. Women with CMV-positive amniotic fluid who declined to receive hyperimmune-globulin infusions were followed as a comparison group. Those in the prevention group, consisting of women with a recent primary infection before 21 weeks’ gestation or who declined amniocentesis, were offered monthly hyperimmune globulin (100 U/kg intravenously). Pregnant women who declined monthly administration of hyperimmune globulin were followed as a comparison group.

RESULTS. In the therapy group, 31 women received hyperimmune globulin, only 1 (3%) of whom gave birth to an infant with symptomatic CMV disease, compared with 7 (50%) of 14 women who did not receive hyperimmune globulin. Thus, hyperimmune-globulin therapy was associated with a significantly lower risk of congenital CMV disease (adjusted odds ratio: 0.02; 95% confidence interval: −∞ to 0.15; P = .001). In the prevention group, 37 women received hyperimmune globulin, 6 (16%) of whom had infants with congenital CMV infection, compared with 19 (40%) of 47 women who did not receive hyperimmune globulin. Thus, hyperimmune-globulin therapy was associated with a significantly lower risk of congenital CMV infection (adjusted odds ratio: 0.32; 95% confidence interval: 0.10 to 0.94; P = .04). No adverse effects resulted from CMV-specific hyperimmune globulin administration.

CONCLUSIONS. Treatment of pregnant women with CMV-specific hyperimmune globulin is safe, and the findings of this nonrandomized study suggest that it may be effective in the treatment and prevention of congenital CMV infection. A controlled trial of this agent may be appropriate.

REVIEWER COMMENTS. The risk of congenital CMV infection is high after primary maternal CMV infection. Although the majority of congenitally acquired CMV infections are asymptomatic, symptomatic infections result in significant morbidity and possible mortality. The implementation of CMV-specific hyperimmune globulin may reduce or prevent the devastating effects of symptomatic congenital CMV.

Jennifer M. Maloney, MD
Scott H. Sicherer, MD
New York, NY

Information Leaflet and Antibiotic Prescribing Strategies for Acute Lower Respiratory Tract Infection: A Randomized, Controlled Trial
PURPOSE OF THE STUDY. Acute lower respiratory tract infection is the most common condition treated in primary care. Many physicians still prescribe antibiotics; however, systematic reviews of the use of antibiotics are small and have diverse conclusions. This study evaluated the effectiveness of 3 prescribing strategies and an information leaflet for acute lower respiratory tract infection.

STUDY POPULATION. A randomized, controlled trial conducted from August 18, 1998, to July 30, 2003, of 807 patients presenting to a primary care setting with acute uncomplicated lower respiratory tract infection. Patients were assigned to 1 of 6 groups by a factorial design: leaflet or no leaflet and 1 of 3 antibiotic groups (immediate antibiotics, no offer of antibiotics, and delayed antibiotics).

METHODS. Three strategies, immediate antibiotics ($n = 262$), a delayed antibiotic prescription ($n = 272$), and no offer of antibiotics ($n = 273$), were prescribed. Approximately half of the patients in each group received an information leaflet (129 for immediate antibiotics, 136 for delayed antibiotic prescription, and 140 for no antibiotics).

RESULTS. A total of 562 patients (70%) returned complete diaries, and 78 (10%) provided information about both symptom duration and severity. Cough rated at least “a slight problem” lasted a mean of 11.7 days (25% of the patients had a cough lasting ≥17 days). An information leaflet had no effect on the main outcomes. Compared with no offer of antibiotics, other strategies did not alter cough duration (delayed prescription, 0.75 days; 95% confidence interval: −0.37–1.88; immediate prescription, 0.11 days; 95% confidence interval: −1.01–1.24) or other primary outcomes. Compared with those in the immediate-antibiotic group, slightly fewer patients in the delayed-prescription and control groups used antibiotics (96%, 20%, and 16%, respectively; $P < .001$). Fewer patients were “very satisfied” (86%, 77%, and 72%, respectively; $P = .005$), and fewer patients believed in the effectiveness of antibiotics (75%, 40%, and 47%, respectively; $P < .001$). There were lower reattendances within a month with antibiotics (mean attendances for no antibiotics: 0.19; delayed prescription: 0.12; immediate prescription: 0.11; $P = .04$) and higher attendance with a leaflet (mean attendances for no leaflet: 0.11; mean attendances for leaflet: 0.17; $P = .02$).

CONCLUSIONS. No offer or a delayed offer of antibiotics for acute uncomplicated lower respiratory tract infection is acceptable, associated with little difference in symptom resolution, and is likely to considerably reduce antibiotic use and beliefs in the effectiveness of antibiotics.

REVIEWER COMMENTS. This is good that we do not need yet another patient-information leaflet. I have always liked the “delayed-offer” approach, because it is a compromise to the patient, and most of the time they get better and never need the drug.
Individual and Neighborhood-Level Factors in Predicting Asthma

Sally Joo Bailey

Pediatrics 2006;118;S8
DOI: 10.1542/peds.2006-0900N

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/118/Supplement_1/S8.1

References
This article cites 1 articles, 0 of which you can access for free at:
http://pediatrics.aappublications.org/content/118/Supplement_1/S8.1.full#ref-list-1

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2006 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .
Individual and Neighborhood-Level Factors in Predicting Asthma

Sally Joo Bailey

*Pediatrics* 2006;118;S8

DOI: 10.1542/peds.2006-0900N

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/118/Supplement_1/S8.1