main outcome measure was maternal report of a provider’s diagnosis of eczema or atopic dermatitis in the first 6 months of life.

**Methods.** The authors used a prospective birth cohort study design and multiple logistic-regression models to assess the associations between potential predictors and incidence of atopic dermatitis.

**Results.** The incidence of atopic dermatitis in the first 6 months of life was 17.1%. The risk of atopic dermatitis was increased among infants born to black or Asian mothers (adjusted odds ratio [OR]: 2.41 and 2.58, respectively) and among infants whose mothers had eczema (OR: 2.67). Other predictors included increased gestational age at birth (OR: 1.14; 95% confidence interval: 1.02, 1.27, for each 1-week increment) and male gender (OR: 1.76).

**Conclusions.** These findings suggest that genetic and prenatal and perinatal influences are important in the early presentation of atopic dermatitis.

**Reviewer’s Comments.** There are relatively little data about risk factors for atopic dermatitis in the United States, and the strengths of this study are the prospective evaluation of risk factors in a large population with data collection beginning in the prenatal period. The results of the study point to a number of risk factors related to heredity and potentially genetics as being important in early onset of eczema. The preponderance of affected males is interesting given that infant boys are also more likely to wheeze. Although this may be due in part to changes in airway mechanics, the results of this study, together with data demonstrating higher total serum IgE levels in boys, suggest that immune development is also related to gender. Environmental factors were not prominent as risk factors for eczema, although there was a trend toward an association with greater cockroach exposure. It is likely that environmental exposures play a greater role in determining the persistence of atopic dermatitis or perhaps the incidence after the first 6 months of age.

JAMES E. GERN, MD
Madison, WI

**REDUCED INTERFERON \( \gamma \) PRODUCTION AND SOLUBLE CD14 LEVELS IN EARLY LIFE PREDICT RECURRENT WHEEZING BY 1 YEAR OF AGE**


**Purpose of the Study.** To determine if interferon \( \gamma \) (IFN\( \gamma \)) production and soluble CD14 (sCD14) levels correlate longitudinally with the risk of developing recurrent wheezing in the first year of life. Both environmental risk factors and variation in the maturation of the immune system seem to have a role in the development of asthma. Previous studies have demonstrated reduced IFN\( \gamma \) production in atopic and nonatopic wheezers. IFN\( \gamma \) production correlates positively with endotoxin exposure and with sCD14 levels, and CD14 functions as a receptor for endotoxin. Thus, the investigators reasoned that a CD14-mediated response to endotoxin might play a role in the maturation of IFN\( \gamma \) production, possibly preventing the onset of recurrent wheezing.

**Study Population.** Subjects were 238 infants followed prospectively from birth to 12 months as part of the Infant Immune Study in Arizona.

**Methods.** Mothers of enrolled infants completed questionnaires about known environmental risk factors for wheezing before birth and throughout the infant’s first 12 months of life. At 12 months, the mothers were also asked how often their infant’s chest had ever sounded “wheezy” or “whistling” and the age of the first wheezing episode. Frequency of wheezing was quantified, and any response more than “very rarely” was classified as recurrent wheezing. Blood was obtained at birth and 3 months of age for the measurement of sCD14 levels in plasma and IFN\( \gamma \) production from stimulated peripheral blood mononuclear cells.

**Results.** Wheezing episodes during the first year of life were experienced by 94 infants (39.5%), and 41 experienced recurrent episodes. The mean IFN\( \gamma \) production and sCD14 levels increased from birth to 3 months. Infants in the lowest quartile of IFN\( \gamma \) production at 3 months and of sCD14 levels at birth had up to 4.5 and 3.2 increased odds, respectively, of developing recurrent wheezing compared with children in the medium and high quartiles for these parameters. These relationships persisted after adjusting for demographic and environmental asthma risk factors.

**Conclusions.** The authors concluded that reduced plasma sCD14 at birth and impaired IFN\( \gamma \) production at 3 months of age increase the risk of recurrent wheezing in the first year of life. Because of the interrelationship of CD14 and IFN\( \gamma \), a CD14-mediated response to endotoxin may play an important role in enhancing the maturation of IFN\( \gamma \) production and preventing the inception of recurrent wheezing.

**Reviewers’ Comments.** The relation of CD14 and IFN with endotoxin exposure lends support for the “hygiene hypothesis,” which postulates that decreased exposure to infectious agents in infancy increases the risk for atopy. From this study, it is impossible to assess whether sCD14 levels at birth and IFN\( \gamma \) production at 3 months of age are simply independent markers that correlate with recurrent wheeze or whether they are truly in the same causal pathway to recurrent wheezing. Additional studies will need to be done to confirm causality. Unfortunately, the design of the study did not allow the investigators to explore whether IFN\( \gamma \) production and sCD14 levels were important in atopic versus nonatopic recurrent wheezing.

IVAN K. CHINN, MD
VAISHALI S. MANKAD, MD
LARRY W. WILLIAMS, MD
Durham, NC

**SOLUBLE CD14 AS A PREDICTOR OF SUBSEQUENT DEVELOPMENT OF RECURRENT WHEEZING IN HOSPITALIZED YOUNG CHILDREN WITH RESPIRATORY SYNCTIAL VIRUS-INDUCED BRONCHIOLITIS**


**Purpose of the Study.** To investigate the relationship between the serum level of soluble CD14 (sCD14) in children hospitalized because of respiratory syncytial virus (RSV)-induced bronchiolitis and the subsequent development of recurrent wheezing.

**Study Population.** Twenty-one infants aged 2 to 14 months who were hospitalized because of RSV bronchiolitis in the winter of 2001–2002. All were at least 37 weeks’ gestation without any neonatal complications or prior illness.

**Methods.** sCD14 was measured on admission to the hospital. RSV infection was documented by direct immunofluorescence. Children were assessed every 2 months for 1 year after discharge for the development of recurrent wheezing.

**Results.** Nineteen patients completed the study. Six children did not have recurrent wheezing in the 12-month
follow-up period (group A), and 13 had recurrent wheezing (group B). There was no significant difference in birth weight, male-to-female ratio (1:1), or age at hospitalization (group A: 6.3 ± 5.3 months; group B: 4.2 ± 3.3 months) between groups. There was a trend for children in group A to have been breastfed more than those in group B (83% vs 46%; P = .18). Similarly, children in group A tended to have higher birth weight than those in group B (3303 ± 647 vs 2864 ± 486 g; P = .15). Children in group A (non-wheezeers) had significantly higher sCD14 levels on hospital admission than those in group B (wheezeers) (14521 ± 1773 vs 11243 ± 3264 pg/mL; P < .05). sCD14 levels correlated with age at hospitalization (P < .01). The sCD14 level was >11 000 pg/mL in 5 of 6 (83%) children in group A and 6 of 13 (46%) children in group B. This level was chosen as it was felt to be the best predictor for subsequent recurrent wheezing.

Conclusions. In infants hospitalized for RSV bronchiolitis, high serum sCD14 levels correlate with protection from subsequent recurrent wheezing and may modulate the influence of RSV development of lower airway disease.

Reviewers’ Comments. Membrane-bound CD14 on monocytes and macrophages binds lipopolysaccharide (LPS) and transfers it from LPS-binding protein to Toll-like receptors (TLRs). CD14/TLR activation by LPS enhances interleukin 12 and interleukin 18 synthesis, TTR differential, and inhibition of the atopic phenotype. It is not clear from this study if increased sCD14 levels are the result of a differential responsiveness to RSV in group A or if sCD14 levels predated acquisition of the RSV infection. Nonetheless, this study adds another layer to our understanding of the early role of innate immune responsiveness and the subsequent risk of development of atopic disease.

MITCHELL R. LESTER, MD
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THE INTRODUCTION OF SOLIDS IN RELATION TO ASTHMA AND ECZEMA


Purpose of the Study. Some feeding guidelines recommend delayed introduction of solids for the prevention of asthma and allergy. This study sought to explore whether late introduction of solids is protective against the development of asthma, eczema, and atopy.

Study Population. A total of 642 unselected children recruited before birth and followed to the age of 5.5 years.

Methods. A questionnaire was administered yearly. Food exposure was derived from the first-year questionnaire: “When did you start feeding your son/daughter the following foods?: fruits, vegetables, infant rice, cereal products, meat, fish, milk products, egg.” Median age at which each solid food was introduced and length of time the infant was breastfed were determined. Wheezing was defined as wheezing in the absence of a cold or infection in the preceding 12 months, and eczema was defined as a positive response to “has a doctor ever told you that your son/daughter has eczema?” Skin-prick tests to grass, cats, and dust mites were performed at age 5.5 years, and atopy was defined as at least 1 positive skin test. Clinical outcomes were compared for early (before the median age) or late (after the median age) introduction of foods and how long the infants were breastfed.

Results. No effect of the early or late introduction of solid foods in relation to any of the outcomes was observed. No association between exclusive breastfeeding at the age of 8 weeks and any of the outcomes was found.

Conclusion. The results do not support the recommendations given by present feeding guidelines, which state that a delayed introduction of solids is protective against the development of asthma and allergy.

Reviewer’s Comments. Published feeding guidelines on the delayed introduction of solid foods to prevent allergy state that “conclusive studies are not yet available to permit definitive recommendations.” Nonetheless, recommendations are made regarding delaying the introduction of certain foods until certain ages. Some meta-analyses have favored breastfeeding for prevention of eczema (and other atopic diseases), but individual studies on both sides continue to be published. This study suggests that delayed introduction of solid foods does not prevent asthma, eczema, or atopy. The most obvious type of allergy that such a delay might prevent is allergy to the food itself, but this “prevention” is somewhat self-fulfilling, because you cannot become allergic to a food to which you have not been exposed. This is complicated further by exposure to foods in breast milk. Additionally, many toddlers who become allergic to foods, particularly milk and egg, routinely outgrow the allergy. Although this study is helpful in examining the relationship (or lack thereof) between the introduction of solid foods and asthma, eczema, and atopy, we need more research to tell us if delayed introduction of solid foods will prevent or merely delay the development of food allergy.

JOHN M. KELSO, MD
San Diego, CA

EFFECTS OF BREAST-FEEDING OF THE DEVELOPMENT OF ATOPIC DERMATITIS DURING THE FIRST 3 YEARS OF LIFE—RESULTS FROM THE GINI-BIRTH COHORT STUDY


Purpose of the Study. Most studies have shown a protective effect of breastfeeding on atopic disease, but some have shown an increased risk. This study examined the impact of exclusive breastfeeding for the first 4 months of infancy on the prevalence of atopic dermatitis (AD) during the first 3 years of life.

Study Population. A large birth cohort of healthy term neonates in Germany enrolled between 1995 and 1998 for a study designed to investigate risk factors for and course and prevention of allergic disease.

Methods. Group I (interventional) consisted of infants with a family history of allergy who were either exclusively breastfed for the first 4 months or were not breastfed or supplemented (by randomization) with hydrolyzed formula (study formula) or conventional cow’s milk formula. Group II (noninterventional) consisted of infants whose parents did not wish to participate in the intervention trial or who did not have a family history of allergy. Both groups received a yearly self-administered questionnaire on health, nutrition, and living conditions. Parents in group I also received dietary recommendations to avoid allergenic food and participated in structured interviews at the study centers.

Results. Of the 5538 infants recruited at birth, 4194 (75.7%) completed the 3-year questionnaires. Of these, 3903 (93.1%) completed data on feeding regimen and physician-diagnosed AD. Fifty-two percent of these infants were breastfed exclusively and 522 (13.4%) were bottle-fed exclusively during the first 4 months of life. The overall prevalence of physician-diagnosed AD and intermittent itchy rash for at least 6 months was 20% and 9.1%, respec-
tively. There was no significant adverse association between exclusive breastfeeding and physician-diagnosed AD in infants with a family history of AD (odds ratio [OR]: 0.92), in those without a family history of AD (OR: 0.97), or in those with itchy rash (OR: 1.2 and 0.92, respectively). In group I, exclusive breastfeeding was protective for AD, compared with feeding with a conventional cow’s milk formula (OR: 0.64). If stratified by family history of AD, there was no difference in effect of breastfeeding on physician-diagnosed AD and itchy rash in group I. The difference in the NI group was not determined because of the small number of participants.

Conclusions. Exclusive breastfeeding for the first 4 months of infancy was not shown to increase the risk of developing AD in infants with or without a family history of AD.

Reviewers’ Comments. A number of studies have shown that breastfeeding could be a risk factor for atopic dermatitis and even suggest a detrimental effect of continuing to breastfeed infants with severe AD and food allergy. The role of breastfeeding in allergic diseases has been controversial, but the weight of the evidence in meta-analyses and in this study support a protective effect in regard to prevention.

Sheila Bonilla, MD
Michael S. Kaplan, MD
Los Angeles, CA

THREE-YEAR OUTCOMES OF DIETARY FATTY ACID MODIFICATION AND HOUSE DUST MITE REDUCTION IN THE CHILDHOOD ASTHMA PREVENTION STUDY


Purpose of the Study. To measure the effects of dietary supplementation with ω-3 fatty acids and house dust mite (HDM) allergen avoidance in children with a family history of asthma.

Study Population. Children at high risk for asthma, defined by having at least 1 parent or sibling with current asthma or frequent wheeze.

Methods. A total of 616 children at high risk for asthma were enrolled antenatally, and 526 children remained in the trial when they were 3 years old. HDM allergen avoidance involved the use of both physical and chemical methods for the reduction of allergen concentrations. Dietary intervention included supplementation of the infant’s/s’ child’s diet with tuna fish oil and use by the family of canola-based oils and spreads. Participants were randomized to 1 of 4 study groups: placebo diet and active HDM controls, active diet supplements and active HDM controls, placebo diet and no HDM controls, and active diet supplements and no HDM controls. The outcomes were symptoms of allergic disease and HDM allergen sensitization at 3 years.

Results. There was a significant 10.0% (95% confidence interval [CI]: 3.7, 16.4) reduction in the prevalence of cough in atopic children in the active-diet group (P = .003; number needed to treat: 10) but a negligible 1.1% (95% CI: −7.1, 9.5) reduction in cough among nonatopic children. There was a 7.2% (95% CI: 10.11, 14.3) reduction in sensitization to HDM in the active allergen-avoidance group (P = .05; number needed to treat: 14). No significant differences in wheeze were found with either intervention.

Conclusions. These results suggest that HDM allergen avoidance and dietary supplementation with foods rich in ω-3 fatty acids may have a role in preventing the development of allergic sensitization and airways disease in early childhood, which offers the prospect of reducing allergic disease in later life.

Reviewer’s Comments. Although the reported risk reduction in the active-intervention groups was modest, this study suggests that a relatively simple intervention may be used in public health to modulate the development of allergic sensitization and airways disease at an early age. Hopefully, a follow-up study will determine the long-term effect of combined dietary ω-3 fatty acid supplementation and environmental HDM allergen avoidance.

Anna Nowak-Wegrzyn, MD
New York, NY

EARLY INFANT MULTIVITAMIN SUPPLEMENTATION IS ASSOCIATED WITH INCREASED RISK FOR FOOD ALLERGY IN ASTHMA


Purpose of the Study. Dietary vitamins have immunomodulating effects in vitro, and individual vitamins have been shown to skew T cells toward either T-helper 1 or T-helper 2 phenotypic classes, suggesting that they may participate in inflammatory or allergic disease. The objective of the study was to determine if early vitamin supplementation during infancy affects the risk for asthma and allergic disease during early childhood.

Study Population. Cohort data were analyzed from the National Center for Health Statistics 1988 National Materials–Infant Health Survey, which followed pregnant women and their newborns, and the 1991 longitudinal follow-up of the same patients, which measured health and disease outcomes. There were >8000 patients in this study.

Methods. Patients were stratified by race and breastfeeding status. Factors that are known to be associated with alteration of risk for asthma or food allergies were identified by using univariate logistic regression. Those factors were then analyzed in multivariate logistic-regression models. Early vitamin supplementation was defined as vitamin use within the first 6 months.

Results. The overall incidence of asthma was 10.5% and of food allergy was 4.9%. In univariate analysis, being male gender, having a smoker in the household, being in child care, being premature (<37 weeks’ gestation), being black, having no history of breastfeeding, and having lower income and lower education were associated with higher risk for asthma. Being in child care, having higher levels of education and income, and having a history of breastfeeding were associated with a higher risk for food allergies. In multivariate logistic analyses, a history of vitamin use within the first 6 months of life was associated with a higher risk for asthma in black infants (odds ratio [OR]: 1.27; 95% confidence interval [CI]: 1.04, 1.56). Early vitamin use was also associated with a higher risk for food allergies in the exclusively formula-fed population (OR: 1.63; 95% CI: 1.21, 2.20). Vitamin use at 3 years of age was associated with increased risk for food allergies but not asthma in both breastfed (OR: 1.62; 95% CI: 1.19, 2.21) and exclusively formula-fed (OR: 1.39; 95% CI: 1.03, 1.88) infants.

Conclusions. The conclusions of the authors were that early vitamin introduction is related to increased likelihood for asthma in black children and food allergies in exclusively formula-fed children.

Reviewer’s Comments. Although there are some laboratory data to support the potential for some vitamins to
cause naive T cells to differentiate to T-helper 2 phenotypes (allergy promoting), at this time the findings of this study are associational and not causal. There are numerous confounding factors that may have resulted in the observed associations. The authors proposed that there may have been cultural biases in diagnosis. It is also unusual that this association only held for vitamin use at 3 and 6 months of age but not at 3 years of age. It was noted that formula-fed infants who received (but did not need) multivitamins were at higher risk of food allergy than breastfed infants who received multivitamins. The authors could not evaluate the possibility that formula-fed infants were given multivitamins, because they had illnesses (such as atopic dermatitis or food allergy) that may have led to such interventions. The authors also indicated that it is possible that persons inclined to use multivitamins are also persons who are more likely to report their child’s health problems or seek more medical diagnoses for their child’s symptoms. Last, these data were collected ~15 years ago, and since then the rates of asthma and food allergy have apparently increased significantly. It is not clear that the results would be similar today. The numerous potential confounding influences in this study require that the results be confirmed in other studies before any specific recommendations can be made.

Christopher Randolph, MD
Waterbury, CT

ENDOTOXIN EXPOSURE AND ECZEMA IN THE FIRST YEAR OF LIFE


Purpose of the Study. To examine the relationship between endotoxin exposure early in life and eczema during the first year of life in children with parental history of asthma or allergy.

Study Population. A birth cohort of children in metropolitan Boston, Massachusetts, selected for a history of allergy or asthma in at least 1 parent.

Methods. A total of 505 infants from 499 Boston families were enrolled between September 1994 and August 1996 and followed prospectively. Seven children followed for ≤4 months were excluded from analysis. Adequate analysis of endotoxin was obtained from house dust sampled from 401 living rooms. Endotoxin exposure was categorized into quartiles by concentration of endotoxin units per milligram of house dust (EU/mg). Potential predictors of eczema and confounders were considered for multivariate analysis including socioeconomic data, birth weight, maternal age, season of birth, breastfeeding, ingestion of allergenic foods, family history of atopic diseases, pets in the home, and day care. Maternal serum was analyzed for allergen-specific IgE to several common allergens. Every 2 months the primary caregiver was asked, “Has a doctor or nurse ever said that your child has eczema?”

Results. Of the 498 children, 140 (28%) had eczema in the first year of life. Exposure to high levels of endotoxin (80.48–713.2 EU/mg) at 2 to 3 months of age were inversely associated with eczema during that time. For every quartile increase in endotoxin measured in living room house dust, there was a decrease in the odds of developing eczema in the first year of life (odds ratio [OR] for each quartile increment: 0.76). Exposure to a dog in the home at 2 to 3 months of life compared with no dog exposure decreased the odds of having eczema in the first year of life by half; however, this association became less significant when adjusted for endotoxin exposure. In the multivariate analyses, paternal history of eczema (OR: 1.91) and maternal sensitization to at least 1 allergen (OR: 1.61) were associated with developing eczema.

Conclusions. In children with parental history of asthma or allergy, exposure to high levels of endotoxin at 2 to 3 months of age may protect against eczema development in the first year of life. Additionally, both paternal history of eczema and maternal sensitization to ≥1 allergen are associated with increased risk of eczema in the first year of life.

Reviewer’s Comments. A great deal of faith has been placed in the “hygiene hypothesis” being correct despite relatively few prospective birth cohort evaluations. Although previous studies have focused on allergic sensitization, cytokine production, and development of asthma, this study makes an association between endotoxin levels in the living rooms (but not bedrooms) of children’s homes and the development of eczema in the first year of life. This lends another facet, and end-organ effect, to support the argument to validate the hygiene hypothesis. Additional data from this and other high-risk birth cohorts will provide additional data to fuel this debate.

Mark H. Moss, MD
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PERTUSSIS VACCINATION IN INFANCY AND ASTHMA OR ALLERGY IN LATER CHILDHOOD: BIRTH COHORT STUDY


Purpose of the Study. To examine the association of pertussis vaccination in infancy to asthma or atopy by the age of 7.5 years.


Methods. Vaccination status for each child from the child health surveillance was obtained. Children were categorized as fully vaccinated (primary course of diphtheria, tetanus, and pertussis vaccines), partially vaccinated (completed primary course of diphtheria and tetanus vaccines but did not receive pertussis vaccine), or nonvaccinated. Wheeze outcomes were parental report of asthma at age 69 to 81 months, wheeze with whistling in the chest at age 69 to 81 months, and asthma diagnosed by a doctor at 91 months. A positive outcome of atopy was defined by any positive allergy skin tests at 7 years old. Multivariable logistic regression was used to evaluate associations between immunization status and asthma and allergy outcomes.

Results. Vaccination history was available for 13,810 children: 13,109 (94.9%) were fully vaccinated, and 1446 did not have pertussis vaccination (340 nonvaccinated; 106 partially vaccinated). Prevalence of reported asthma at age 69 to 81 months was 12.4%, reported wheeze with whistling at 69 to 81 months was 9.8%, and atopy at 7 years was 20.5%. Unadjusted analyses showed significant associations between partial vaccination and asthma at age 69 to 81 months (odds ratio [OR]: 2.84; 95% confidence interval [CI]: 1.24, 6.53) and doctor-diagnosed asthma (OR: 3.03; 95% CI: 1.51, 6.09), but these associations did not remain in multivariate analysis. In multivariate analyses, there were no significant associations between the vaccinated categories and any of the outcomes.

Conclusion. There is lack of an independent association between pertussis vaccination in infancy and inactivated,
whole-cell vaccine and the subsequent development of asthma or atopy during later childhood.

Reviewer's Comments. This is a nice study evaluating whether there is an association between pertussis vaccination in infancy and the development of asthma or allergy in a large birth cohort. The lack of association by multivariate analysis agrees with some of the more recent studies that have looked at cross-sectional or earlier childhood outcomes. The results of this study in older children are encouraging and provide additional evidence that the benefits of vaccination far outweigh any risks.

WANDA PHIPATANAKUL, MD, MS
Boston, MA

NO EPIDEMIOLOGICAL EVIDENCE FOR INFANT VACCINATION TO CAUSE ALLERGIC DISEASE


Purpose of the Study. Because the prevalence of allergic disease has increased in the last decades and one theory for the increase is immune dysregulation associated with hygiene and reduced infection, the study sought to determine if healthy children vaccinated at an early age have an increased risk for the development of allergic disease.

Methods. Epidemiologic studies with original data on the correlation between vaccination with diptheria, pertussis, tetanus (DPT), measles, mumps, rubella (MMR), and bacille Calmette-Guérin (BCG) immunizations in infancy and the development of allergic diseases were selected and reviewed for their quality and validity. To increase the likelihood of considering all relevant literature, Medline searches (from January 1966 to March 2003) were performed, bibliographic lists from retrieved articles were reviewed, and experts in the field were asked to identify relevant articles.

Results. Methodologic design and quality varied markedly between the studies reviewed. Ethical issues regarding vaccination precluded randomized, controlled trials (only 1 such study was found). Many studies did not address possible confounders such as the presence of lifestyle factors, which resulted in bias. The studies offering the stronger evidence indicate that the investigated infant vaccinations do not increase the risk of developing allergic disease. Furthermore, BCG does not seem to reduce the risk of allergies.

Conclusions. The authors concluded that the reviewed epidemiologic evidence indicates that current infant vaccines do not cause allergic diseases.

Reviewers' Comments. In an effort to reduce the risk of development of allergies, families knowledgeable about the “hygiene hypothesis” sometimes worry that vaccination of their children will increase the risk of allergic disease. Although most pediatricians can easily point out that vaccination carries clear advantages for their use and that a concern for allergy would not be a good reason to defer immunization, this analysis of available data additionally supports the argument that there is no evidence to indicate that childhood vaccinations are the cause of the increase in allergic disease in Westernized countries. There is likely a complex interplay of environmental factors contributing to the apparent skewing toward an allergic, or T-helper 2–dominant, immune response and the resulting increased prevalence of atopic disease.

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ALLERGENS AND ENVIRONMENTAL EXPOSURES

DOG ALLERGEN (Can f 1) AND CAT ALLERGEN (Fel d 1) IN US HOMES: RESULTS FROM THE NATIONAL SURVEY OF LEAD AND ALLERGENS IN HOUSING


Purpose of the Study. To estimate the levels of dog and cat allergens in US homes and provide the characteristics of households associated with these allergens.

Study Population. A total of 2456 individuals from 831 permanently occupied, noninstitutional housing units in 75 US locations that permit resident children.

Methods. Data for this study were obtained from the National Survey of Lead and Allergens in Housing conducted by the National Institute of Environmental Health Sciences and the US Department of Housing and Urban Development from 1998 to 1999. Vacuum-collected dust samples from a bedroom floor, bed, living room floor, living room sofa, or equivalent piece of upholstered living room furniture were analyzed for concentrations of primary dog allergen (Can f1) and primary cat allergen (Fel d1) in micrograms of allergen per gram of dust by using monoclonal antibody enzyme-linked immunosorbent assays. Housing and household characteristics were determined by questionnaire or observation. Bivariate associations between housing characteristics and the presence of an indoor dog and cat were examined.

Results. At the time of the survey, 55% had no cat or dog in the home for the past 6 months, 10% had both a cat and a dog, 21% had at least 1 dog and no cat, and 13% had at least 1 cat and no dog. The percentage of homes with an indoor dog was higher if they were outside of the Northeast US, were a single family, owned versus rented, had >1 occupant, had an income greater than $20 000.00 per year, and were white. The percentage of homes with an indoor cat was higher if they were in the Northeast or West or were white. A greater concentration of Can f1 was associated with single-family homes with >1 occupant, higher income levels, white race, and forced-air heating and air conditioning and presence of an indoor cat or dog. For Fel d1, a higher geometric mean concentration was associated with living in the West, being white, having an education above the high school level, and presence of an indoor dog or cat. The presence or absence of a cat had the greatest influence. Respectively, Can f1 and Fel d1 were detectable in 93.8% and 96.6% of beds, 95.6% and 96.9% of bedroom floors, 94.9% and 96.1% of living room floors, and 98% and 97.9% of sofas. Of the 97.7% of homes with detectable antigen, 99.9% had detectable Can f1 in at least 1 sample location. Of the 99% of homes with detectable antigen, 100% had detectable Fel d1 in at least 1 sample location. For Can f1 and Fel d1, 55.7% and 66% of US homes exceeded previously published sensitization threshold levels of >2 and >1 μg/g, respectively. Additionally, 34.9% and 34.7% of US homes exceeded the asthma-symptoms threshold for Can f1 and Fel d1.

Conclusions. Can f1 and Fel d1 are ubiquitous allergens in US homes. Levels associated with both sensitization and exacerbation of asthma are found even in homes without cats or dogs. Demographic groups associated with greater likelihood of pet ownership implicate the role of the community as a source of the allergens.

Reviewers' Comments. This study demonstrates the need for greater consideration of the role of dog and cat allergens in both the sensitization and symptom exacerba-
ALLERGEN AVOIDANCE DOES NOT ALTER AIRBORNE CAT ALLERGEN LEVELS IN CLASSROOMS


Purpose of the Study. To determine if feasible and economically defensible classroom interventions that do not interfere with pet ownership can alter airborne levels of cat allergen.

Study Population. Intermediate-level school classrooms (n = 25, grades 1–6) in a suburb north of Stockholm, Sweden. Only classrooms with a single group of students using the class during the study period were used. Flooring materials, ventilation, cleaning routines, and room size were similar. The mean number of children per classroom was 25 (range: 18–30), and 21% had cats at home.

Methods. Three categories of classrooms were compared: 14 control classrooms, 5 previously established allergy-prevention classrooms using criteria for allergen avoidance established by the Swedish National Institute of Public Health and Swedish Asthma and Allergy Association (ie, new building; increased cleaning routines; removal of upholstery, curtains, carpets, and plants; and replacement of open bookshelves with closed cupboards to reduce dust accumulation), and 6 were intervention classrooms. The study involved 1 school year divided into 2 terms. At the start of the second term, avoidance measures were introduced into the intervention classrooms. These classrooms were cleaned thoroughly, bookshelves were replaced with closed cupboards, curtains, upholstery, and plants were removed, upholstered staff chairs were treated with tannic acid, and fabric notice boards were coated with an acrylic paint. Classroom cleaning was increased from twice weekly to daily. Airborne dust was sampled continuously by using weekly Petri-dish collections and personal air-sampler collections. All dish samples and air samples were analyzed for cat allergen (Fel d1) by immunoassay.

Results. No significant difference was noted for airborne cat-allergen levels during the study period between allergy prevention, intervention, and control classes by either Petri-dish collection or personal air sampling. Additionally, there was no difference in cat-allergen level in the intervention classroom before or after the intervention measurement. Airborne cat-allergen levels were significantly lower in classes with few cat owners (<21%) compared with classes with many cat owners (>21%).

Conclusions. Multiple simultaneous allergen-avoidance measures failed to influence airborne cat-allergen levels. The number of cat owners associated with each classroom was the predominant factor contributing to the level of cat allergen found.

Reviewers’ Comments. Several studies have shown that pet allergens can be found in school classrooms. The relationship between cat-allergen level in classrooms and the number of cat owners per class has also been established. Indirect transfer of the allergen, primarily by clothing, has been implicated. In this study, practical, economical measures failed to impact the cat-allergen levels. Although clinical outcomes were not measured in this study, it is probable that no improvement would have been seen for cat-allergic children. These results suggest that, as the authors indicated in their concluding remarks, more significant interventions such as minimization of pet ownership and use and development of special clothing may be required for seriously pet-allergic children.

RESULTS OF A HOME-BASED ENVIRONMENTAL INTERVENTION AMONG URBAN CHILDREN WITH ASTHMA


Purpose of the Study. To determine if environmental modification reduces asthma morbidity in inner-city, atopic children.

Study Population. Asthmatic children (age range: 5–11 years) from inner cities who were skin-test positive to at least 1 of 11 indoor allergens. To be eligible for the study, the children had to have had 1 hospitalization or 2 unscheduled medical visits for asthma in the previous 6 months.

Methods. Nine hundred thirty-seven children with atopic asthma (age range: 5–11 years) in 7 major US cities were enrolled in a randomized, controlled trial of an environmental intervention that lasted 1 year and included education and remediation for exposure to both allergens and environmental tobacco smoke. Home environmental exposures were assessed every 6 months, and asthma-related complications were assessed every 2 months during the intervention and for 1 year after the intervention.

Results. For every 2-week period, the intervention group had fewer days with symptoms than did the control group during both the intervention year (3.39 vs 4.20 days; P < .001) and the year afterward (2.62 vs 3.21 days; P = .001). The intervention group had greater declines in the levels of allergens at home, such as Dermatophagoides farinae (Der f1) allergen in the bed (P < .001) and on the bedroom floor (P = .004), Dermatophagoides pteronyssinus in the bed (P = .007), and cockroach allergen on the bedroom floor (P < .001). Reductions in the levels of cockroach allergen and dust-mite allergen (Der f1) on the bedroom floor were significantly correlated with reduced complications of asthma (P < .001).

Conclusions. Among inner-city children with atopic asthma, an individualized, home-based, comprehensive environmental intervention decreases exposure to indoor allergens including cockroach and dust-mite allergens, resulting in reduced asthma-associated morbidity.

Reviewers’ Comments. Inner-city children with asthma are exposed to many indoor allergens. Reducing the concentrations of these allergens can be extremely challenging, and there has been limited evidence to prove the efficacy of such measures. This study demonstrates that aggressive environmental modification targeting specific allergens can reduce the asthma-related morbidity in this population. Asthmatic children allergic to cockroach and/or dust mite allergens are most likely to benefit from diligent environmental control.
PARENTAL MANAGEMENT OF ASTHMA TRIGGERS WITHIN A CHILD’S ENVIRONMENT


Purpose of the Study. To assess the type and frequency of attempts by families to control environmental precipitants of asthma symptoms and their degree of consistency with current National Heart, Lung, and Blood Institute (NHLBI) asthma guidelines.

Study Population. A nationwide sample of 896 children (ages 2–12 years) with asthma who had used asthma-related health care within the previous 2 years. Patients were selected randomly from the panels of 106 primary care clinicians participating in a trial to evaluate the effect of physician asthma education on health care utilization.

Methods. A cross-sectional, telephone-based survey was conducted. Respondents were asked open-ended questions to identify triggers for their child’s asthma and to describe specific actions taken to eliminate these triggers in the home. Demographic information regarding the caregiver was collected. Specific queries were used to discern patient asthma severity, if smokers resided in the home, and if the family had received asthma education from their primary care manager. Actions to address asthma triggers were categorized as recommended, reasonable, neutral, or not recommended based on NHLBI recommendations.

Results. Eighty percent of parents (717 of 896) could identify at least 1 asthma trigger (mean: 2.2; range: 0–9). Eighty-two percent (582 of 717) of these parents had attempted an environmental-control measure. Of the 1788 actions reported by these respondents, 51% were not likely to be useful for the specified trigger (eg, the purchase of an air filter when the environmental trigger reported would not likely be addressed by an air filter). Two hundred sixteen (24%) children lived with a smoker. Only 16 of these 216 families (7%) attempted to reduce or eliminate smoke exposure. No specific demographic characteristic predicted which parents were more likely to institute environmental controls. Characteristics positively associated with addressing triggers included receiving asthma education (odds ratio [OR]: 1.78; 95% confidence interval [CI]: 1.26, 2.52) and the number of primary care office visits in the last year (OR: 1.05; 95% CI: 1.00, 1.10).

Conclusions. More than half of the environmental modifications initiated by families are not consistent with current NHLBI guidelines. Despite the proven benefits of reducing tobacco-smoke exposure, few families reported any attempt to decrease smoke exposure. The lack of reliable correlation between an identifiable demographic group and environmental modification underscores the importance of education and encouragement in all families.

Reviews’ Comments. Physician contact and physician asthma education, rather than family education or finances, seemed to correlate with attempts at environmental modifications. However, it is unclear from this study if the modifications instituted were endorsed by physicians. The NHLBI guidelines describe tobacco smoke as the “most important environmental indoor irritant.” Tobacco smoke remains a difficult challenge. Continued effort by health care providers to encourage smoking cessation is essential.

Karla R. Lowe, MD
Cecilia P. Mikita, MD
Washington, DC

INCREASED PREVALENCE OF LATEX-SENSITIZATION AMONG CHILDREN WITH CHRONIC RENAL FAILURE


Purpose of the Study. To assess the prevalence of latex sensitization and identify risk factors for latex sensitization among children with chronic renal failure.

Study Population. Ninety-three patients (44 boys and 49 girls; median age: 10.5 ± 6.0 years) with chronic renal failure who presented to the University of Vienna Children’s Hospital Nephrology Clinic between 1997 and 2000.

Methods. Latex sensitization was assessed by a questionnaire-based history and measurement of total and latex-specific serum IgE by solid-phase immunoassay. Patients and parents were queried regarding the etiology of renal failure, age at onset, number of renal transplantations, surgical procedures, hemodialysis, clinical symptoms with latex exposure, personal and family history of allergy, and history of pacifier use. Patient responses were compared with medical histories and were consistent. Patients were designated as latex sensitized if their latex-specific serum IgE was ≥0.35 kilounits of allergen-specific IgE per liter (kU/A/L). Neither skin-prick testing nor provocation testing was performed.

Results. Of the 93 patients enrolled, 10 (10.8%) were found to have latex-specific IgE levels (0.35–9.44 kU/A/L). Of those, only 1 patient reported clinical symptoms on latex exposure compared with 4 patients with no demonstrable latex-specific IgE. No reactions to latex were reported to occur during medical care. A personal or family history of allergy, a greater number of urogenital surgeries, and hemodialysis were reported more frequently in latex-sensitized children. Gender, age at enrollment, age at first urogenital surgery, renal transplantation, and the use of pacifiers did not differ between latex-sensitized and -nonsensitized children.

Conclusions. The prevalence of latex sensitization among children with chronic renal failure is greater than that previously reported for the general pediatric population (10 of 93 vs 8 of 1175 in an unselected pediatric population). Eight of the 10 sensitized patients in this study had renal disease diagnosed within the first year of life and therefore had early and repeated exposures to latex. The small sample size prevented detection of significant associations with any determinant of renal disease or definite risk factor for sensitization.

Reviews’ Comments. Atopy and repeated exposure to latex allergen have been previously associated with sensitization to latex. Children with chronic renal failure are frequently exposed to latex and therefore are likely at increased risk. A larger study population would be required to further characterize this increased risk. This study raises interesting questions regarding the impact of both timing and cumulative amount of latex exposure for all children with chronic illnesses.

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FOOD ALLERGY

PREVALENCE OF PEANUT AND TREE NUT ALLERGY IN THE UNITED STATES DETERMINED BY MEANS OF A RANDOM DIGIT DIAL TELEPHONE SURVEY: A 5-YEAR FOLLOW-UP STUDY


Karla R. Lowe, MD
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Purpose of the Study. To determine the prevalence of self-reported peanut and tree-nut allergy among the general population of the United States in 2002 and compare it with prevalence rates obtained 5 years earlier.

Study Population. A total of 4855 households representing a census of 13 493 participated.

Methods. A nationwide, cross-sectional survey was administered by telephone to persons called by a random sampling of telephone numbers in the continental United States. Adults acted as surrogates for minors with peanut or tree-nut allergy. Differences in responses between groups were tested by χ² analysis.

Results. Fifty-three percent of contacted homes participated. Peanut allergy, tree-nut allergy, or both was self-reported in 166 (1.2%; 95% confidence interval [CI]: 1.0%, 1.4%) individuals in 155 (3.2%; 95% CI: 2.7%, 3.7%) households. These prevalence rates were similar to those reported in 1997. Any differences in prevalence rates between people of different race/ethnicity did not reach statistical significance. There was an overall male predominance of peanut or tree-nut allergy in children (P = .02) and a female predominance in adults (P = .0008). The prevalence of reported peanut allergy among children increased significantly from 0.4% in 1997 to 0.8% in 2002 (P = .05), but the rate of tree-nut allergy did not change significantly. The prevalence of peanut and tree-nut allergy in adults did not change significantly between 1997 and 2002. Overall, the adjusted prevalence rate taking into account individuals with reported allergy without convincing histories was 1.04% (95% CI: 0.9%, 1.2%). Of the reported reactions, 79% involved either respiratory symptoms or multiple organ systems. Only 74% of children and 44% of adults were evaluated by a physician for their allergic reactions, and self-injectable epinephrine was prescribed for 46% of the children and 23% of the adults.

Conclusions. The authors reported similar overall rates of peanut and tree-nut allergy in the United States, as was noted in 1997, but over this 5-year period the prevalence of peanut allergy in children doubled.

Reviewers’ Comments. The findings of increased prevalence of peanut allergy may be expected with the well-documented increase of atopic diseases in the past decades. Why the prevalence of tree-nut allergy would be unchanged during this same period will require additional investigation. A notable finding in this study is that >25% of children and 50% of adults who reported peanut or tree-nut allergy did not seek medical evaluation. Even more remarkable is that after medical evaluation for peanut or tree-nut allergy, self-injectable epinephrine was prescribed to approximately half of the children and less than one quarter of the adults. This underscores the need for continued improvement in the care of patients with food allergy, which is increasing in prevalence.

PEANUT ALLERGY: RECURRENCE AND ITS MANAGEMENT


Purpose of the Study. To determine the rate of peanut allergy recurrence, identify risk factors for recurrent peanut allergy, and develop specific recommendations for the treatment of patients with resolved peanut allergy.

Study Population. Children >4 years old with prior diagnosis of peanut allergy who had undergone and passed an oral peanut challenge.

Methods. Children were evaluated by using questionnaires, skin tests, and peanut-specific IgE levels. Patients were invited to undergo a double-blind, placebo-controlled food challenge (DBPCFC) unless the history of a possible recurrence reaction was so convincing that a challenge would be potentially dangerous.

Results. Sixty-eight patients were evaluated. Forty-seven patients continued to tolerate peanut, of whom 34 ingested concentrated peanut products at least once per month and 13 ate peanut infrequently or in limited amounts but passed a DBPCFC. The status of 18 patients was indeterminate because they ate peanut infrequently or in limited amounts and declined to have a DBPCFC. After excluding 12 patients originally diagnosed with peanut allergy based solely on a positive skin-prick test or peanut-specific IgE level, 3 of 15 patients who consumed peanut infrequently or in limited amounts had recurrences, compared with no recurrences in the 23 patients who ate peanut frequently (P = .025). The recurrence rate was 7.9 (95% confidence interval: 1.7%, 21.4%).

Conclusions. Children who outgrow peanut allergy are at risk for recurrence, and this risk is significantly higher for patients who continue largely to avoid peanut after resolution of their allergy. It is recommended that patients eat peanut frequently and carry epinephrine indefinitely until they have demonstrated ongoing peanut tolerance.

Reviewer’s Comments. Recent studies reported that up to 20% of peanut-allergic children may outgrow this condition, giving hope to many patients. Follow-up of the children who passed an oral peanut challenge showed that some children experienced acute allergic reactions to peanut some time after having passed a challenge. Children avoiding peanut were more likely to have recurrence of their peanut allergy than those ingesting peanut on a regular basis. The possibility of recurrence of peanut allergy and importance of regular dietary peanut intake should be discussed with patients and their parents when considering oral peanut challenges. It should be noted that recurrence has been reported solely for peanut and fish allergy, whereas recurrence of other food allergies such as those to cow’s milk, egg, soy, or wheat have not been described in the literature.

Anna Nowak-Wegrzyn, MD
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DISTRIBUTION OF PEANUT ALLERGEN IN THE ENVIRONMENT


Purpose of the Study. To determine the amount of peanut protein detectable in a variety of common exposure settings and examine the effectiveness of measures used to clean peanut from tables and hands.

Methods. A monoclonal-based enzyme-linked immunosorbent assay was used to detect 1 of the major peanut proteins (Ara h1) from surface-wipe samples of hands, tables, and other surfaces and from air samples.

Results. After purposeful handling of a teaspoon of peanut butter, hand-washing with liquid soap, bar soap, or commercial wipes resulted in no detectable Ara h1. However, using plain water without soap or an antibacterial hand sanitizer left detectable Ara h1 on 3 of 12 and 0 of 12 hands, respectively. Purposeful placement of a teaspoon of peanut butter on 1 square foot of tabletop followed by
cleaning resulted in no detectable Ara h1 when common household cleaning agents (such as Formula 409 or even plain water) were used; however, dishwashing liquid left Ara h1 on 4 of 12 tables (possibly by leaving a film). Six schools were assessed without special prior preparation (2 used peanut-free tables/preparation areas, and 1 was totally peanut-free). Of the 6 preschools and schools evaluated, Ara h1 was found on 1 of 13 water fountains (130 ng/mL), 0 of 22 desks, and 0 of 36 cafeteria tables. Airborne Ara h1 was undetectable in simulated real-life situations when participants consumed peanut butter, shelled peanuts, and unshelled peanuts.

Conclusions. The major peanut allergen, Ara h1, is relatively easily cleaned from hands and tabletops with common cleaning agents and does not seem to be widely distributed in preschools and schools. Airborne Ara h1 was not detectable in many simulated environments.

Reviewer’s Comments. A major concern for those with peanut allergy is the potential for reactions to casual contact. This study is reassuring in that areas tested without obvious peanut contamination generally had no detectable Ara h1, and eating surfaces and hands, purposefully smeared with peanut, were cleaned adequately with simple, available methods. A limitation of the study is that the assay detected only 1 of several peanut allergens, so the total amount of peanut allergen on these items is unknown. Nonetheless, in most cases no peanut was detectable, providing a level of reassurance for families. On the other hand, it is known that a very small amount (although typically a visible amount) of peanut, if ingested, could cause a severe reaction in some children. Therefore, caution would still be advised about exposure to peanut and the need for careful cleaning practices, particularly with young peanut-allergic children. These children may be around messy eaters and may be inclined to place contaminated fingers and other objects into their mouths.

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FOOD ALLERGY AND ATOPIC DERMATITIS IN INFANCY: AN EPIDEMIOLOGIC STUDY


Purpose of the Study. To examine the relationship between atopic dermatitis and IgE-mediated food allergy in infancy.

Study Population. A birth cohort of 620 infants from the Melbourne Atopy Cohort Study, a cohort with a family history of eczema, asthma, hay fever, or immediate food allergy in a parent or sibling.

Methods. A total of 487 children had complete data including skin-prick tests to evaluate IgE-mediated food allergy to cow’s milk, egg, and peanut at the age of 1 year. Participants were grouped as no atopic dermatitis (group 0) or in quartiles of increasing severity of atopic dermatitis (groups 1–4) quantified by days of topical steroid use as follows: group 0, 43 of 346; group 1, 4 of 36; group 2, 8 of 35; group 3, 12 of 35; group 4, 24 of 35; $x^2 = 76$; $P < 10^{-6}$). The frequency of reported adverse food reactions was as follows: group 0, 43 of 346; group 1, 4 of 36; group 2, 8 of 35; group 3, 5 of 35; group 4, 13 of 35 ($x^2 = 17$; $P = .002$). The relative risk of an infant with atopic dermatitis having IgE-mediated food allergy is 5.9 for the most severely affected group.

Conclusions. Atopic dermatitis is common in infancy. There is a strong association between IgE-mediated food allergy and atopic dermatitis in this age group.


Purpose of the Study. To evaluate the frequency of late-phase atopic dermatitis (AD) reactions to foods during double-blind placebo-controlled food challenges (DBPFCs) and correlate the results with food-specific IgE and patch tests.

Study Population. Sixty-four children aged 1 to 10 years (median: 2 years) with mild to severe AD evaluated in an outpatient dermatology and allergy department in Germany.

Methods. The inclusion criterion was suspicion of food-related AD by parents and/or a referring physician. The children underwent testing for food-specific IgE ($n = 64$). Allergen patch testing (APT) to suspected foods was performed if they did not have a rash on their back ($n = 41$). The first day was an incremental food challenge up to a full serving as tolerated, and on the second day the children were given a full dose of the food/placebo. The children were observed for 48 hours after the challenges. Reactions occurring within 6 hours were considered immediate, and those occurring after >6 hours were considered late reactions.

Results. A total of 106 food challenges were performed to milk, egg, wheat, or soy, with 64% of the children reacting to at least 1 food; of those who reacted, 83% reacted to only 1 food, 15% reacted to 2 foods, and 1 child reacted to 3 foods. The most common trigger was egg (62%), followed by milk (47%) and wheat and soy (35%) each. Immediate reactions occurred in 88% of the challenges. Late AD reactions were seen in 28 of 49 (57%) of positive challenges. Sensitivity of history in predicting immediate reactions was only 34%, and for late reactions only 25%; reactions to milk had the highest sensitivity (50–67%), and soy had the lowest (0%). In general, sensitivity (77% vs 68%), specificity (60% vs 50%), and positive predictive values (57% vs 33%) were higher for immediate reactions versus late reactions. Diagnostic accuracy of food-specific serum IgE was greater for children <2 years old. There was no difference in sensitivity (67%) or specificity (38%) of APT for predicting immediate or late AD reactions. The positive predictive value of APT was greater for immediate reactions (38% vs 24%). It is notable that 19% of patients reacted on day 2 of the challenge, having previously tolerated the food on day 1.

Conclusions. Food allergy should be considered in any child with AD who is not responding to standard therapy.

LATE ECZEMATOUS REACTIONS TO FOOD IN CHILDREN WITH ATOPIC DERMATITIS

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Allergy should be considered in any child with AD who is not responding to standard therapy.
with DBPCFCs still considered the “gold standard” for this diagnosis.

**Reviewer’s Comments.** This study adds support to the current literature demonstrating a link between food allergy and AD. The interesting finding of late reactions observed in this study should be considered, because most observation periods after food challenges are not generally that long.

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Baltimore, MD

**LYMPHOID NODULAR HYPERPLASIA AND COW’S MILK HYPERSENSITIVITY IN CHILDREN WITH CHRONIC CONSTIPATION**


**Purpose of the Study.** To investigate the incidence of cow’s milk allergy as evidenced by milk challenge and the findings of endoscopic and immunohistochemical examinations in children with chronic and refractory constipation.

**Study Population.** Thirty-five children aged 3 to 15 years with recalcitrant constipation and 15 control subjects.

**Methods.** All children underwent colonoscopy with visual inspection for lymphoid nodular hyperplasia. Mucosal samples were taken from the terminal ileum, cecum, transverse colon, and rectum. Biopsy specimens were evaluated for the presence of lymphoid nodules, lamina propria eosinophils, and mononuclear cells. Immunohistochemical staining was done for CD3 T cells, αβ and γδ T-cell receptor–bearing intraepithelial lymphocytes, and HLA-DR expression. Subjects were placed on a 4-week milk-elimination diet. Other recommendations included a fiber-rich diet and medical treatment with lactulose and sodium picosulfate. For those who responded to elimination, milk was used as a challenge in the ensuing 4-week period. Total serum concentrations of IgA and IgE were measured.

**Results.** Lymphoid nodular hyperplasia was the most prominent endoscopic finding and was detected in 46% of subjects. During the period of milk elimination/supportive medication, 83% of subjects remitted. Relapse occurred in 34% of children after challenge with milk. These children had significantly higher densities of intraepithelial γδ+ T cells (P < .001) in biopsy samples from the terminal ileum.

**Conclusions.** The authors concluded that these results indicate formal evidence of cow’s milk allergy in children with chronic constipation.

**Reviewer’s Comments.** It is fairly common that parents blame cow’s milk formulas for constipation. This study showed that a subset of children (those with higher densities of intraepithelial γδ+ T cells in the terminal ileum) whose constipation improved with a regimen that included cow’s milk avoidance had a relapse of constipation when reexposed to cow’s milk. These results are intriguing and suggest an immunologic link but do not provide formal evidence of cow’s milk allergy. Proof of cow’s milk hypersensitivity would require demonstration of specific recognition of cow’s milk protein by the immune system.

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**CORRELATION OF INITIAL FOOD REACTIONS TO OBSERVED REACTIONS ON CHALLENGES**


**Purpose of the Study.** Allergic reactions from food can range from mild urticaria to fatal anaphylaxis. There are no clinical or laboratory features that can be used to predict the severity of a subsequent allergic reaction. This study evaluates whether the organ system or the specific food involved in the initial allergic reaction predicts the outcome of a subsequent oral food challenge.

**Study Population.** All food-sensitive children with a history of a food-allergic reaction and a positive skin-test result who underwent food challenges at the Children’s Hospital of Philadelphia (Philadelphia, PA) over a 5-year period.

**Methods.** Open food challenges were offered to all patients with a history of food-allergic reactions and positive skin-test results. If the initial reaction was thought to be significant, the challenge was offered 1 year after their last reaction; if the initial reaction was equivocal, the challenge was performed earlier. The specific food, initial symptom on presentation, and reaction on open challenge were recorded and evaluated retrospectively.

**Results.** A total of 413 of 998 food challenges were positive. Milk, egg, and peanut accounted for 83% of the positive challenges. Milk, egg, and peanut were also more likely than soy or wheat to cause a multiorgan system reaction on challenge. Patients were most likely to experience symptoms similar to those experienced during their initial presentation. Allergy-test results did not reliably predict the severity of a reaction.

**Conclusions.** Milk, egg, and peanut are the most common foods associated with food challenges. A patient typically will experience a similar reaction on reexposure to the initial allergen. However, multiorgan system reactions can occur after any initial clinical presentation, with milk, egg, and peanut causing a greater proportion of multiorgan system reactions than other foods.

**Reviewer’s Comments.** Although subsequent food-allergic reactions were similar to previous ones, more severe reactions can occur. Many patients erroneously believe that subsequent reactions will automatically be more severe than the first. This study suggests that this is not the case. However, the results also support the instruction to families that subsequent reactions could be more severe. In the same context, the study results highlight the importance of educating parents on food-allergen avoidance and how to identify and treat allergic reactions, including the use of self-injectable epinephrine.

Helen Skolnick, MD
Princeton, NJ

**PREDICTION OF THE DEVELOPMENT OF TOLERANCE TO MILK IN CHILDREN WITH COW’S MILK HYPERSENSITIVITY**


**Purpose of the Study.** To investigate whether the development of tolerance to cow’s milk (CM) by the age of 4 years can be predicted with a skin-prick test (SPT) and measurements of total or specific IgE in the serum taken at the time of diagnosis of CM hypersensitivity (CMH).

**Study Population and Methods.** Infants with immediate (n = 95) or delayed (n = 67) challenge reactions to CM...
were prospectively followed to 4 years of age. CMH status was assessed annually by CM challenges, initially with double-blind placebo-controlled food challenges and subsequently with open food challenges.

**Results.** By the ages of 2, 3, and 4 years, children with delayed reactions developed tolerance to CM faster than those with immediate reactions (64%, 92%, and 96% vs 31%, 53%, and 63%, respectively). A wheal size of <5 mm in SPTs correctly identified 83% of 124 infants who developed tolerance to CM by the age of 4 years, and a wheal size of ≥5 mm in SPTs correctly identified 71% of 39 infants with persistent CMH. Milk-specific IgE of <2 kU/L correctly identified 82% of infants who developed tolerance to CM, and milk-specific IgE of ≥2 kU/L correctly identified 71% of infants with persistent CMH.

**Conclusion.** SPTs and milk-specific IgE in the serum are useful prognostic indicators of the development of tolerance to CM in infants with CMH.

**Reviewer’s Comments.** Previous investigations have reported certain SPT wheal sizes and milk-specific IgE levels that predict a high likelihood of tolerance developing in infants and children with IgE-mediated CM allergy. The Vanto et al article addresses this very important clinical issue. In general, the study design is well done, but it would have been preferable for the investigators to have been consistent throughout the investigation and performed double-blind placebo-controlled food challenges instead of using open food challenges at the assigned follow-up evaluations. In addition, there was a mixture of patients in this investigation with 1 group encompassing classic IgE-mediated CMH and the other group representing children with non–IgE-mediated and delayed hypersensitivity reactions to CM. Despite this, the investigation does demonstrate that SPT wheal size of <5 mm and milk-specific IgE of <2 kU/L are useful prognostic indicators for the development of tolerance in children with CMH. It does not come as any real surprise that the infants with the IgE-mediated form of CMH were more likely to have a more persistent involvement than those with the non–IgE-mediated (often delayed and isolated to gastrointestinal symptoms) form of CMH and who almost always become tolerant by the age of 4 years. These data should provide useful and practical information to the clinician who manages infants and children with CMH.

**John James, MD**
Fort Collins, CO

**DETERMINATION OF FOOD SPECIFIC IgE LEVELS OVER TIME CAN PREDICT THE DEVELOPMENT OF TOLERANCE IN COW’S MILK AND HEN’S EGG ALLERGY**


**Purpose of the Study.** To determine if monitoring food-specific IgE levels over time could be used as a predictor for determining when patients develop clinical tolerance.

**Study Population.** Eighty-eight patients with hen’s egg allergy and 49 patients with cow’s milk allergy who underwent repeated double-blind placebo-controlled food challenges were included in the study.

**Methods.** Using the Pharmacia CAP System FEIA, specific IgE (sIgE) levels to cow’s milk and hen’s egg were determined retrospectively from stored serum samples obtained at the time of the food challenges. Logistic regression was used to evaluate the relationship between tolerance development and the decrease in sIgE levels over a specific time period between the 2 challenges.

**Results.** Twenty-eight of the 66 egg-allergic and 16 of the 33 milk-allergic patients lost their allergy over time. The decrease in egg sIgE levels (P = .0014) was significantly related to the probability of developing clinical tolerance, with the duration between challenges having an influence (P = .06). For milk, there was also a significant relationship between the decrease in sIgE levels (P = .0175) and the probability of developing tolerance, but there was no significant contribution with regard to time. Stratification into those <4 years of age and those ≥4 years of age at time of first challenge revealed that the younger age group was more likely to develop clinical tolerance in relation to the rate of decrease in sIgE. The median food sIgE level at diagnosis was significantly lower for the group developing “tolerance” to egg (P < .001), and a similar trend was seen for milk allergy (P = .06). Using these results, a model for predicting the likelihood of developing tolerance in milk and egg allergy based on the decrease in food sIgE over time was constructed.

**Conclusions.** The rate of decrease in food sIgE levels over time was predictive for the likelihood of developing tolerance in milk and egg allergy. Using the likelihood estimates from this study could aid clinicians in providing prognostic information and in the timing of subsequent food challenges, thereby decreasing the number of premature and unnecessary double-blind placebo-controlled food challenges.

**Reviewers’ Comments.** The majority of children with milk and egg allergy eventually develop clinical tolerance; however, there are no reliable tools to predict when and in which patients this may occur. The authors demonstrated a relationship between the degree of decrease in food-specific IgE concentrations over time and the likelihood of developing tolerance. This may be a useful model, allowing clinicians to time food challenges appropriately and provide more prognostic information to patients.

**Julie Wang, MD**
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**MICROARRAY IMMUNOASSAY: ASSOCIATION OF CLINICAL HISTORY, IN VITRO IgE FUNCTION, AND HETEROGENEITY OF ALLERGENIC PEANUT EPITOPES**


**Purpose of the Study.** To develop a peptide microarray-based immunoassay to map IgE-binding segments (epitopes) of peanut allergens by using microliter quantities of serum.

**Study Population.** Sera from 77 peanut-allergic patients and 15 non–peanut-allergic control patients were analyzed.

**Methods.** A set of 213 overlapping 20-residue peptides was synthesized corresponding to the primary sequences of the major peanut allergens, Ara h1, Ara h2, and Ara h3. These were arrayed in triplicate along with the corresponding recombinant proteins onto glass slides and used for immunolabeling.

**Results.** The majority of patients (97%) had specific IgE to at least 1 of the recombinant allergens, and 87% had detectable IgE to sequential epitopes. Microarray mapping correlated well with previous studies. However, the analysis of individual patients revealed remarkable heterogeneity in the number and patterns of epitope recognition. High epitope diversity was found in patients with a history of more severe allergic reactions. Also, sensitization of
effector cells with more diverse IgE antibodies conferred greater reactivity to specific allergens.

Conclusions. The protein microarray immunoassay confirmed that Ara h1, Ara h2, and Ara h3 are major peanut allergens and allows for parallel epitope analysis. This has led to the discovery of an additional important epitope of Ara h1 and the recognition of a high degree of patient heterogeneity. This qualitative difference in epitope diversity might provide prognostic information about the patient.

Reviewers’ Comments. Current techniques for mapping large numbers of epitopes by using individual patient sera are relatively time consuming, labor intensive, expensive, and prone to error. However, such studies have been useful, because identification of certain IgE-binding segments correlates with clinical outcomes such as likelihood for an allergy to resolve. Peptide microarray technology is a novel assay that allows characterization of large numbers of individual patient samples simultaneously with minimal amounts of blood. Microarray technology may be a useful diagnostic tool to assess differences in epitope recognition among patients and may provide more prognostic information regarding patients’ peanut allergies. In addition, these assessments of allergens may speed the production of allergy vaccines engineered in the future.

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THE EFFECTS OF A DOUBLE BLIND, PLACEBO CONTROLLED, ARTIFICIAL FOOD COLOURINGS AND BENZOATE PRESERVATIVE CHALLENGE ON HYPERACTIVITY IN A GENERAL POPULATION OF PRESCHOOL CHILDREN


Purpose of the Study. To test whether food additives, specifically a limited number of food dyes and a preservative, have a pharmacologic effect on behavior irrespective of other characteristics of the child.

Study Population. This study started with 2878 children who were resident and registered with a general practitioner on the Isle of Wight, United Kingdom, on their third birthday. The dates of birth were between September 1994 and August 1996. After screening and the signing of consent forms, the eventual study population was 397, of which 277 completed most aspects of the study.

Methods. There were 2 scales used to assess hyperactivity: the Emotionality, Activity, and Sociability Hyperactivity Scale and the Weiss-Werry-Peters Activity Scale. Atopic status was determined by skin-test reactivity to house dust mites, grass pollen, cat, milk, egg, or peanut. The children were divided into 4 groups and entered into a randomized, placebo-controlled, double-blind, crossover challenge study. The groups were hyperactive and atopic, nonhyperactive but atopic, hyperactive but not atopic, and nonhyperactive and nonatopic. This was a 4-week study period that followed a lead-in week in which the diet was free of artificial colorings and sodium benzoate. During the second or fourth week they received either the placebo or the active challenge diet. During the day they would be required to drink 300 mL of a fruit juice that was placebo or contained a total of 20 mg (5 mg each) of sunset yellow, tartrazine, carmoisine, and ponceau 4R. The juice also contained 45 mg of sodium benzoate. The child’s behavior was assessed weekly in the clinic with validated tests, and the parents also rated behavior. Compliance was assessed and indicated that 81% of the children drank all or nearly all of the challenge drinks. There was also a “snack” diary in which parents reported ingestion of foods that contained artificial color or preservatives. From the original starting group of 397, 30% failed to complete all 4 weeks of the study.

Results. All 4 groups of children were similar in terms of gender, age at baseline testing, other behavior problems, and maternal age at leaving full-time education. There was no difference in the activity scores measured in the clinic during any time period of the study. However, parental ratings of behavior showed a reduction in hyperactive behavior when the food additives were removed from the diet. There was a significantly greater increase in hyperactive behavior reported by the parents during the active versus placebo phase of the challenge. These effects were not influenced by the presence or absence of hyperactivity in the child nor by the presence or absence of atopy.

Conclusions. There is an effect of artificial food coloring and benzoate preservative on the activity of 3-year-old children that is detectable by the parent but not at all detectable by an assessment of activity in the clinic. Subgroups are not made more vulnerable to this effect by prior level or history of hyperactivity or by atopy.

Reviewer’s Comments. This was a very different article to review. The authors have taken the gold-standard model of “testing” and applied it with behavior as the outcome. A potential problem is the fact that this was done at home and over an extended period of challenge and was not done solely in the clinic. Also, there is precious little “allergy” in the article notwithstanding the use of limited skin testing, the mention of IgE, and histamine. What is of note here is a very common issue for pediatricians. Not too infrequently do parents seek allergy referral for behavior issues. This is a vexing problem, and rarely is the issue an IgE-mediated condition. Also of note is that the dyes and preservatives are not available for skin testing. The take-home message that may be of help to a primary care provider includes the fact that being allergic to inhalants did not predispose the child to react to the additives. Another message in this study is that the tools and the situation that is offered in the office to assess behavior do not match the parental observations.

FREDERICK E. LEICKLY, MD
INDIANAPOLIS, IN

ANAPHYLAXIS AND INSECT ALLERGY

A POPULATION-BASED STUDY OF THE INCIDENCE, CAUSE, AND SEVERITY OF ANAPHYLAXIS IN THE UNITED KINGDOM


Purpose of the Study. To determine the incidence, severity, and causes of anaphylaxis in the United Kingdom.

Study Population. United Kingdom residents born between 1912 and 1999 who were registered in the General Practice Research Database between 1994 and 1999.

Methods. The General Practice Research Database includes demographic and clinical data provided by general practitioners in the United Kingdom. Inclusion criteria for this study were an age of <80 years and having at least 6 months of recorded data in the database. After all cases were identified, 70 cases were selected randomly to undergo a more detailed evaluation that included contacting the general practitioner involved in the case. The investigators defined anaphylaxis as an acute allergic reaction characterized by generalized urticaria, often accompanied
by swollen tongue, wheezing, flushing, gastrointestinal symptoms, or hypotension. The reaction was considered mild if the symptoms were primarily limited to generalized urticaria and did not require treatment in an emergency department; the reaction was considered to be moderate if a hospital or emergency department visit was initiated for treatment and the symptoms were treated with epinephrine; and the event was considered to be severe if there was hypotension.

**Results.** A total of 898 patients were identified, and a random sample of 70 (9%) cases with a coded diagnosis and 50 (43%) cases with a comment diagnosis underwent additional evaluation. Relevant information on the diagnosis was available for >90% of these cases. Criteria for anaphylaxis was met in 87 of the 120 cases, so that an estimated 675 cases of the total 783 were estimated to have confirmed anaphylaxis, resulting in an incidence of 8.4 cases per 100 000 person-years. Insect stings were responsible for 32% and medications for 30% of cases. Food was implicated in 22% of cases, and more than half of these were due to a tree nut or peanut. Severity of the cases was as follows: mild, 29%; moderate, 45%; severe, 9%; indeterminate, 17%. One death was identified.

**Conclusions.** In the United Kingdom, the estimated incidence rate of anaphylaxis was 8.4 cases per 100 000 person-years, and ~10% of these cases were life threatening.

**Reviewer’s Comments.** Although anaphylaxis is a relatively uncommon event, 10% of cases are characterized by hypotension. The estimated percentage of severe, life-threatening events would have been even higher if lower-airway symptoms were considered as a manifestation of severe anaphylaxis. Physicians evaluating patients with suspected allergic reactions should be prepared to treat life-threatening symptoms.

**ANAPHYLAXIS: A 7-YEAR FOLLOW-UP SURVEY OF 46 CHILDREN**


**Purpose of the Study.** To follow children with a previous history of anaphylaxis to determine the clinical course of this syndrome.

**Study Population.** A total of 76 children referred between 1994 and 1996 with clinical features of anaphylaxis, which included at least 2 indicators (hypotension, inspiratory dyspnea, urticaria/angioedema) within 2 hours of exposure of the suspected causative agents.

**Methods.** After a mean duration of 7 years, 46 (61%) children were interviewed by telephone.

**Results.** Of the 46 patients, 14 (30%) had experienced a recurrence of anaphylaxis. Ten had single episodes, 2 had 2 episodes, 1 had 3 recurrences, and 1 had 4 recurrences. None of the patients died or experienced biphasic reactions. Patients who were sensitive to at least 1 food allergen were more likely to have recurrent episodes of anaphylaxis than those without food sensitivity (93% vs 56%; *P* < .04). For 14 of the 46 who experienced recurrence of anaphylaxis, no specific cause was clearly associated with the recurrence. Children with atopic dermatitis at initial presentation (95% vs 31%; *P* = .004) and those with angioedema and urticaria at the time of the current study (93% vs 37%; *P* = .0002) were found to be at significantly higher risk for recurrent anaphylaxis.

**Conclusions.** Patients may have a greater risk for recurrent anaphylaxis if they have atopic dermatitis, angioedema, or urticaria and 1 positive food skin test.

**Reviewer’s Comments.** This is the first study to help define the natural history of pediatric anaphylaxis. It emphasizes the need for a thorough work-up, education, and provision of autoinjectable epinephrine in all of these patients.

**ELIZABETH MATSUI, MD**

**Baltimore, MD**

**CLINICAL FEATURES AND ANAPHYLAXIS IN CHILDREN WITH COLD URTICARIA**

Alangari AA, Twarog FJ, Shih MC, Schneider LC. *Pediatrics.* 2004;113:e313–e317

**Purpose of the Study.** To characterize the features of cold urticaria in children, focusing particularly on systemic reactions.

**Study Population.** Thirty children (chart reviewed) who were evaluated over a 3-year period in an academic allergy program and a private practice.

**Methods.** Cold urticaria was diagnosed based on the patient’s history and was supported by an ice-cube–challenge test using a standard protocol (17 of 30 positive). The degree of symptoms was categorized into 3 types: localized urticaria/angioedema, generalized urticaria and/or angioedema without hypotension or respiratory symptoms, or severe systemic reactions with episodes suggesting respiratory distress and/or hypotension.

**Results.** There were 17 females, and the mean age of patients was 12 years (range: 2–18.5 years). Mean age of onset of cold urticaria was 7 years. The duration of cold urticaria was 3.2 years (range: 0.5–13.5 years). Data on progression were available for 27 of the 30 patients. Symptoms resolved spontaneously in only 2 patients. Swimming was the only trigger in 10 of the 30 patients; touching cold objects triggered urticaria in 9 patients; and cold weather was a trigger for the remaining 11 patients. Six of the patients experienced other causes of urticaria. The rate of atopic disease in the patient’s families was 89.3%. Response to antihistamine was variable, with 24 of 30 patients responding (8 had a poor response, 7 had a moderate response, and 9 had a good response).

**Conclusions.** Cold urticaria occurs in children and may be associated with anaphylaxis. No secondary causes were found. The primary determinants for reactions were body surface area exposed, temperature, and duration of exposure. All patients with cold urticaria were counseled and received autoinjector epinephrine.

**Reviewer’s Comments.** The natural history of cold urticaria, which seems to be primarily idiopathic, has not been well defined in children. There seems to be a higher rate of personal atopy and a family history of atopy in the patients. Counseling should include caution regarding aquatic activity, the most common trigger.

**BRADLEY E. CHIPPS, MD**

**Sacramento, CA**

**OUTCOMES OF ALLERGY TO INSECT STINGS IN CHILDREN, WITH AND WITHOUT VENOM IMMUNOTHERAPY**

Purpose of the Study. To determine if children outgrow their allergy to insect stings and to determine the long-term efficacy of venom immunotherapy.

Study Population. Subjects included were patients who had a reaction after an insect sting as a child. Reactions varied in severity and included large local reaction, mild (cutaneous) systemic reaction, and moderate-to-severe systemic reactions. Patients in the study either received venom immunotherapy or did not receive venom immunotherapy after their initial reaction.

Methods. Between 1978 and 1985, allergic reactions to insect stings were diagnosed in 1033 children, of whom 356 received venom immunotherapy. A survey of these patients was conducted by telephone and mail between January 1997 and January 2000 to determine the outcome of stings that occurred in the period from 1987 to 1999.

Results. Of the 1033 patients, 512 (50%) responded, with a mean follow-up period of 18 years, a mean duration of venom immunotherapy of 3.5 years in treated patients, and a sting incidence of 43%. Systemic reactions occurred less frequently in patients who had received venom immunotherapy (2 of 64 patients [3%]) than in untreated patients (19 of 111 patients [17%]; P = .007). Patients with a history of moderate-to-severe reactions had a higher rate of reaction if they had not been treated (7 of 22 patients [32%]) than if they had received venom immunotherapy (2 of 43 patients [5%]; P = .007). In patients who had been treated and had a history of mild (cutaneous) systemic reaction, none of the 21 subjects who received stings had a systemic reaction; however, there was not statistical significance between the rates of reaction when comparing the treated versus the untreated groups. Among the patients who had not received venom immunotherapy, there were no severe systemic reactions after a subsequent sting. Twenty-seven percent of patients who had moderate-to-severe initial reactions sustained subsequent reactions of similar severity (otherwise, the reactions were less severe), and 67.0% of patients with initial mild (cutaneous) systemic reactions developed moderate systemic reactions on subsequent stings (otherwise, the reactions were less severe than the original [87% had no subsequent systemic allergic reaction]).

Conclusions. A clinically important number of children do not outgrow allergic reactions to insect stings. Venom immunotherapy in children leads to a significantly lower risk of systemic reaction to stings even 10 to 20 years after treatment is stopped, and this prolonged benefit is greater than the benefit seen in adults.

Reviewers’ Comments. This study demonstrates that a significant number of children do not outgrow their insect allergy and that venom immunotherapy can have long-lasting protective effects. Venom immunotherapy should be offered to children with systemic reactions who test positive for venom-specific IgE (performed by skin testing and serum tests only if skin tests are negative); however, it is not usually recommended for children ≤16 years old who have generalized cutaneous reactions without other symptoms. Venom immunotherapy is also generally not recommended for persons with large local reactions. The study emphasizes the important role of allergen immunotherapy in the treatment of a potentially fatal allergic disorder.

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scores to differentiate pediatric patients with and without CRS based on radiographic criteria. Based on these data and analysis, we can use the CT scan to discriminate between children with and without CRS. Nevertheless, the positive and negative predictive values of this test are substantially dependent on the prevalence of CRS, and this must be factored into clinical decision-making. This study highlights the fact that CRS is primarily a clinical diagnosis, and both the decision to perform a sinus CT and the interpretation of the scan should include this clinical context.

SARA I. PAI, MD, PhD
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Baltimore, MD

EFFECTIVENESS OF ADENOTONSILLECTOMY IN CHILDREN WITH MILD SYMPTOMS OF THROAT INFECTIONS OR ADENOTONSILLAR HYPERTROPHY: OPEN, RANDOMISED CONTROLLED TRIAL


Purpose of the Study. To evaluate the effectiveness of adenotonsillectomy in children with a small number of recurrent sore throat infections or with mild obstructive symptoms from adenotonsillar hypertrophy.

Study Population. Three hundred otherwise healthy children in the Netherlands, aged 2 to 8 years, who were being considered for adenotonsillectomy to treat recurrent throat infections or obstructive symptoms. Excluded from the study were children with frequent throat infections (>7 in the past year, ≥5 in each of the past 2 years, or ≥3 in each of the past 3 years), children with suspected obstructive sleep apnea (as indicated by a Brouillette score of >3.5), and children with craniofacial anomalies, Down syndrome, and certain immunodeficiencies.

Methods. Subjects were randomized to receive surgical intervention with adenotonsillectomy within 6 weeks or observation. Patients were followed at regular intervals for 2 years, and outcomes were assessed by review of disease-specific diaries and quality-of-life surveys. The primary outcome measure was incidence of fever; secondary outcomes were frequency of sore throats, upper respiratory infections, school or day care absence resulting from upper respiratory infection, health-related quality of life, sleeping and eating patterns, height, and weight.

Results. Over a mean follow-up period of 22 months, children in the adenotonsillectomy group compared with children in the watchful-waiting group as follows: 2.97 fevers per person-year compared with 3.18 (difference: −0.21, 95% confidence interval [CI]), 0.38 throat infections compared with 0.77 (difference: −0.21, 95% CI), and 3.45 upper respiratory tract infections compared with 6.60 (difference: −0.35, 95% CI). The subgroup of patients with 3 to 6 throat infections in the preceding year did show more pronounced results than the subgroup of 0 to 2 infections. Health-related quality-of-life scores revealed no clinical differences at 2 years. The Brouillette score of obstructive sleep apnea was lower in the group receiving surgery after 6 months but not at 24 months.

Conclusions. Adenotonsillectomy in young children with mild symptoms of sore throat or adenotonsillar hypertrophy has no major clinical benefit after 2 years of follow-up.

Reviewers' Comments. Adenotonsillectomy is one of the most common surgical procedures performed on children, and these authors noted a tonsillectomy rate in the Netherlands more than twice that seen in the United States. The children in this study do not have the well-established indications for adenotonsillectomy, namely very frequent pharyngitis or documented obstructive sleep apnea. It is certainly not a new concept that only modest benefits are afforded by adenotonsillectomy to children "moderately affected" by throat infection (see Pediatrics. 2002;110:7–15). This study supports continued use of well-defined severity criteria to select children for treatment with adenotonsillectomy, because sustained major benefits of surgery were not demonstrated in children with mild illnesses. However, more than 34% of the children randomized to observation in this study underwent adenotonsillectomy during the follow-up period. The analysis of outcomes was performed based on initial randomization, not on the eventual treatment. We are also concerned that children with mild obstructive symptoms of adenotonsillar hypertrophy may have upper airway resistance or obstructive sleep apnea of physiologic consequence. These children may need additional evaluation and/or consideration for adenotonsillectomy to avoid complications of upper airway obstruction.

KARIN S. HOTCHKISS, MD
DAVID E. TUNKEL, MD
Baltimore, MD

SIMILAR ALLERGIC INFLAMMATION IN THE MIDDLE EAR AND THE UPPER AIRWAY: EVIDENCE LINKING OTITIS MEDIA WITH EFFUSION TO THE UNITED AIRWAYS CONCEPT


Purpose of the Study. To determine if the middle-ear compartment may be a component of the united airways in allergic disease by comparing the inflammatory profiles of the middle ear to the upper airway.

Study Population. Children (aged 2–18 years) undergoing myringotomy, tympanostomy tube placement, and adenoidectomy were recruited prospectively and consecutively for the study. All children had documented conductive hearing loss, flat tympanograms, and middle-ear effusions that persisted for >3 months and were unresponsive to antibiotics and symptomatic nasal obstruction caused by adenoid hypertrophy.

Methods. Middle-ear effusions, torus tubarius (eustachian tube mucosa at the nasopharyngeal orifice), and adenoidal tissue biopsies were obtained from 45 patients undergoing simultaneous tympanostomy tube placement for otitis media with effusion (OME) and adenoidectomy for adenoid hypertrophy. The cellular and cytokine profiles of each site were investigated by using immunocytochemistry (elastase, CD3, major basic protein) and in situ hybridization (interleukin [IL]-4, IL-5, interferon [IFN]-γ mRNA). Allergic sensitization to 12 common perennial and seasonal airborne allergens was determined with skin-prick testing.

Results. Of the 45 patients with OME, 11 (24%) were atopic. The middle-ear effusions of atopic patients had significantly higher levels of eosinophils, T lymphocytes, and IL-4 mRNA+ cells (P < .01) and significantly lower levels of neutrophils and IFN-γ mRNA+ cells (P < .01) compared with nonatopic patients. The nasopharyngeal tissue biopsies revealed similar cellular and cytokine profiles.

Conclusions. In atopic patients with OME, the allergic inflammation occurs on both sides of the eustachian tube,
Efficacy of Sublingual Immunotherapy in Children with Severe Grass Pollen Allergic Symptoms: A Double-Blind Placebo-Controlled Study


Purpose of the Study. To determine the clinical efficacy of high-dose sublingual immunotherapy (SLIT) in children with grass-pollen allergy by using a double-blind placebo-controlled study.

Study Population. A total of 161 children with seasonal rhinoconjunctivitis, 82 in the treatment group and 79 in the placebo group, were enrolled from 33 centers in Germany.

Methods. For the first year, patients were given either treatment or placebo; for the remaining 2 years, all patients were given treatment in an open-controlled manner. Symptom scores and medication usage were assessed during the pollen seasons and combined to determine a clinical index (CI), the primary end point of the study. Titrated skin-prick tests and specific IgE and IgG subclass antibodies were measured each year.

Results. A total of 132 patients completed the study. Analysis after 1 year of SLIT and analysis of the change in CIs during the 3 grass-pollen seasons showed that there was no significant difference in the CIs between the treatment and placebo groups. However, subgroup analysis in a repeated-measures model revealed that patients with SLIT and severe symptoms before beginning treatment showed a 30% improvement after 3 years, compared with 10% improvement in the placebo group. Allergen-specific IgE and IgG subclass antibodies increased in both the treatment and placebo groups.

Conclusions. Efficacy of SLIT could only be seen in children with severe clinical symptoms after 3 years of therapy. There was also a significant placebo effect.

Reviewers’ Comments. SLIT is readily given to allergic patients in European countries, but its use in the United States is limited. SLIT use in children is an attractive alternative to subcutaneous injections, given its lack of pain and decreased chance of systemic adverse effects. Although early controlled studies analyzing SLIT did not demonstrate clear clinical effects, SLIT has proved to have some reproducible value in adults, and a small number of other studies have also shown it to be effective in children. Only additional long-term comparative studies will show whether SLIT can compete with the established subcutaneous treatment.

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PREVALENCE OF MIGRAINE IN PATIENTS WITH A HISTORY OF SELF-REPORTED OR PHYSICIAN-DIAGNOSED “SINUS” HEADACHE


Purpose of the Study. Symptoms referable to the sinus area are frequently reported during migraine attacks but are not recognized in diagnostic criteria. Underrecognition of migraine may be partly attributed to a variable clinical presentation, and migraines with “sinus” symptoms contribute to this problem. This study was conducted to determine the prevalence of migraine-type headache (International Headache Society [IHS]-defined migraine without aura [IHS 1.1], migraine with aura [IHS 1.2], or migrainous disorder [IHS 1.7]) in patients with a history of self-described or physician-diagnosed “sinus” headache.

Patient Population and Methods. During a clinic visit, patients with a history of “sinus” headache, no previous diagnosis of migraine, and no evidence of infection were assigned an IHS headache diagnosis on the basis of headache histories and reported symptoms.

Results. A total of 2991 patients were screened. The majority (88%) of these patients with a history of self-described or physician-diagnosed “sinus” headache were diagnosed at the screening visit as fulfilling IHS migraine criteria (80% of patients) or migrainous criteria (8% of patients). The most common symptoms referable to the sinus area reported by patients at screening were sinus pressure (84%), sinus pain (82%), and nasal congestion (65%).

Conclusions. In this study, 88% of patients with a history of “sinus” headache were determined to have migraine-type headache. In patients with recurrent headaches without fever or purulent discharge, the presence of sinus-area symptoms may be part of the migraine process. Migraine should be included in the differential diagnosis of these patients.

Reviewers’ Comments. There is not much question that patients with chronic rhinosinusitis can have facial pain and headache. However, as allergists, we are often presented with patients who have little or minimal nasal symptoms and/or normal sinus radiographs who complain of “sinus pain.” This study confirms the results of at least one earlier report, strongly suggesting that, in this context, the overwhelming majority of sinus pain really is a form of migraine. Because activation and sensitization of the trigeminal vascular system is the primary mechanism of pain in migraines, nasal congestion, rhinorrhea, and ocular symptoms can accompany the headaches.

Allen Adinoff, MD
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Asthma

PATHOPHYSIOLOGY

PERSISTENCE OF ASTHMA SYMPTOMS DURING ADOLESCENCE: ROLE OF OBESITY AND AGE AT THE ONSET OF PUBERTY


Purpose of the Study. To evaluate factors that may influence the persistence or remission of childhood asthma after the onset of puberty.


Methods. The population underwent a series of evaluations and questionnaires at years 2, 3, 6, 8, 11, 13, and 16. Questions regarding the onset of puberty appeared at years 13 and 16. Questions were also asked about the presence and frequency of wheezing. Onset of puberty was defined by parental report of early signs; asthma was defined by frequent wheezing or any wheezing with a physician-confirmed diagnosis. Infrquent wheezing was defined by <3 episodes in the previous year. The category of “unremitting” was applied if any wheezing was reported after the onset of puberty and “remitting” if no wheezing was reported.

Results. Information on wheezing before and after the onset of puberty was available for 781 subjects. In this cohort, 401 (51%) never experienced wheezing, and 83 (11%) reported wheezing after the onset of puberty. Of the 297 who were wheezing before puberty, 131 (44%) had only infrequent wheezing; and 166 (21%) fulfilled the definition for asthma. Most children (92 of 131 [70%]) with infrequent wheezing experienced remission after puberty. Of those children with the diagnosis of asthma in the prepubertal period, 97 (58%) of the 166 had wheezing episodes after the onset of puberty, and 69 (42%) had remitting asthma. The early onset of puberty was associated with the persistence of asthma into adolescence and with children in the unremitting-wheezing and asthma groups having the onset of puberty significantly earlier than children in the corresponding remitting groups (unremitting wheezing/remitting asthma = 11.74/11.95 years versus remitting wheezing/remitting asthma = 12.34/12.7 years). The mean body mass index was significantly higher in unremitting-wheezing/asthma groups compared with remitting groups at each point over 10 years of surveys. Other factors associated with the persistence of symptoms included the amount of wheezing in the per-pubertal period and the presence of active sinus disease and rhinitis in the year before the survey. There were a limited number for whom a measure of airway hyperresponsiveness was available. In the unremitting-wheezing group, 27% had a positive methacholine challenge, and in the unremitting-asthma group, 68% were positive. Persistence of wheezing and asthma into adolescence was also associated with a positive skin test to the mold Alternaria. Children sensitized before puberty were 1.6 to 2.0 as likely to experience unremitting wheezing/asthma into adolescence.

Conclusions. Overall, 30% of children with infrequent wheezing and 60% of children with asthma in the prepubertal period will keep experiencing wheezing in the first 4 years after the onset of puberty. The prepubertal risk factors for the persistence of asthma include presence of frequent or continuous wheezing, obesity, early-onset puberty, active sinus disease, and skin-test sensitization.

Reviewer's Comments. How often has it been said that a child will “outgrow” their asthma during adolescence? Where is the evidence that supports such a statement? This study challenges that notion. This is an excellent and very informative work by a group that has continued to advance our understanding of the natural history of wheezing and asthma in children. A potential limitation is that these findings may be “population specific.” As most good studies do, this one begs for verification in other populations and regions in the country.

FREDERICK E. LEICKLY, MD
Indianapolis, IN

IS OBESITY ASSOCIATED WITH ASTHMA IN YOUNG CHILDREN?


Purpose of the Study. The aim of this study was to evaluate the association between obesity and asthma.

Study Population. A population-based sample of Canadian schoolchildren.

Methods. Baseline data from the National Longitudinal Survey of Children and Youth were used in this cross-sectional study. The investigators included 11 199 children aged 4 to 11 years whose biological mothers reported data on asthma, height, and weight. Body mass index was categorized, and obesity was defined as a body mass index in the 85th percentile. Children with asthma had parents who reported the diagnosis, and they took prescribed inhalants, had wheezing or an attack in the previous year, or had their activities limited by asthma. Multiple logistic regression was used.

Results. The prevalence of asthma was 9.9%. Maternal history of asthma was a risk factor for asthma among all children. Single-child status and maternal depression were risk factors for girls. The odds ratio for asthma, comparing highest and lowest body-mass-index categories, was 1.02 (99% confidence interval: 0.70, 1.46) for boys and 1.06 (99% confidence interval: 0.67, 1.69) for girls.

Conclusions. This study suggests that there is no statistical association between obesity and asthma among 4- to 11-year-old Canadian children.

Reviewer’s Comments. This article addresses a highly contentious issue, focusing on the possible association between obesity and asthma, which has been investigated in both pediatric and adult populations. Both asthma and obesity are common chronic conditions, and in recent years, the prevalence of both of these conditions has increased in North America. Although a number of published studies have documented a positive association between obesity and asthma prevalence and incidence in adults, results from pediatric studies have not been consistent. There has been no clear explanation or consensus for this discrepancy. In this investigation, To and colleagues did not find a significant statistical association between obesity and asthma prevalence and incidence in adults, results from pediatric studies have not been consistent. There has been no clear explanation or consensus for this discrepancy. In this investigation, To and colleagues did not find a significant statistical association between obesity and asthma, but they did find that the single-most important risk factor for asthma was a maternal history of asthma, which has been a common, consistent finding in other pediatric asthma studies. Additional studies in pediatric populations addressing this issue will likely continue and hopefully will help to resolve whether there is a real association between obesity and asthma in children.

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EFFECT OF BODY SIZE ON BREATHING PATTERN AND FINE-PARTICLE DEPOSITION IN CHILDREN

Bennett WD, Zeman KL. J Appl Physiol. 2004;97:821–826

Purpose of the Study. The fractional deposition (DF) of fine particles was measured in the lower airways of healthy children during their resting breathing pattern to allow for additional investigation of the epidemiologic link between airborne particulates and respiratory morbidity in children.

Study Population. The study included 36 children, aged 6 to 13 years, with no acute respiratory infections within the past 4 weeks or previous history of lung disease.

Methods. To avoid the higher minute ventilation induced in children by breathing on a mouthpiece, resting breathing pattern was measured by respiratory inductance plethysmography using elastic inductance bands around the chest and abdomen with expansion and contraction calibrated to spirometry. The DF of 2-μm carnauba wax aerosol was then measured by using light-scattering photometry at the mouth, with the child breathing according to their previously determined resting breathing pattern. The numbers of inhaled and expired particles were calculated as a function of the inspiratory and expiratory times, tidal flow, and particle concentrations, and the DF was reported as the proportion of particles not expired. The rate of particle deposition (D$_{95}$) was a function of the DF and the minute ventilation.

Results. There was good correlation between resting breathing pattern measured by respiratory inductance plethysmography and the breathing pattern measured during DF ascertainment. The mean DF was 0.22 ± 0.10, similar to resting DF measured in adults in previous studies. Tidal volume was the best predictor of DF (r = 0.79; P < .001), and DF was also correlated with body mass index (BMI) (r = 0.47; P = .004). Children with a BMI in the >95th percentile had nearly twice the DF of those with a BMI in the <25th percentile (0.28 ± 0.13 vs 0.15 ± 0.06; P < .02). Resting minute ventilation was also higher in the overweight children (8.5 ± 2.2 vs 5.9 ± 1.1 L/min; P < .01). D$_{95}$ was correlated with BMI (r = 0.46; P = .004) and was 2.8 times higher in children with a BMI in the >95th percentile compared with those with a BMI in the <25th percentile (P < .02).

Conclusions. Children with higher BMIs may be at greater risk of respiratory morbidity associated with inhalation of airborne fine-particulate matter.

Reviewers’ Comments. A focus of this study was the determination of resting particle deposition; however, the higher minute ventilation seen with traditional mouthpiece breathing in children may be a closer approximation of how a child would breathe during activity. Assessment of fine-particle deposition during both types of breathing patterns may provide useful information. The higher resting rate of 2-μm particle deposition in children with enlarged BMIs suggests that fine particulates may make a greater contribution to respiratory morbidity in obese children, possibly contributing to the association between obesity and the incidence of asthma symptoms. Additional study of a larger number of children, including those with a BMI of >30, would be helpful to confirm these findings.

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AEROBIC EXERCISE ATTENUATES AIRWAY INFLAMMATORY RESPONSES IN A MOUSE MODEL OF ATOPIC ASTHMA


Purpose of the Study. To determine the effect of moderate aerobic exercise on pulmonary inflammatory responses in a mouse model of atopic asthma.

Methods. BALB/cj mice were assigned to 1 of 4 groups: sedentary and nonsensitized, sedentary and ovalbumin (OVA) sensitized, exercised and nonsensitized, and exercised and OVA sensitized. Sensitized mice were boosted with nebulized OVA for the duration of the study, and nonsensitized mice received nebulized saline. Mice assigned to the exercise group ran on a motorized treadmill 3 times a week for 4 weeks, for up to 45 minutes. Mice were euthanized 24 hours after completing the exercise regimen, and their lungs were fixed, stained, and assessed for the extent of the leukocytic infiltrate, epithelial cell hypertrophy, goblet cells and mucin production, and the nuclear factor κB (NF-κB) subunit p65. Bronchoalveolar lavage (BAL) fluid was collected, and leukocyte counts and protein content were quantified. Cytokine and chemokine levels were quantified by enzyme-linked immunosorbent assay (ELISA). Serum was collected and analyzed for total IgE and OVA-specific IgE by ELISA.

Results. Exercised, sensitized mice had a statistically significantly decreased cellular infiltrate, epithelial hyperplasia, and goblet cells and mucin production compared with sedentary, sensitized mice. Exercise also decreased the total BAL fluid protein in sensitized mice. Exercised, sensitized mice had significantly fewer macrophages, lymphocytes, neutrophils, and eosinophils in BAL fluid samples than sedentary, sensitized mice. Exercise also decreased KC (murine homolog of interleukin [IL]-8) levels in sensitized mice to the baseline levels observed in nonsensitized mice but had no effect on monocyte chemoattractant protein 1 levels. Exercise did not reduce intercellular adhesion molecule 1 expression in lung epithelium of sensitized mice. Exercise did not reduce intercellular adhesion molecule 1 expression in lung epithelium of sensitized mice. Exercise also decreased BAL fluid levels of the T-helper 2 cytokines, IL-4 and IL-5, by 13- and 3-fold, respectively. Exercised, sensitized mice had lower levels of OVA-specific IgE levels but not total IgE levels than sedentary, sensitized mice. Exercise also decreased nuclear translocation of NF-κB, a molecule that is involved in transcriptional activation of inflammatory genes.

Conclusions. Moderate aerobic exercise attenuates airway inflammation by decreasing NF-κB activation. Aerobic exercise is a promising treatment for asthma.

Reviewer’s Comments. Although several observational studies have suggested that aerobic exercise improves lung function and decreases asthma symptoms, it has been unclear if exercise had a direct effect on the pulmonary inflammatory response that is characteristic of asthma. The findings in this article, however, suggest that aerobic exercise may directly inhibit pulmonary inflammatory responses. Aerobic exercise would be an attractive, nonpharmacologic treatment option if proven to be effective in human trials.

ELIZABETH MATSUI, MD
Baltimore, MD

THE EFFECT OF AIR POLLUTION ON LUNG DEVELOPMENT FROM 10 TO 18 YEARS OF AGE

Purpose of the Study. To determine if long-term exposure to air pollution adversely affects the growth of lung function during rapid lung development and if it has clinically significant adverse effects on final lung function attained during adolescence.

Study Population. Fourth-grade children (average age: 10 years) were enrolled and followed prospectively for 8 years.

Methods. Fourth-grade children (n = 1759) were recruited from elementary schools in 12 communities of southern California. Spirometric data were attained annually for 8 years. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and midexpiratory flow rate were evaluated. The attrition rate of subjects was ~10% of subjects per year. Air pollution–monitoring stations were set up in the 12 study communities to measure exposures to ozone, acid vapor, nitrogen dioxide, particulate matter, elemental carbon, and organic carbon. Linear regression was used to examine the relationship of air pollution to the FEV1 and other spirometric measures.

Results. Over the 8-year period, deficits in the growth of FEV1 were associated with exposure to nitrogen dioxide (P = .005), acid vapor (P = .004), particulate matter with an aerodynamic diameter of <2.5 μm (PM2.5) (P = .04), and elemental carbon (P = .007) even after adjustment for several potential confounders and effect modifiers. Associations were also observed for other spirometric measures. Exposure to pollutants was associated with clinically and statistically significant deficits in the FEV1 attained at the age of 18 years. For example, the estimated proportion of 18-year-old subjects with a low FEV1 (defined as a ratio of observed to expected FEV1 of <80%) was 4.9 times as great at the highest level of exposure to PM2.5 as at the lowest level of exposure (7.9% vs 1.6%; P = .002). Exposure to ozone was not proven to be a contributor to lung-function deficit.

Conclusions. The results of this study indicate that current levels of air pollution in the communities evaluated have chronic, adverse effects on lung development in children from the age of 10 to 18 years. This long-term exposure leads to clinically significant deficits in attained FEV1 as children reach adulthood.

Reviewers’ Comments. This prospective study illustrates how exposure to air pollutants negatively impacts the progression of lung function. From a public health perspective, it is important to consider and ameliorate environmental exposures that can have an adverse effect on final attainment of lung function.

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

Characterization of a Common Susceptibility Locus for Asthma-Related Traits


Purpose of the Study. Susceptibility to asthma is known to be hereditary, but the specific genes that determine the risk for asthma are not understood completely.

Study Population. The initial studies were conducted on a geographically isolated cohort in northern Finland, and the genetic associations were then confirmed in a separate cohort from Quebec. Finally, a mouse model of ovalbumin-induced lung inflammation was used to address mechanistic questions.

Methods and Results. Positional cloning was used to identify a 133-kilobase segment containing 2 genes that were associated with asthma risk and high IgE. One of these genes coded for a G protein-coupled receptor named G protein-coupled receptor for asthma susceptibility (GPRA); the B isoform of this protein was found to be elevated in bronchial biopsies and smooth muscle from asthmatic individuals. Lung tissue of sensitized mice also expressed higher levels of GPRA mRNA.

Conclusions. Together, these data implicate GPRA in the pathogenesis of atopy and asthma and provide a novel therapeutic target for these disorders.


Purpose of the Study. To evaluate the role of vascular endothelial growth factor (VEGF) in T-helper type 2 (Th2) cell-mediated airway inflammation.

Study Population. Lung-targeted VEGF165 transgenic and wild-type mice.

Methods. Phenotypes of transgenic mice with elevated VEGF induced by doxycycline were studied and compared with wild-type mice. Airway histologic and physiologic assessments with special stains of microvasculature, epithelium cells, inflammatory cells, smooth muscle cells, and dendritic cells (DCs) were performed.

Results. Both Th2 and epithelial cells were primary sources of VEGF. Mice with overexpressed VEGF in the airways demonstrated increased neovascularization, mucous gland metaplasia, edema, collagen deposition, myocyte hyperplasia with enlarged smooth muscle bundles, inflammatory cells, activated DCs, airway hyperresponsiveness, interleukin 13 mRNA expression, Th2 responses, and allergen sensitization.

Conclusions. VEGF is a potent mediator of allergic airway inflammation by enhancing allergen sensitization, airway hyperresponsiveness, Th2 inflammation, and airway remodeling.

Reviewers’ Comments. Well-described airway pathology in asthma includes epithelial desquamation, goblet cell hyperplasia, collagen deposition below the basement membrane, smooth muscle hypertrophy/hyperplasia, and the growth and proliferation of new blood vessels. Al-
though its pathogenesis is still unclear, VEGF (an inducer of angiogenesis) recently attracted considerable attention as a major contributor to airway remodeling. VEGF was first discovered as a vascular permeability factor >20 years ago. Subsequently, it was revealed to be a potent inducer of endothelial cell activation and growth. Overexpression of VEGF and its receptor in the airways has been demonstrated in stable asthma and during asthma exacerbations and are reduced by conventional asthma therapies (ie, inhaled corticosteroids and leukotriene receptor antagonists). The findings of this study imply an essential role of VEGF in asthma pathogenesis with links to Th2-mediated airway inflammation and remodeling. The results of this study may also inform the link of respiratory syncytial virus infection and asthma development in children, because respiratory syncytial virus up-regulates VEGF production. This disclosed role of VEGF highlights a potential therapeutic role for a VEGF receptor antagonist in asthma.

Akaluck Thatayatikom, MD
St Louis, MO
Andrew H. Liu, MD
Denver, CO

RELATION OF CD4+CD25+ REGULATORY T-CELL SUPPRESSION OF ALLERGEN-DRIVEN T-CELL ACTIVATION TO ATOPIC STATUS AND EXPRESSION OF ALLERGIC DISEASE

LING EM, SMITH T, NGUYEN XD, ET AL. LANCASTER 2004;363: 608–615

Purpose of the Study. The investigators proposed to determine if the amount of inhibition of allergic responses by CD4+CD25+ T cells was related to atopy and allergic disease.

Study Population. Volunteers who were atopic (n = 12) or nonatopic (n = 9) or had hay fever (n = 11) were recruited by advertisement and from among hospital staff and allergy clinic patients.

Methods. Cells were isolated from atopic donors (positive serum-specific IgE or skin tests and a history of allergic symptoms), nonatopic donors (no history of allergic symptoms, negative skin-prick tests, and normal amounts of serum IgE), and patients with hay fever (rinitis symptoms between June and August and positive skin-prick tests to grass pollen extract but not to other allergens). Peripheral blood mononuclear cells (PBMCs), CD4+CD25+ T cells, CD4+CD25− T cells, and 2:1 ratios of CD4+CD25− and CD4+CD25+ T cells were cultured for 6 days with cat dander, grass pollen, or medium alone (negative control). The supernatant was analyzed for cytokines, and incorporation of [3H]-thymidine was used as an index of proliferation.

Results. In allergen-driven cultures, CD4+CD25+ T cells from nonatopic donors showed little proliferation and suppressed CD4+CD25− T cell proliferation in a dose-dependent manner. CD4+CD25− T cells showed enhanced production of interleukin (IL)-5 compared with unseparated PBMCs (P = .0056). Compared with nonatopic individuals, suppression of allergen-driven proliferation of CD4+CD25− T cells by CD4+CD25+ T cells was lower in atopic patients (P = .012) and lowest in patients with hay fever who had active rhinitis (P = .0033). Suppression of IL-5 production was also lowest in patients with hay fever who had active rhinitis (P = .0166). When the patients with hay fever were studied outside of their allergy season, the suppression of proliferation was greater than during their allergy season but less than in nonatopic individuals (P = .0028) and similar to the atopic group.

Conclusions. In atopic individuals, especially those with active rhinitis symptoms, CD4+CD25+ regulatory T cells showed a decreased ability to regulate allergen-driven responses, compared with nonatopic individuals.

Reviewers’ Comments. In vitro, the decreased suppression of allergen-driven responses by CD4+CD25+ regulatory T cells from atopic individuals supports the associa-
tion between unchecked T-helper 2 responses and the development of atopy. As the authors suggested, mechanisms may include a deficiency in the regulatory activity of CD4+CD25+ T cells in atopic individuals or an activation and expansion of CD4+CD25+ T cells in response to allergen exposure to a degree that overcomes the regulatory capacity of the CD4+CD25+ T cells. Although additional study will be necessary before these results can be applied clinically, augmentation of CD4+CD25+ T cell suppression of the T-helper 2 response may represent a future therapy for atopic disease.

Elinor Simons, MD
Robert A. Wood, MD
Baltimore, MD

DIAGNOSIS AND MANAGEMENT

CLASSIFYING ASTHMA SEVERITY IN CHILDREN: MISMATCH BETWEEN SYMPTOMS, MEDICATION USE, AND LUNG FUNCTION


Purpose of the Study. To determine if lung-function measures are consistent with levels of asthma severity as defined by the National Asthma Education and Prevention Program/Expert Panel Report 2 guidelines.

Study Population. Children (n = 219) aged 5 to 18 years (mean age: 10.1 ± 3.4 years) with asthma attending 2 academic medical center subspecialty clinics for routine evaluation of asthma.

Methods. Parents completed questionnaires regarding asthma medication use and symptom frequency. Children performed spirometry. Symptom frequency (daytime, nighttime, and exertional) was used to classify severity of asthma according to the National Asthma Education and Prevention Program/Expert Panel Report 2 guidelines. Asthma severity was also categorized by medication use suggested in the guidelines. For inhaled corticosteroid (ICS) use, the average daily microgram dose actually taken was classified as low, medium, or high based on the guidelines. Patients receiving low-dose ICS or another controller medication (leukotriene receptor antagonists, cromolyn, nedocromil, or theophylline) alone were assigned mild persistent asthma status. Patients receiving low-dose ICS plus 1 additional controller medication or a medium dose of an ICS alone were classified as moderate persistent. The use of moderate-dose ICS with additional controller medication, the use of high-dose ICS, or the use of >2 controller medications resulted in a classification of severe persistent asthma (Table 1).

Results. Patients tended to report very good levels of asthma symptom control, with 68.1% of patients being classified as intermittent or mild persistent based on symptom frequency. However, because the majority of patients were receiving controller therapy, the distribution of severity assignments was shifted toward more severe disease when medication use alone was considered.

Conclusions. The authors concluded that in children, asthma severity classified by symptom frequency and medication usage does not correlate with forced expiratory volume in 1 second (FEV1) categories defined by National Asthma Education and Prevention Program guidelines. FEV1 is generally normal even in severe persistent childhood asthma.

Reviewer’s Comments. As the authors’ noted, “classification of asthma severity is complex and is influenced by the variability of disease severity within a patient over time as well as being confounded by current asthma treatment.” Rather than trying to hit the moving target of asthma severity classification, I believe it is preferable to focus on achieving good asthma control, defined by normal and/or personal-best spirometry and rare need for albuterol. If assignment to a severity category is still desired, this can be based on the amount of medication required to achieve good asthma control.

John M. Kelso, MD
San Diego, CA

PEAK FLOW MONITORING FOR GUIDED SELF-MANAGEMENT IN CHILDHOOD ASTHMA: A RANDOMIZED CONTROLLED TRIAL


Purpose of the Study. To determine if the addition of peak expiratory flow (PEF) recordings to a symptom-based self-management plan improved outcome in schoolchildren with asthma.

Study Population. Children (n = 90), aged 7 to 14 years with physician-diagnosed asthma, who are on regular inhaled corticosteroid therapy.

Methods. Children were randomized to receive a management plan based on either symptoms alone or symptoms plus PEF readings for 12 weeks. Children were asked to perform twice-daily spirometry (using an electronic recording spirometer that revealed PEF results only to the symptoms-plus-PEF group) and record a symptom diary. The child and the main caregiver were taught self-management at a training session. A printed plan, based on the child’s best previous PEF and incorporating the child’s own medication regimen, was color coded: green: PEF > 70%, few symptoms (carry on as usual); yellow: PEF 50% to 70% after β2 agonist (double-inhaled corticosteroid as well as taking additional β2-agonist therapy); red: PEF < 50% after taking additional inhaled β2 agonist, severe symptoms (commence oral prednisolone and/or seek medical help).

Results. There were no differences between groups in mean symptom score or in spirometric lung function, PEF, quality-of-life score, or reported use of health services. During acute episodes, children responded to changes in symptoms by increasing their inhaled steroids at a mean PEF value of >70% of best so that overall PEF did not contribute to this important self-management decision.

Conclusions. This trial does not support the hypothesis that the routine incorporation of PEF monitoring into guided self-management protocols for schoolchildren with asthma improves the outcome. Knowledge of PEF did not enhance self-management even during acute exacerbations.


TABLE 1. Distribution of Patients by Level of Severity

<table>
<thead>
<tr>
<th>Basis for Severity Classifications</th>
<th>Symptoms, %</th>
<th>Medications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild intermittent</td>
<td>39.3</td>
<td>18.0</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>28.8</td>
<td>26.7</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>15.1</td>
<td>20.4</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>16.9</td>
<td>35.0</td>
</tr>
</tbody>
</table>

Forced expiratory volume in 1 second (%) predicted did not differ by level of asthma severity.
Coughing in Pre-School Children in General Practice: When Are RASTs for Inhalation Allergy Indicated?


Purpose of the Study. To identify patterns of clinical history associated with extreme (high or low) probabilities of allergic sensitization in coughing children to restrict allergy testing to those with an intermediate probability of sensitization.

Study Population. A total of 752 children in the Netherlands, aged 1 to 4 years, visiting their general practitioners for coughing (≥5 days), were studied.

Methods. Parents completed a questionnaire on family history of atopy, breastfeeding, smoking, pets, and floor covering. Sera from the children were tested for IgE antibodies to house dust mite, cat, and dog by using the RadioAllergoSorbent Test (RAST). Data of 640 children could be analyzed; 83 children (13%) were IgE positive to at least 1 allergen. In a logistic-regression analysis, a scoring formula for the prediction of being IgE positive was constructed by using variables from the patient’s history.

Results. Significant contributors for sensitization were: 3 to 4 years old (odds ratio[OR]: 2.6), infantile eczema (OR: 5.4), positive family history of mite allergy (OR: 2.2), sibling(s) with pollen allergy (OR: 5.5), and smoking by parents (OR: 1.8). If only 1 of these characteristics is present, the probability of sensitization was <25%.

Conclusions. Patient history–derived information contributes to distinguishing children who are at low risk for sensitization to house dust mite, cat, and dog. Watchful waiting may be preferred over testing if only 1 risk factor is present. Otherwise, a negative RAST may help to exclude sensitization, whereas a positive RAST helps to establish the diagnosis.

Reviewers’ Comments. Chronic cough is a very common symptom in childhood and accounts for a large number of visits to the pediatrician each year. Although many allergic children have symptoms of cough, there are numerous diagnoses that also need to be considered during an evaluation for chronic cough. This study supports limiting allergy testing in children with persistent cough to those with particular multiple risk factors for atopy to decrease unnecessary testing in young children.

Julie Wang, MD
Scott H. Sicherer, MD
New York, NY

Benefits of a School-Based Asthma Treatment Program in the Absence of Secondhand Smoke Exposure: Results of a Randomized Clinical Trial


Purpose of the Study. To evaluate the impact of providing inhaled corticosteroids in the school setting on asthma symptoms of urban children with asthma.

Study Population. Children aged 3 to 7 years from 54 urban schools in Rochester, New York, with asthma ranging in severity from mild persistent to severe.

Methods. The study had 2 arms into which patients were randomized: a school-based care group or a usual-care group. In the school-based care group, 2 puffs of fluticasone, 110 μg per puff, were given with a spacer each day that the children were in school. Identical medication with a spacer was given for home use on days that the children were not in school. Those children who were using >1 preventive medication were instructed to continue their other medications at the discretion of their primary care providers. For the patients in the usual-care group, their primary care providers and parents were informed of the severity of their asthma, but there were no other interventions. The main outcome measure was the number of symptom-free days during the 2 weeks leading up to the follow-up interviews.

Results. Of 242 eligible children, 184 were enrolled; 93 children were allocated to the school-based group, and 91 were allocated to the usual-care group. The overall response rate for the follow-up interviews was 94%. Although there was not a significant difference in symptom-free days between the treatment groups, there were significant improvements in the school-based group in secondary measures such as caregiver quality of life (0.63 change score vs 0.24; P = .047), missed school days because of asthma (6.8 vs 8.8 days; P = .047), and symptom-free days during early winter months (mean days per 2-week period: 9.2 vs 7.3; P = .02). A posthoc analysis revealed that all the significant changes were among children where were not exposed to smoking in the home. Furthermore, among children who were not exposed to second-hand smoke, the school-based care group had more symptom-free days overall (11.5 vs 10.5 days; P = .046), had fewer days needing rescue medications (1.6 vs 2.3 days; P = .03), and were less likely to have had ≥3 acute visits for asthma (6 of 47 vs 17 of 54 children; P = .03).

Conclusions. This study demonstrates that a system involving the provision of inhaled corticosteroids in the school improves a number of outcome measures of asthma including missed school days and quality of life of caregivers. This study also demonstrates that such improvements in asthma outcomes are negated by smoke exposure in the home.

Reviewers’ Comments. Health care providers of children with asthma are often frustrated with patients’ poor adherence to medical treatment plans. This study demonstrated that a change in the system of care, using resources that are available in schools, led to improved outcomes. The investigators did not report specifics about actual adherence to the medical treatment given but stated that the children in the school-based treatment group received their medication 84% of days that school was in session, whereas 63% of those in the usual-care group reported using the daily medication. The difference in outcome measures between the school-based and usual-care groups may have been greater if the authors had controlled for several confounding factors (weekend management,
A SCHOOL-BASED CASE IDENTIFICATION PROCESS FOR IDENTIFYING INNER CITY CHILDREN WITH ASTHMA: THE BREATHMOBILE PROGRAM


Purpose of the Study. To evaluate the effectiveness of a school-based screening survey to detect asthma in a large population of inner-city schoolchildren

Methods. A bilingual 7-question self-administered parental asthma-screening survey was administered to 675 consecutive parents before enrolling their children in a free mobile asthma program, the Breathmobile. Participants were recruited by either fliers distributed at the school or referral from school nurses. Surveys were validated by comparing responses to the presence and severity of asthma as determined by the allergist evaluating the patient on the Breathmobile using National Heart, Lung, and Blood Institute guidelines. The surveys (n = 27 526) then were distributed to 1212 classrooms in 24 participating schools, with incentives offered to the teachers for high return rates.

Results. For survey validation, parental responses for 636 children were compared with physician classification, and the combination of questions that provided the best overall sensitivity and specificity were determined. Based on this algorithm, an abbreviated 5-question survey was developed with a positive classification resulting from a “yes” to asthma diagnosis or to any 3 of the following: chest tightness, trouble breathing, or exercise-induced and daytime symptoms. This survey was validated in a larger population of schoolchildren, yielding a sensitivity of 83.4%, specificity of 85.4%, positive predictive value of 93.9%, and negative predictive value of 65.5%. Offering a $25 school-supply gift-certificate incentive increased survey return rates from 35.3% to 65%, with return rates of ≥80% in many classrooms. A prevalence estimate of 14.1% children with probable asthma in Los Angeles schoolchildren was calculated by using this model.

Conclusions. The abbreviated 5-question survey yielded similar results when compared with the 7-question original survey. The surveys were easily distributed and analyzed with limited personnel using scanning software. The survey has been a useful tool for screening schoolchildren who may benefit from Breathmobile services and is an effective screening tool to identify children with probable asthma in this population of inner-city schoolchildren.

Reviewer’s Comments. This article describes the utility of a brief survey in identifying children with asthma in an inner-city, primarily Hispanic population. This survey has been used by the Los Angeles Breathmobile to screen >25 000 children, and it has been the model for similar surveys used by the 4 other Breathmobile programs in the country. Jones et al should be commended for their trail-
blazing work in the development and success of the Breathmobile. We look forward to additional publications describing this very successful program.

MARY BETH BOLLINGER, DO
Baltimore, MD

IMPLEMENTATION OF EVIDENCE BASED GUIDELINES FOR PAEDIATRIC ASTHMA MANAGEMENT IN A TEACHING HOSPITAL

Purpose of the Study. To evaluate a systemic and coordinated approach to the development and implementation of evidence-based asthma guidelines for a pediatric hospital.

Study Population. This was a comparative study conducted at the Royal Children’s Hospital in Melbourne, Australia. There were 3 cohorts of children evaluated between the ages of 2 and 18 years who presented with acute asthma to the emergency department. Cohort 1 presented before the development of asthma guidelines, cohort 2 was recruited to assess the effectiveness of guideline implementation, and cohort 3 was recruited 1 year later to assess the sustainability of guideline changes.

Methods. The Royal Children’s Hospital best-practice guidelines for the care of asthma were established after careful review of established national/international guidelines and consideration of evidence-based reviews in the literature. The guidelines also took into consideration recommendations from Improving Child and Adolescent Asthma Management members. There was a detailed launch of the guidelines in the institution, with a major focus on implementation of the guideline recommendations through a variety of vectors. The primary outcome measures of this study were rates of readmission and readmission to the hospital, a change in asthma morbidity, and quality of life.

Results. There were 374 children in cohort 1, 363 in cohort 2, and 377 in cohort 3. There was no difference in baseline characteristics between the cohorts (age, gender, asthma severity). There was no statistically significant difference in the proportion of patients who revisited the emergency department or were admitted to the hospital between the 3 groups within 6 months of the initial presentation (21–27% for revisits to the emergency department and 11% rehospitalization). There also were no differences in measures of morbidity between the cohorts across 3 domains (interval symptoms, exercise compromise, and bronchodilator usage) or in parent or child quality-of-life scores between the groups. However, there was a significa
cance in those who were given asthma-management plans with the implementation of the practice guidelines.

Conclusions. The implementation of evidence-based guidelines made no difference in readmission to the hospital, return visits to the emergency department, asthma morbidity, or quality of life but did increase the provision of asthma-management plans. The authors concluded that future efforts to improve asthma management should target specific components of asthma care.

Reviewer’s Comments. Certainly the results of this study are disappointing, especially for those of us who develop, implement, advocate, and teach guidelines. Were the guidelines at fault? Were the guidelines implemented properly? Were they carried through for both sides of the illness, and if so, for how long? It was not clear what went on after the first encounter. Was there appropriate follow-up with guideline-savvy primary caretakers who were able to emphasize the guidelines? My guess is that perhaps more emphasis and more “implementation” is needed more frequently at the patient/caretaker level, and I would not give up on guidelines just yet.

FREDERICK E. LEICKLY, MD
Indianapolis, IN

EMOTIONAL QUALITY-OF-LIFE AND OUTCOMES IN ADOLESCENTS WITH ASTHMA

Purpose of the Study. To examine the association between emotional quality of life (QOL) and asthma morbidity in adolescents with asthma.

Study Population. The study included 185 adolescents (aged 11–17 years) with asthma from 3 different managed care organizations in the United States.

Methods. A voluntary cross-sectional survey was mailed to parents of a sample of adolescents with asthma. Parents completed questions related to asthma symptoms, health service use, and impact of asthma on physical function. Adolescents completed the Child Health and Illness Profile-Adolescent Edition and the Pediatric Asthma Quality of Life Questionnaire. Outcomes assessed for the prior 12-month period included parent reports of emergency department (ED) visits for asthma, hospitalizations for asthma, doctor visits for worsening asthma, and the number of days of school missed for asthma in the prior 4-week period. The Pediatric Asthma Control Score, comprised of items that assess asthma symptoms, impact of asthma on planned activities, and asthma medication use, was also used as an outcome.

Results. In the prior 12 months, 10% of the subjects had been hospitalized, 41% had had ED visits, and 77% had had physician visits for worsening asthma; 30% missed ≥1 day of school in the previous 4 weeks. Regarding emotional QOL, 75% of parents reported having worried about their child’s emotional health in the prior 4 weeks. During the same 4-week period, adolescents commonly reported emotional symptoms: 45% felt depressed, 24% cried a lot, and 48% felt nervous. In bivariate analyses, worse Pediatric Asthma Quality of Life Questionnaire scores were significantly related to worse asthma control, more days of missed school (odds ratio: 7.1; \( P < .05 \)), and doctor visits for worsening asthma (odds ratio: 7.0; \( P < .05 \)). Among measures of asthma morbidity, the Pediatric Asthma Control Score showed the strongest and most consistent relationship with measures of emotional QOL: there were significantly fewer asthma-control problems for adolescents with the best levels of emotional function and emotional discomfort.

Conclusions. Poor emotional QOL was common in adolescents with persistent asthma. More frequent school absence, worse asthma control, and more doctor visits for asthma were reported by adolescents with worse asthma-specific emotional QOL. This study does not answer the question of whether emotional QOL is a result or cause of greater asthma morbidity, but it indicates the importance of ascertaining this asthma-specific emotional QOL as a risk factor.

Reviewer’s Comments. Poorly controlled asthma has a tremendous impact on the school-aged child. This study emphasizes the need for clinicians to consider not only outcomes such as ED visits, forced expiratory volume in 1 second, and rescue inhaler use but also emotional QOL. It is likely that lower emotional QOL increases asthma morbidity and that greater asthma morbidity reduces emo-
tional QOL. It may be difficult to determine where the process begins in an individual child, but it may well result in a vicious cycle. The clinician should utilize not only appropriate medications for treatment of asthma but also asthma education and psychological assessment and referrals when indicated.

JOHN E. DUPLANTIER, MD
Indianapolis, IN

ASTHMA DEATHS DURING SPORTS: REPORT OF A 7-YEAR EXPERIENCE


Purpose of the Study. To characterize fatal asthma that occurs while participating in sports activities.

Study Population. Potential subjects with asthma who died while participating in sports activities from 1993–2000 were identified by using a nationwide information service that reviews ~10 000 newspapers.

Methods. For each potential qualifying subject, autopsy results and family interviews were sought. To be included in the study, the subject had to be participating in physical activity at the time of asthma-symptom onset and appear well beforehand, and the medical examiner had to have concluded that the subject died of asthma.

Results. There were 263 potential asthma-related deaths identified, but only 61 met the criteria. Of these, 81% were subjects <21 years of age, and only 3% were >31 years of age. Sixty-nine percent of the subjects were male; 91% had a known history of asthma. There were 35 competitive and 26 recreational athletes. Only 51% of competitive athletes had their fatal event during participation in their organized sport, with 78% of these occurring during practice situations and the rest during active competition. Basketball was the most common activity at time of death (21%) in both competitive and recreational groups, compared with track/running (11%), gym class (10%), football and recreational play (each 8%), and other (42%). Only 5% of the subjects had been using asthma-controller therapy, although the medication status of 18% of the subjects could not be determined. No mention was made of the use of an inhaled β-agonist before exercise.

Conclusions. Sudden fatal asthma exacerbations occur in both competitive and recreational athletes and can be precipitated by sporting activity. Subjects who had fatal asthma attacks during exercise were usually white males between 10 and 20 years of age. Few had evidence of histories of persistent asthma, based on medication use. Extra care is needed to identify the athlete with asthma and ensure that such individuals receive proper evaluation, treatment, and monitoring. If asthma were reportable as a cause of death, a better understanding of asthma fatality during exercise might follow.

Reviewers’ Comments. One unsettling question is why the incidence of fatal asthma with exercise is heavily weighted toward those individuals with presumed mild intermittent disease. Granted, there are more people with mild intermittent asthma than any other severity class, and these individuals are more likely to participate in aerobic exercise than their peers with more severe disease. However, it is hard to accept that these persons could suddenly evolve such profound airway obstruction. Do these persons have suboptimal perception of airway obstruction chronically or during times of increased cardiopulmonary demand? Are they driven to “tough it out” even with recreational activity? Although the answers to some of these questions might be “yes,” it is more likely that these ill-fated young people had more asthma at rest than had met the eye or the ear of the patient, family, and physician. It is not uncommon to see significant airway obstruction in an adolescent with few asthma symptoms. Such individuals might be spared much of their exercise risk if spirometry were part of their asthma evaluation and monitoring. Finally, should we lower the bar for the introduction of asthma-controller therapy?

TIMOTHY ANDREWS, MD
JAMES R. BANKS, MD
Arnold, MD

A PILOT SURVEY OF β2-AGONIST INHALER AVAILABILITY FOR CHILDREN WITH ASTHMA DURING ORGANIZED SPORTING EVENTS


Purpose of the Study. Nearly 90% of asthmatic patients experience exercise-induced bronchospasm (EIB). This study investigated the level of preparedness for EIB in suburban children involved in recreational sports.

Study Population. Five hundred seventy-nine children ≤12 old who were enrolled in a community sports league in Pennsylvania were studied. Seventy-four percent were male, and 96% were white. Four hundred sixty-four children (80%) played soccer, and 115 (20%) played baseball.

Methods. A 3-question survey was administered during a face-to-face interview with the parent or caretaker of the child.

Results. Of the 579 parents/caretakers, 80 (14%; 63 for soccer and 17 for baseball) reported a history of physician-diagnosed asthma for their child. Of the soccer players, 16 (25%) had their inhalers immediately available, and of the baseball players, 2 (12%) had their inhalers immediately available, giving a total of 18 (22%) children having inhalers available.

Conclusions. More than 75% of children with asthma who participated in organized sports were unprepared for a potential episode of EIB.

Reviewers’ Comments. This was a small pilot study, but it demonstrates that children with asthma who participate in organized sports may be unprepared for a possible asthma exacerbation. It is unfortunate that this study did not go further and explore asthma severity or the reasons why the families did not have a short-acting, inhaled β2-agonist available. I presume that, in this primarily middle-class/upper-middle-class community, there were no financial barriers to obtaining the medication or medical care. As physicians we need to emphasize to patients that exercise is a primary trigger of asthma and that patients should have their inhalers available when they participate in sporting events.

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INFLUENZA VACCINATION IN CHILDREN WITH ASTHMA: RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL


Purpose of the Study. To investigate if influenza vaccination in children with asthma prevents asthma exacerbations provoked by influenza infection.
Study Population. Subjects were asthmatic children aged 6 to 18 years who had no other chronic illness. There were 347 children assigned to the vaccine group and 349 assigned to the placebo group.

Methods. The primary outcome was the number of asthma exacerbations associated with virologically proven influenza infection. Study subjects and their families scored daily symptoms in a diary, and when symptoms reached a predefined level, a pharyngeal swab for influenza was taken. The symptom diary was maintained from the day after administration of inactivated influenza vaccine or placebo on approximately November 1 until April 1 of the following year. Secondary outcomes included the duration and severity of the asthma exacerbations, adverse effects of vaccination, and the number, duration, and severity of all asthma exacerbations. Influenza virus–specific antibody titers were measured before vaccination, 14 to 21 days afterward, and at the end of the influenza season.

Results. In each group, 344 participants provided diary data for the primary outcome. The groups were generally similar in baseline characteristics, with almost 90% of children having used maintenance medication for asthma in the previous 12 months. There were 486 reports of symptom scores that met the predefined criteria for an asthma exacerbation (vaccine group: 251; placebo group: 235), with 42 of the resultant throat swabs testing positive for influenza (vaccine group: 24; placebo group: 18). The difference in the number of asthma exacerbations was not significant (95% confidence interval: 34% reduction to 161% increase). There were no significant differences found between the 2 groups for any of the secondary outcomes measured. Antibody levels 14 to 21 days after vaccination were increased only in the vaccine group. However, when comparing the 14- to 21-day titers to those at the end of the season, ~23% of subjects in the placebo group and 10% in the vaccine group had a fourfold increase in influenza-specific titers.

Conclusions. The authors concluded that influenza vaccination was not more effective than placebo in reducing the number of asthma exacerbations caused by influenza infections in children.

Reviewers’ Comments. Current guidelines that recommend the use of influenza vaccination in asthmatics are based on epidemiologic evidence. A recent Cochrane review on influenza vaccination in asthmatics found insufficient evidence to make conclusions about the risks or benefits of influenza vaccination, primarily because of a lack of randomized trials. Although this study was a randomized trial, the low attack rate of influenza (~6% of subjects tested positive by pharyngeal swab) makes it difficult to draw conclusions from the results. The study’s sample size was calculated based on the assumption of a 30% influenza attack rate, leaving it significantly underpowered to detect an effect at such a low attack rate. If the question of efficacy of influenza vaccine in reducing asthma morbidity is ever to be answered convincingly, a large randomized trial, probably over several influenza seasons, will be needed.

ARIANA D. BUCHANAN, MD
LARRY W. WILLIAMS, MD
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RHINITIS THERAPY AND THE PREVENTION OF HOSPITAL CARE FOR ASThma: A CASE-CONTROL STUDY


Purpose of the Study. To examine the effect of treatment of allergic rhinitis on hospitalization and emergency department visits in patients with concomitant allergic rhinitis and asthma.

Study Population. Three hundred sixty-one subjects and 1444 control patients with allergic rhinitis and asthma who were at least 6 years of age.

Methods. A case-control analysis of patients with asthma and concomitant allergic rhinitis was performed between 1996 and 1997 in a large managed care organization in northeastern United States. Diagnosis, procedure, laboratory, health care utilization, and pharmacy records were analyzed to determine if treatment of allergic rhinitis affected the frequency of asthma exacerbations. Patients fulfilled the requirements for diagnosis of asthma and allergic rhinitis within a 12-month period. Patients were defined as asthmatic if they had ≥2 claims with diagnostic codes for asthma; had claims with 1 asthma diagnosis code and 1 asthma-related prescription; or filled 2 asthma-related prescriptions. Patients with allergic rhinitis had ≥2 claims with allergic rhinitis diagnosis codes; ≥2 prescriptions for second-generation antihistamine; ≥2 prescriptions for nasal corticosteroids; 1 prescription for a second-generation antihistamine and 1 prescription for a nasal corticosteroid; or a claim with 1 allergic rhinitis diagnosis code and at least 1 prescription for a second-generation antihistamine and a nasal corticosteroid.

Results. Treatment of allergic rhinitis was associated with a lower frequency of emergency department visits and hospitalization resulting from asthma. Patients receiving monotherapy with a nasal corticosteroid had significantly lower risk of emergency department visits (odds ratio [OR]: 0.75) and hospitalization (OR: 0.56). A similar trend was seen with treatment with a second-generation antihistamine alone. Treatment with a combination of nasal corticosteroids and second-generation antihistamines was associated with additional lower risk of emergency department visits (OR: 0.37) and hospitalization (OR: 0.22).

Conclusions. Treatment of allergic rhinitis lowers the risk of asthma-related health care utilization in patients with concomitant allergic rhinitis and asthma.

Reviewer’s Comments. This was a useful study in that it supports the National Heart, Lung, and Blood Institute guidelines for long-term successful management of patients with asthma and concomitant allergic rhinitis. This is the first large case-control study to definitively show a positive relationship between treatment of allergic rhinitis and lowered risk for asthma health care utilization. Findings support the idea of “one airway,” and physicians should remain cognizant of the benefits of treating the upper airway in patients with lower-airway disease.

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HOW DO PATIENTS DETERMINE THAT THEIR METERED-DOSE INHALER IS EMPTY?

Rubin BK, Durotuye L. Chest. 2004;126:1134–1137

Purpose of the Study. To evaluate how patients determine that their metered-dose inhalers (MDIs) are empty and to measure doses available of MDIs in different laboratory conditions.

Study Population. Fifty consecutive patients attending a pediatric asthma center at Wake Forest University (Winston-Salem, NC).

Methods. Fifty new pediatric patients and their caregivers who used MDIs regularly were asked the question “How do you know when it is time to replace your inhaler?” and then were asked to elaborate on their answers.
For the second part of the study, samples of MDIs (Flovent, Serevent, albuterol, and Qvar) were obtained from the manufacturers and studied in the laboratory. They evaluated the MDIs to determine how many actuations could be emitted and obtained weights during the process. They evaluated the usefulness of floating the MDIs in water to determine if they were full or empty, as has been suggested in the past for tracking the content of MDIs.

**Results.** The survey revealed that 72% of subjects determined that their MDI was empty when they could no longer hear a sound when actuated. Another 20% said they replaced it when it was “old” without giving specific details, although most said “within a month or so” or “after a while.” Four patients stated that they were told to float their MDI in water to determine if it was full (sinks to the bottom) or empty (floats), although none had actually done it. The majority (78%) said they knew they were supposed to shake the MDI before using it, but only half shook the MDI when their technique was evaluated later. In the laboratory, MDIs had similar flotation patterns, with mean flotation angles of 27.6 to 31.7° when empty. Water obstructed the valve or collected near the valve during this procedure 27% of the time. The chlorofluorocarbon inhalers (Flovent, Serevent, and albuterol) had a mean of 86% more audible puffs and Qvar 54% more than the stated manufacturer actuations. Shaking the MDI before actuation increased the doses available for the chlorofluorocarbon inhalers significantly.

**Conclusions.** Most patients studied did not know how to tell if their MDI was empty, and many did not shake the MDI before actuation, which can limit the amount of drug delivered. These results may in part explain the poor adherence with refills for MDIs, because patients may not realize that they are not receiving a full dose of active drug (because all of the MDIs studied had significantly more actuations than noted on the canister), which the authors termed “pseudo-adherence.” The only way to truly track the number of remaining doses in MDIs is to count each dose. Most MDIs will emit more drug doses if the device is shaken before actuation. Floating MDIs in water is not accurate for assessing remaining doses and often will clog the valve.

**Reviewer’s Comments.** This article demonstrates one of the limitations of MDIs in the inability of patients to accurately assess when they are empty without counting each dose. It illustrates the need for better devices to track doses remaining (an advantage of dry-powder inhalers).

**MEDICAL THERAPIES**

**DOUBLING THE DOSE OF INHALED CORTICOSTEROID TO PREVENT ASTHMA EXACERBATIONS: RANDOMISED CONTROLLED TRIAL**


**Purpose of the Study.** The investigators proposed to determine if doubling the dose of inhaled corticosteroids (ICSs) to treat deteriorating asthma control reduced the need for starting oral corticosteroids.

**Study Population.** The study population included 390 nonsmoking individuals aged ≥16 years, with stable asthma requiring regular ICS use and a course of oral corticosteroids or doubled dose of ICS in the past 12 months.

**Methods.** Participants recorded their daily morning peak flow and daytime symptom score on a 4-point scale. After a 2- to 4-week run-in period, an independent pharmacist randomly allocated participants to receive active or placebo study inhalers, matched to their usual ICS, inhaler type, and dose. Participants were stratified into low-to-moderate–dose (equivalent of beclomethasone dipropionate, ≤1000 µg/day) and high-dose groups based on their dose of ICS at study entry. They continued their usual ICS and added the study inhaler for 14 days if their morning peak flow fell by 15% or their daytime symptom score increased by 1 point compared with the run-in period means. Participants took 10 days of oral prednisolone (30 mg/day) if their peak flow fell 40% from the mean run-in value or if their asthma control deteriorated to where they would usually start oral corticosteroids.

**Results.** Of the 192 participants in the active-inhaler group, 110 started their study inhaler (88 in the low-to-moderate–dose group), and of the 198 participants in the placebo-inhaler group, 97 started their study inhaler (74 in the low-to-moderate-dose group). Twenty-two participants (11%) in the active-inhaler group and 24 (12%) in the placebo group started prednisolone, for a risk ratio of 0.95 (95% confidence interval [CI]: 0.55, 1.64). Prednisolone was started because of a 40% peak-flow drop in 6 participants in the active group and 4 controls. In the low-to-moderate-dose group, 13 of 158 in the active group and 17 of 162 in the placebo group started prednisolone, for a risk ratio of 0.8 (95% CI: 0.4, 1.6). Doubling the dose of ICS led to a small reduction in the mean maximum fall of peak flow but did not change the time taken for peak flow or symptom scores to return to the baseline.

**Conclusions.** These findings do not support the effectiveness of doubling the dose of ICS to prevent the need for oral corticosteroids during asthma exacerbations.

**Reviewers’ Comments.** This randomized, control trial questions a recommendation that is part of many asthma-exacerbation–management plans. Although the results of at least 1 other study support these findings, a longer study following individuals beyond their first need for oral corticosteroids, involving larger increases as well as doubling of ICS doses, evaluating objective measures such as peak flow and symptom scores in all patients at the time of starting oral corticosteroids, and including younger patients and those with milder disease may reveal a benefit to increasing the ICS dose in some situations and subgroups of asthmatics. However, if this study’s findings can be consistently replicated in children, we may need to modify our recommendations for early management of asthma exacerbations.

**COST-EFFECTIVENESS ANALYSIS OF EARLY INTERVENTION WITH BUDERSONIDE IN MILD PERSISTENT ASTHMA**


**Purpose of the Study.** These investigators analyzed cost-effectiveness of a commonly prescribed inhaled corticosteroid from the perspectives of both direct and indirect costs.

**Study Population.** Patients aged 5 to 66 years from 32 countries were enrolled in the Inhaled Steroid as Regular Therapy in Early Asthma (START) study. Patients were eligible if they were diagnosed with asthma within 2 years of randomization and lacked significant comorbidity.
Methods. START was a randomized, 3-year controlled trial of budesonide versus usual asthma therapy in early-onset asthma among 7165 subjects. Three age groups (5–10, 11–17, and ≥18 years) were studied separately and collectively. All patients were allowed to receive other asthma treatments including inhaled and oral corticosteroids, according to local practice. The cost-effectiveness evaluation of the START study was conducted primarily from the health care payer perspective (direct costs) and secondarily from the societal perspective (indirect costs). The primary outcome measure for effectiveness was the number of symptom-free days. This parameter was defined as a complete 24-hour period with no asthma symptoms and has been recognized as a clinical outcome with relevance to patients, providers, and other decision-makers. Unit costs in US dollars were based on reimbursed amounts for each of the health care–resource items such as hospital days, emergency department visits, physician and nurse visits, and telephone contacts. These costs were derived from a large medical- and pharmacy-claims database. The costs for school and work losses were estimated by using standard methods.

Results. Compared with usual therapy, patients receiving budesonide had 14.1 more symptom-free days per year, fewer hospital days and emergency department visits, and less school and work absence. Budesonide added $0.41 per day to direct costs. After considering indirect cost offsets related to lower school and work absence, the net expense dropped to $0.14 per day. Early intervention was most effective and cost saving in the youngest age group.

Conclusion. Long-term treatment with budesonide seems to be cost-effective in patients with mild persistent asthma of recent onset.

Reviewers’ Comments. The health care system in the United States is only now beginning to experiment with methods that will raise awareness of direct health costs for patients/consumers. Although $0.14 per day for better asthma control sounds like a great value, any comments that we currently make to patients or parents regarding the cost-effectiveness of a given therapy usually fall on deaf ears. At the present time, we can better appeal to them by touting the improved quality of life associated with fewer days with symptoms, fewer asthma attacks, and lowered hospitalization risk and also by making it clear that the risks of disease far outweigh the risks of usual doses of ICS. This latter fact, so obvious to us, needs continued restating.

Risks of disease far outweigh the risks of usual doses of ICS.

EFFECTS OF SHORT-TERM TREATMENT WITH INHALED CORTICOSTEROID ON AIRWAY WALL THICKENING IN ASTHMA


Purpose of the Study. To examine the effect of inhaled corticosteroids (ICSs) on thickening of the asthmatic airway wall as measured by computed tomography (CT), pulmonary function, and serum levels of eosinophilic cationic protein (ECP).

Study Population. Fifty-one patients (mean age: 48.1 ± 15.9 years) with persistent asthma and 28 healthy controls (mean age: 48.1 ± 15.9 years).

Methods. Patients fulfilled American Thoracic Society criteria for asthma, and none had ever received systemic or inhaled steroids, cromones, or antileukotriene agents. Exclusion criteria included asthma exacerbations or respiratory tract infections within 8 weeks before enrollment or a history of smoking. Cross-sectional, thin-section CT images of the right upper lobe apical bronchus were obtained before and after treatment. Using an enlarged image on a workstation, luminal and total airway areas (in millimeters squared) were calculated after manually tracing the internal and external perimeters of the airway. The airway wall area and airway wall area as a percentage of total wall area were used as indices of airway wall thickness. In asthmatic patients, CT, blood sampling for ECP, and pulmonary function tests were performed before and after treatment with beclomethasone dipropionate (400 μg) administered twice daily for 12 weeks.

Results. Before treatment, airway wall thickness was greater in asthma patients than controls (P < .0001). After treatment, airway wall thickness decreased by 11% (P < .001) but remained high (P < .0001 vs control). Serum ECP levels decreased significantly after treatment (P < .001). Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC improved significantly after treatment, but the values remained lower than in controls. The decrease in wall thickness was associated with a decrease in the level of ECP (r = 0.39; P = .009) and an increase in the FEV1 (r = 0.45; P = .003) and was inversely related to disease duration at entry (r = −0.38; P = .009). Posttreatment wall thickness was related to disease duration (r = 0.45; P = .003) and remaining airflow obstruction.

Conclusions. In patients with persistent asthma, treatment with inhaled beclomethasone for 12 weeks significantly reduced airway wall thickness as assessed by CT. Airway wall thickness remained significantly greater than in controls. ICSs had less of an effect on airway wall thickening in patients with long-standing asthma.

Reviewers’ Comments. This study raises questions. Is the reduction in airway wall thickness indicative of reductions in airway inflammation? Additional studies (eg, with airway biopsy specimens) are needed to confirm this. Would earlier intervention with ICSs result in normalization of airway wall thickness? This is a particularly important question for those who treat children with asthma.

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EFFECTS OF INHALED FLUTICASONE PROPIONATE IN CHILDREN LESS THAN 2 YEARS OLD WITH RECURRENT WHEEZING


Purpose of the Study. To evaluate the efficacy and safety of inhaled fluticasone propionate in children <2 years old with a history of recurrent wheezing and risk factors for asthma persisting into late childhood.

Study Population. Subjects were 30 children, aged 7 to 24 months, with ≥3 episodes of wheeze responsive to bronchodilators and a family history of asthma, allergic rhinitis, or eczema.

Methods. In this double-blind study, subjects were randomized to receive either inhaled 50 μg of fluticasone twice daily, 125 μg of fluticasone twice daily, or placebo for 6 months. Medication was administered with a metered-dose inhaler using an Aerohammer and mask. Efficacy end points included number of wheezing episodes and number of days on which albuterol was required. Parents were trained to record these clinical symptoms and medication use on a chart. Subjects were seen monthly to assess proper use of the medication device and evaluate daily symptom
records. Safety end points included measurement of growth, serum insulin-like growth factor–binding protein 3, cortisol, osteocalcin, and alkaline phosphatase. Clinical and safety outcomes were assessed before and after 6 months of treatment in both treatment and placebo groups.

Results. Mean wheezing episodes were $6.0 \pm 1.9, 1.9 \pm 1.9$, and $2.8 \pm 1.2$ per patient for placebo, $100-\mu g$ fluticasone, and $250-\mu g$ fluticasone groups, respectively. Mean days of albuterol use were $24.3 \pm 1.3, 6.5 \pm 0.8$, and $9.1 \pm 0.8$ for placebo, $100-\mu g$ fluticasone, and $250-\mu g$ fluticasone groups, respectively. There was a significant reduction in wheezing episodes and albuterol use in the $2$ fluticasone groups compared with placebo ($P < .01$), but there were no significant differences between the $2$ fluticasone groups. After treatment, there were no significant differences observed in serum cortisol, bone metabolism markers (insulin-like growth factor–binding protein $3$, alkaline phosphatase, and osteocalcin), or growth among the groups.

Conclusions. The authors concluded that inhaled fluticasone ($50$ or $125 \mu g$) given twice daily over a $6$-month period improved asthmatic symptoms and had no significant adverse effects on growth, bone metabolism, or serum cortisol in children aged $7$ to $24$ months.

Reviewers' Comments. This study suggests that the use of inhaled fluticasone in young children with recurrent wheezing and a positive family history is both safe and effective. In addition, the study is one of the few pieces of evidence that off-label use of inhaled steroid administered with a metered-dose inhaler with a holding chamber and mask is effective in chronic asthma in the very young (with the caveat of monthly review of technique). The safety findings of the study are limited, unfortunately, by its very small size. It is encouraging that the children studied, who would be predicted by the Tucson Children’s Respiratory Study data to be likely to develop persisting asthma, clearly respond to the therapy. The study does not address whether wheezy infants without risk factors for persisting asthma would respond to similar therapy. Larger studies including other subgroups of wheezy infants are needed to support these results.

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Todd D Green, MD
Larry W Williams, MD
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INHALED CORTICOSTEROIDS AND GROWTH OF AIRWAY FUNCTION IN ASThmATIC CHILDREN


Purpose of the Study. To investigate the growth of airways and airspaces in children with moderate asthma who were treated at random with inhaled placebo or corticosteroids in a fixed dose irrespective of symptoms.

Study Population. Patients with moderate to severe persistent asthma who participated in a clinical trial recruited from the entire cohort, 77 children (2.1%) and $64$ of $306$ children (21%) with recurrent bronchial obstruction had received ICS by $2$ years of age. Baseline $\text{tPTEF}/\text{IE}$ was significantly lower at the first visit in ICS$^+$ subjects, as
compared with ICS+ subjects, as well as in ICS− and ICS−
subjects as compared with controls. The mean difference in
baseline IPTEFIE from the first to second visit was bor-
derline{derline statistically significant in the ICS+ group only and
correlated significantly with the duration of ICS treatment.}

Conclusions. The present observational cohort study
demonstrated that one fifth of young children with recur-
rent bronchial obstruction had received ICSs. Early ICS
treatment improved lung function by the age of 2 years,
mostly in those with the longest duration of treatment.

Reviewer’s Comments. There is little information avail-
able concerning how often inhaled steroids are used dur-
ing the first 2 years of life in the treatment of obstructive
airway disease and limited information on the modifying
effects of ICSs on the development of lung function in early
life. As expected, infants with recurrent bronchial obstruc-
tion and lower lung function were treated more often with
ICS compared with matched controls. Improvement in
lung function in these children increased with increasing
duration of treatment. This study suggests that the choice
of medical therapy is often determined by the clinical state
of the child, and once started, it may be a factor that can
influence later outcome. More studies such as this are
desirable to fully understand the role of ICSs in early life.

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LONG-TERM EFFECT OF BUDESONIDE ON
HYPOTHALAMIC-PITUITARY-ADRENAL AXIS
FUNCTION IN CHILDREN WITH MILD TO
MODERATE ASTHMA

Bacharier LB, Raissy HH, Wilson L, McWilliams B,

Purpose of the Study. To determine the safety of 36
months of inhaled budesonide administration on hypotha-
lamic-pituitary-adrenal (HPA) axis function in children
with mild to moderate asthma.

Study Population. Sixty-three children enrolled in the
previously published Childhood Asthma Management
Program (CAMP) study with mild to moderate asthma
(mean age: 9.5 ± 1.9 years). CAMP participants were
between 5 and 12 years of age.

Methods. Children received placebo, nedocromil (16
mg/day by metered-dose inhaler), or budesonide (400 µg/
day by Turbuhaler). HPA axis function was assessed at
baseline and after 12 and 36 months of continuous treat-
ment using serum cortisol levels at 0, 30, and 60 minutes
after administration of 0.25 mg of adrenocorticotropic
hormone (ACTH) and 24-hour urinary free-cortisol (UFC)
excretion. Data for children treated with placebo and
nedocromil were combined and compared with those
treated with budesonide.

Results. Serum cortisol measurements were obtained
for 54 children at 12 months (5 missed the study visit, and
4 had declines in cortisol after ACTH) and 56 children at 36
months (5 missed the visit, and 2 declined participation).
After adjusting for age at randomization, race, gender,
clinic, body surface area, and baseline serum cortisol level,
there were no differences in serum cortisol levels during
ACTH stimulation testing between treatment groups. Dur-
ing the study, the serum cortisol levels at successive time
points tended to decrease in both treatment groups. Addi-
tionally, cortisol levels of children who did and did not
receive supplemental ICSs during the study were similar.
Oral corticosteroids were prescribed to 6 participants be-
fore randomization (3 budesonide and 3 placebo/
nedocromil), and additional courses were used during the
study for exacerbations. When all groups were combined,
oral corticosteroid use 4 months preceding the 12- and
36-month visits did not affect cortisol levels after ACTH
stimulation. Subgroup analyses confirmed these findings,
adjusting for any supplemental corticosteroid use. Techni-
cal problems allowed UFC measurement at only the 36-
month visit for 56 patients. Although UFC levels were
similar in both treatment groups, ICS use within the 4
months before the 36-month visit was borderline signifi-
cantly lower (22 vs 34 µg/m² per 24 hours; P = .05); how-
ever, oral prednisone did not show any effect. Finally,
there was no difference in serum cortisol or UFC between
treatment groups based on cumulative ICS dose.

Conclusions. No effect on HPA axis function was ob-
erved after chronic budesonide treatment at 400 µg/day
in children with mild to moderate asthma. There was no
cumulative effect on HPA axis function over a 3-year pe-
riod.

Reviewer’s Comments. Despite the proven efficacy of
ICSs, there remains concern regarding the long-term ef-
teffects of their use with resultant underutilization. Several
short-term studies of systemic effects related to low-dose
ICSs have demonstrated little effect on HPA axis activity,
but studies on long-term use are lacking. This study is the
first of long-term studies to help detect or refute potential
long-term effects of ICSs in children and thus far dispels
fears regarding the use of ICSs for asthma control.

MARK H. MOSS, MD
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INHALED CORTICOSTEROIDS AND THE RISK OF
FRACTURES IN CHILDREN AND ADOLESCENTS

Schlienger RG, Jick SS, Meier CR. Pediatrics. 2004;114:
469–473

Purpose of the Study. To determine if children or ado-
lescents who are exposed to inhaled corticosteroids (ICS)
(i.e., beclomethasone, budesonide, fluticasone) are at a
higher risk of having bone fractures compared with non-
exposed individuals.

Study Population. This was a population-based study
using the United Kingdom General Practice Research da-
tabase that contains data for >3 million people.

Methods. Within a base population of 273 456 individ-
uals aged 5 to 79 years, the authors used International
Classification of Diseases codes to identify children or ado-
lescents who were aged 5 to 17 years with a fracture
diagnosis and up to 6 control subjects per case matched to
cases on age, gender, general practice attended, calendar
time, and years of history in the database. They compared
the use of ICS steroids before the index date between
fracture cases and control patients.

Results. There was no increased fracture risk associ-
ated with current exposure to ICS when compared with
nonusers even in individuals with current longer-term ex-
posure, i.e., ≥20 prescriptions (adjusted odds ratio: 1.15;
95% confidence interval: 0.89, 1.48). For individuals with
current or previous exposure to oral steroids, the adjusted
odds ratio for current long-term inhaled steroid use com-
pared with nonuse was 1.21 (95% confidence interval: 0.99,
1.49).

Conclusions. The conclusions of the authors were that
exposure to ICS does not substantially enhance the fracture
risk in children and adolescents when compared with non-
exposed individuals.

Reviewer’s Comments. This excellent study verifies gen-
eral consensus in the literature that ICS used in recom-
manded doses do not increase fracture risk in children or
adolescents when compared with controls. There are some
IMMUNODEFICIENCY

PRIMARY IMMUNODEFICIENCY

IMMUNODEFICIENCY AND INFECTIONS IN ATAXIA-TELANGIECTASIA


Purpose of the Study. To describe immunodeficiency in ataxia-telangiectasia (A-T) and its clinical manifestations and course.

Study Population. Patients with A-T who underwent multidisciplinary assessment at Johns Hopkins Hospital (Baltimore, MD).

Methods. Charts from the first 100 consecutive patients with A-T who were assessed at Johns Hopkins Ataxia-Telangiectasia Clinical Center were reviewed. Specific criteria for the diagnosis of A-T had to be met. Immunologic data were obtained by reviewing laboratory assessments of patients’ immune systems. Infections were determined by patient and family interviews and chart review.

Results. A large percentage of patients had immunoglobulin deficiencies at the time of first immunologic assessment: 65% had IgG4 deficiency, 63% had IgA deficiency, 48% had IgG2 deficiency, and 23% had IgE deficiency. Deficiencies did not correlate or progress with age. Lymphopenia occurred in 71% of patients. CD19 B lymphocytes were reduced in 5% of patients. CD4 T cells were decreased in 69% of the patients, and CD8 T cells were decreased in 51% of the patients. Patients had no untoward effects from live viral vaccines. Recurrent upper respiratory infections occurred in one third of the patients regardless of age. Lower respiratory tract infections increased with age. Viral and opportunistic infections were not common.

Conclusions. Patients with A-T have a wide array of laboratory-based immunodeficiencies. However, there seems to be no correlation between laboratory values and clinical manifestation of immunodeficiency in this population.

Reviewers’ Comments. This study confirms previously characterized immunodeficiencies in A-T patients. However, the large number of patients involved in this study allowed for a more extensive review of immunodeficiencies as well as clinical correlation of laboratory values. At this time it seems that clinical immunodeficiency is not common in A-T. Rather, the high rate of respiratory infections may be attributable to other factors of A-T such as neurologic deficits leading to aspiration.

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Michael S. Kaplan, MD
Los Angeles, CA

AUTOSOMAL RECESSIVE HYPERIMMUNOGLOBULIN E SYNDROME: A DISTINCT DISEASE ENTITY


Purpose of the Study. To describe the clinical and immunologic features of a distinct subgroup of patients with hyper-IgE syndrome (HIES) having autosomal recessive inheritance (AR-HIES) as distinct from the form having autosomal dominant inheritance (AD-HIES).

Christopher Randolph, MD
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CLINICAL AND IMMUNOLOGICAL EFFECT OF LOW-DOSE IFN-α TREATMENT IN PATIENTS WITH CORTICOSTEROID-RESISTANT ASTHMA


Purpose of the Study. To evaluate the clinical and immunologic effects of interferon (IFN)-α in patients with corticosteroid-resistant asthma with and without Churg-Strauss syndrome.

Study Population. Ten patients with severe steroid-resistant asthma, 3 of whom had Churg-Strauss syndrome, were studied.

Methods. Subjects were given 3 × 10^6 IU/day of recombinant IFN-α for at least 5 months. The prior systemic corticosteroid doses were maintained until clinical improvement was seen, and then they were decreased gradually. Spirometry, immunophenotyping of peripheral blood mononuclear cells, cytokine measurements, and lymphocyte proliferation assays were performed.

Results. IFN-α rapidly improved patient clinical status as assessed by improved lung-function parameters and decreased prednisone requirements. Immunologic changes included decreased leukocyte numbers, decreased numbers of eosinophils in patients with prior eosinophilia, increased relative numbers of CD4^+ T cells, increased differentiation of T-helper (Th)1 cells, and increased interleukin 10 and IFN-γ levels in peripheral blood mononuclear cells.

Conclusions. Treatment with IFN-α in patients with steroid-resistant asthma with and without Churg-Strauss syndrome was associated with clinical improvement. Possible mechanisms of action include induction of anti-inflammatory interleukin 10 and establishment of a correct Th1/Th2 balance.

Reviewers’ Comments. Although this study involved only a few patients and additional elucidation of the underlying mechanisms is needed, these patients with steroid-resistant asthma improved with IFN-α treatment. Although this study involved only adults, the use of IFN-α as a potential steroid-sparing medication for use in children may also prove beneficial, especially given justified patient, parental, and physician concerns about using long-term oral corticosteroids in children because of the potential for significant toxicity. The use of IFN-α, however, would have to outweigh its inherent potential adverse effects including influenza-like symptoms, nausea, and liver toxicity, to name a few. This preliminary study, however, does make a case for the need for additional, longer-term clinical trials.

David Fleischer, MD
Robert A. Wood, MD
Baltimore, MD
Study Population. Thirteen patients from 6 families having AR-HIES and 68 of their relatives.

Methods. Patients were identified based on exhibiting a classic triad of features of HIES: recurrent skin abscesses, recurrent pneumonias, and elevated serum IgE. Medical records were reviewed, and patients and family members underwent uniform immunologic evaluations.

Results. All families were consanguineous. Five are from Turkey and 1 is from Mexico. According to a previously developed scoring system (>20, HIES possible; >40, HIES highly likely), all 13 patients had scores ranging from 19 to >50. All relatives had scores of <20, supporting an autosomal recessive mode of inheritance. Eight of the 13 patients died between the ages of 6 months and 12 years. Features that are common to both forms of HIES include a chronic eczematous skin eruption with staphylococcal superinfection and upper and lower respiratory tract bacterial infections caused by common pathogens as well as unusual organisms (Proteus mirabilis, Pseudomonas aeruginosa, Cryptococcus neoformans) and chronic mucocutaneous candidiasis. Features that are found in AD-HIES that are not shared in AR-HIES include failure to shed primary dentition, bone fragility, coarse asymmetric facies, and pneumatocele formation. Features found only in AR-HIES include susceptibility to severe infection with molluscum contagiosum and herpesviruses. Patients with AR-HIES also have a high rate of life-threatening inflammatory cerebrovascular complications leading to stroke and/or hemorrhage. Serum IgE in patients with AR-HIES ranged from 4500 to 45 000 IU/mL (similar to AD-HIES). In general, serum immunoglobulin levels were elevated because of general stimulation resulting from infectious burden; specific antibody formation appeared normal. Eosinophil counts in patients with AR-HIES were from 2 500 to 18 000 cells per mm³, somewhat higher than in patients with AD-HIES. There were no major abnormalities of lymphocytes and lymphocyte subpopulations, although in vitro T-cell responses to recall antigens and to a B-cell mitogen were depressed. Some patients with AD-HIES have impaired neutrophil chemotaxis and killing; this was not observed in those with AR-HIES. AD-HIES has been linked to a region on chromosome 4q. This linkage has not been observed in patients with AR-HIES.

Conclusions. AR-HIES is similar to but distinct from AD-HIES and most likely arises from an altogether different genetic basis.

Reviewer’s Comments. HIES is among the earliest described syndromes of immunodeficiency, originally named Job’s syndrome because of the prominence of skin infections in the clinical phenotype. The genetic basis of this disease still eludes investigators. The description of an apparently distinct but very similar entity raises the exciting possibility that we may be seeing the results of defects in molecules that have a functional interaction in vivo. One may hope that defining the genetic bases of these diseases may lead to the same kinds of advances in our understanding of immune system biology, as have resulted from the study of other primary immunodeficiencies, with a potential for novel therapies.

Francisco A. Bonilla, MD, PhD
Boston, MA

THE PRESENTATION AND NATURAL HISTORY OF IMMUNODEFICIENCY CAUSED BY NUCLEAR FACTOR κB ESSENTIAL MODULATOR MUTATION

Purpose of the Study. To describe the clinical and immunologic natural history of patients with immunodeficiency associated with mutation in nuclear factor κB modulator (NEMO).

Study Population. Seven boys who presented to Children’s Hospital Boston (Boston, MA) for immunodeficiency evaluation between 1984 and 2002 and were diagnosed to have a NEMO mutation with immunodeficiency (NEMO-ID).

Methods. Patients with recurrent bacterial infection and ectodermal dysplasia (ED) or atypical mycobacterial infection were evaluated by sequence analysis for NEMO mutation. Functional analyses of these mutations have been described previously. Genomic and complementary DNA from patient leukocytes were sequenced and compared with 40 healthy individuals. Serum immunoglobulin concentrations, leukocyte enumeration, lymphocyte subset numbers and function, nitroblue tetrazolium reduction, total hemolytic complement, and natural killer cell cytotoxicity were measured by using standard assays. Data were obtained both retrospectively and prospectively. NEMO-ID incidence rates were approximated by using US census data for the catchment area of Children’s Hospital Boston. Immunologic measurements were compared with laboratory-specific age-related norms, and significance of differences was assessed by Student’s t test.

Results. The estimated incidence of NEMO-ID is 1 in 250 000 live male births. Four of the 6 independent mutations described (2 patients were half-siblings) affected the C-terminal zinc-finger domain encoded by exon 10. Six of 7 patients presented with ED. All patients had severe pyogenic bacterial infections early in life (median age at first infection: 8.1 months; range: 0.1−60.9 months). Immune deficiency was diagnosed before ED in all patients. Five of 7 patients had infection with atypical mycobacteria (median: 84 months old; range: 14−168 months old). The most severe clinical phenotype was seen in the 2 siblings patients with a mutation resulting in truncation of >50% of the final exon. That mutation was also associated with a pattern of immunoglobulin dysregulation consisting of hyper-IgM and hypo-IgA. All but 1 patient (patient 5) was hypogammaglobulinemic, and all were deficient in specific antibody production. However, 5 of 6 mutations were associated with hyper-IgA. Patient 5, who has an unusual mutation causing deletion of exon 9, was also uniquely unaffected by ED. Lymphocyte subsets and in vitro function were variable, although natural killer cell cytolyis was markedly depressed in all patients tested (n = 5).

Conclusions. NEMO-ID is an X-linked combined immunodeficiency characterized by early susceptibility to pyogenic bacteria and later susceptibility to mycobacterial infection.

Reviewer’s Comments. The majority of reported mutations in NEMO affect exon 10. This report extends our knowledge of NEMO-ID and suggests genotype-phenotype correlations, including for the first time a description of NEMO-ID without ED. The striking incidence of early pyogenic infections deserves emphasis and suggests defects in innate immunity. Severe pyogenic bacterial infection should prompt consideration of nuclear factor κB-activation disorders, especially when accompanied by hyper-IgA.

Wayne G. Shreffler, MD, PhD
New York, NY
GI INFECTION AND MORTALITY IN CHRONIC GRANULOMATOUS DISEASE

Purpose of the Study. To evaluate the clinical presentation, prevalence, and consequences of gastrointestinal (GI) involvement in patients with chronic granulomatous disease (CGD).

Study Population. A registry of 140 patients with CGD (67% X-linked) maintained at the National Institutes of Health.

Methods. This was a retrospective review of records from 1988–2002. GI involvement was defined as abdominal pain, diarrhea, constipation, obstruction or fistulas, and involvement of the esophagus, stomach, or bowel confirmed by endoscopy and/or histology. Other causes of GI involvement were excluded from analysis.

Results. Forty-six (33%) patients had documented GI involvement; 44 (96%) were male. Mean age of CGD diagnosis was 2 years (range: birth to 27 years), and median age of GI involvement was 5 years (range: 10 months to 30 years). Thirty-two (70%) patients experienced GI symptoms in the first decade of life, 9 (20%) in the second decade, and 5 (10%) in the third decade. In 8 (17%) patients, GI manifestations preceded the diagnosis of CGD. A high proportion (89%) of those with GI manifestations had X-linked inheritance. All patients experienced severe infections except for 2 kindred, who only experienced GI involvement. Mortality was equal in GI-affected and unaffected groups and was a result of severe infection. Although all patients experienced abdominal pain, it was the primary presenting complaint in 33% of patients. Other symptoms included diarrhea (39%), nausea and vomiting (24%), and constipation (2%). Obstruction occurred in 35% of patients involving gastric, esophageal, duodenal, and other locations. Despite interferon γ prophylaxis in 89% of GI patients, there seemed to be no protection; 81% of unaffected patients had received similar prophylaxis. After endoscopic confirmation of GI granuloma, successful treatment was initiated by using prednisone (1 mg/kg per day with taper to 0.25 mg/kg every other day), but 71% experienced relapse. Two patients became hypertensive, and 1 developed cataracts. After bone marrow transplantation, 3 patients experienced remission of GI involvement.

Conclusions. GI involvement in CGD is common and recurring, especially in those with X-linked inheritance. Interferon γ prophylaxis does not reduce involvement or affect mortality.

Reviewer’s Comments. Although CGD is a rare disorder, the pediatrician must be aware of the classic presentation involving infection of the skin, deep tissues, and bone and complications such as GI granuloma formation. This is especially true in those with X-linked disease. Abdominal pain or abdominal symptoms voiced by a child with CGD must be evaluated thoroughly and, when not infection-related, treated with corticosteroids (in some cases, long-term). Bone marrow transplantation can be effective in inducing remission of the disease including the GI manifestations.

Mark H. Moss, MD
Madison, WI

HEALTH-RELATED QUALITY OF LIFE OF CHILDREN WITH PRIMARY IMMUNODEFICIENCY DISEASE: A COMPARISON STUDY

Purpose of the Study. To compare parental perceptions of health-related quality of life (HRQOL) in children with primary immunodeficiency (PI) with children with juvenile idiopathic arthritis (JIA) and healthy children.

Study Population. Thirty-six children in each of 3 groups (108 total); those with PI, those with JIA, and those who were healthy. Patients were matched for age, ethnicity, and parental marital status. The age ranged from 4 to 18 years, and 94% were white. All patients with PI received regular infusions of intravenous immunoglobulin. Of the patients with JIA, 77% had either oligoarthritis or polyarthritis. The JIA group had a significantly higher proportion of females.

Methods. Parents were interviewed and completed the Child Health Questionnaire-Parental Form 50. Treating physicians completed forms documenting any complications of the underlying disease.

Results. In comparison to healthy children, those with PI had significantly lower scores on physical functioning, school and social activities, limitations on parental time and family activities, and parental emotional distress. They were equivalent to the healthy group with respect to overall psychosocial health, daily pain and discomfort, social limitations, self-esteem, mental health, general behavior, and family cohesion. In comparison to the JIA group, children with PI were similar. However, they scored lower than the JIA group with respect to perception of general health and limitations on parental time and family activities. The children with JIA had more bodily pain and discomfort than the children with PI.

Conclusions. Children with PI have significant impairment in several measures of HRQOL in comparison to healthy children. These limitations are similar to, and in some cases more severe than, those occurring in another group of chronically ill children, those with JIA.

Reviewer’s Comments. This study begins to fill the gap in our understanding of the impact of PI on the quality of life of children and families. Despite some limitations in size and scope, it is clear that HRQOL in children and families with PI is impaired (even when the disease is treated with intravenous immunoglobulin) to a degree that is on a par with other serious chronic disorders that are generally better recognized. Overall, PI is underdiagnosed, to what extent is unknown. This study suggests that not only is there room for improvement in HRQOL aspects of disease management or patient care in those who already have a diagnosis of PI but also implies that there are gains in HRQOL to be made with improved diagnosis of PI.

Francisco A. Bonilla, MD, PhD
Boston, MA

CHILDREN AND ADULTS WITH PRIMARY ANTIBODY DEFICIENCIES GAIN QUALITY OF LIFE BY SUBCUTANEOUS IgG SELF-INFUSIONS AT HOME

Purpose of the Study. To determine the impact of a change from in-hospital infusion of intravenous immunoglobulin (IVIG) to in-home infusion of subcutaneous immunoglobulin (SCIG) on health-related quality of life (HRQOL) and treatment satisfaction.

Study Population. Fifty-eight patients between the ages of 2 and 75 years (17 patients <14 years old ["children" for the purposes of this study]; 41 patients ≥14 years old ["adults"]) with primary antibody deficiency. Thirty-seven patients were receiving IVIG, and 10 were receiving SCIG.
(a control group to compare for effects specifically related to the switch from IVIG to SCIG); prior therapy for 1 patient was not stated.

Methods. Patients received weekly SCIG infusions at home over a period of 10 months (43 infusions). Questionnaires were administered at baseline and at 6 and 10 months. For assessment of HRQOL in children, parents completed the Child Health Questionnaire-Parental Form 50; adults used the Short Form 36. For assessment of treatment satisfaction, the authors adapted a Life Quality Index instrument previously developed in a study of antibody-deficient patients receiving IVIG.

Results. On the Child Health Questionnaire-Parental Form 50, the children demonstrated significant improvement in 6 of 14 concepts analyzed: “role/social-emotional, behavioral,” “general health perceptions,” “parental impact-emotional,” “parental impact-time,” “family activities,” and “global health.” On the Short Form 36, adults had improvements in vitality, mental health, and social functioning. These differences were found only in those adults who switched from IVIG to SCIG, not in those who were already receiving SCIG, suggesting that the improvement resulted from the change in therapy. Both children and adults had significant improvements in Life Quality Index. Again, in the adults, no change was seen in the group that was already receiving SCIG at enrollment. At study end, all children/parents, the 10 adults on SCIG at enrollment, and 73% of the adults who switched preferred to continue SCIG at home. Two expressed a preference for SCIG regardless of setting, 1 expressed a preference for home regardless of method, 1 expressed no preference for anything, and only 1 expressed a preference for IVIG in the hospital.

Conclusions. Home therapy with SCIG in children and adults with antibody deficiency is generally self-perceived as superior to in-hospital therapy with IVIG with respect to several validated measures of HRQOL.

Reviewer’s Comments. IVIG has been a major mode of therapy for immunodeficiency for 30 years. Many primary care providers have 1 or a few patients who receive this therapy. Less widely recognized, SCIG has also been used with safety and efficacy equivalent to IVIG and has been the major mode of immunoglobulin delivery in some countries (although this is an off-label use in the United States). For a variety of reasons, SCIG is gaining in popularity and may replace IVIG for many patients with immunodeficiency diseases.

Francisco A. Bonilla, MD, PhD
Boston, MA

HUMAN IMMUNODEFICIENCY VIRUS

PERFORMANCE CHARACTERISTICS OF HIV-1
CULTURE AND HIV-1 DNA AND RNA
AMPLIFICATION ASSAYS FOR EARLY DIAGNOSIS
OF PERINATAL HIV-1 INFECTION


Purpose of the Study. The diagnosis of HIV infection in a newborn exposed to HIV in utero is a challenge. In the early years of the epidemic, HIV clinicians monitored the decline of HIV antibody levels for up to 2 years after birth to confirm that a child was not HIV-infected. HIV infection in infants is now typically made by the detection of viral DNA sequences in peripheral blood mononuclear cells by means of a DNA polymerase chain reaction (PCR). Plasma HIV-RNA measurements with PCR may also be valuable but has the theoretic limitation of false-negative reactions resulting from early treatment of the mother and infant. The purpose of this study was to evaluate the performance of HIV DNA PCR, HIV RNA PCR, and HIV culture to identify infected infants exposed to the virus in utero.

Study Population. Infants participating in the Pediatric AIDS Clinical Trials Group protocol 185.

Methods. Specimens from the infants (24 infected and 100 uninfected) obtained prospectively were studied with standard nucleic acid–amplification assays and peripheral blood mononuclear cell microcultures. The sensitivities, specificities, and positive and negative predictive values were calculated for each of the 3 assay systems.

Results. At birth the sensitivity of culture, DNA PCR, and RNA PCR were 21%, 11%, and 27%, respectively. By 6 weeks, the sensitivity had improved to 90%, 83%, and 95%. The specificity was 99% to 100% for all assays at all times.

Conclusions. The authors concluded that the diagnostic performance of the RNA PCR assay matched or exceeded that of culture and DNA PCR. Because RNA assays require less blood volume and often can be performed more quickly at reference laboratories, it is suggested that RNA assays may be used for early diagnosis of HIV infection in infants.

Reviewer’s Comments. This study demonstrates that RNA PCR assays are effective for the diagnosis of HIV infection. However, it must be noted that cryopreserved specimens were used for these PCR assays and may have impacted the sensitivity of the DNA PCR. Additionally, we have had 3 false-positive RNA PCR assays in 2 newborns and 1 adolescent exposed to HIV. A negative RNA PCR at or after 6 weeks of age strongly indicates that an infant is not infected.

Joseph A. Church, MD
Los Angeles, CA

GROWTH HORMONE IN T-LYMPHOCYTE THYMIC
AND POSTTHYMIC DEVELOPMENT: A STUDY IN
HIV-INFECTED CHILDREN


Purpose of the Study. Growth hormone (GH) plays a role in thymic function, and decreased hormone secretion has been reported in HIV-infected children. Highly active antiretroviral therapy suppresses HIV replication and results in increases in CD4+ T cells in HIV-infected patients. The aim of this study was to determine if the level of immune reconstitution associated with antiretroviral therapy is influenced by the status of the GH insulin-like growth factor 1 axis.

Study Population. HIV-infected children (n = 26) were studied. Half of them had GH deficiency as defined by a reduced peak GH response to GH-releasing hormone and arginine-stimulation test. These patients were matched to 13 patients of similar age, pubertal status, and clinical findings but with normal GH-response tests.

Methods. Thymic volume was measured with magnetic resonance imaging. Peripheral blood lymphocyte subsets were evaluated with standard monoclonal antibody techniques. Serum interleukin 7 levels were measured with an enzyme-linked immunosorbent assay.

Results. The 2 patient populations did not differ in age, weight, height, body mass index, pubertal status, clinical or immunologic stage of disease, or number and percentage of CD4+ T cells before beginning antiretroviral therapy. After antiretroviral therapy, children with GH deficiency had reduced CD4+ T-cell numbers and percentages, reduced interleukin 7 concentrations, and reduced thymic
HUMAN IMMUNODEFICIENCY VIRUS-DRIVEN EXPANSION OF CD4+CD25+ REGULATORY T CELLS, WHICH SUPPRESS HIV-SPECIFIC CD4+ T-CELL RESPONSES IN HIV-INFECTED PATIENTS


Purpose of the Study. HIV infection is associated with a progressive decline in CD4+ T-cell numbers. However, multiple mechanisms of HIV-associated T-cell dysfunction have been described, including reduced HIV-specific lymphoproliferative and cytotoxic T-cell responses and failure to generate proinflammatory cytokines. A CD4+ T-cell subset with regulatory properties has been characterized. These cells, regulatory T cells (Tregs), express CD25 and inhibit the proliferation of T lymphocytes both in vitro and in vivo. This suppression may be antigen specific and cytokine mediated.

Methods. Peripheral blood T cells were obtained from clinically stable, antiretroviral-treated HIV-infected individuals with CD4+ T cells >500/μm³ and plasma HIV RNA <50 copies per mL. These cells were used for extensive flow-cytometric analysis, proliferation and suppression assays, and expression of FOXP3, a transcription factor in Tregs.

Results. HIV-infected individuals had increased numbers of CD4+CD25+ T cells with the phenotypic, molecular, and functional characteristics of Tregs. This expanded population persisted despite long-term viral control. Patient Tregs suppressed CD4+ T-cell proliferation to recall antigens and specific HIV proteins. The proliferative capacity of T cells to recall and p24 antigens significantly increased after the depletion of Tregs. Additionally, these T cells responded specifically to p24 antigen with expression of transforming growth factor β and interleukin 10. It is interesting to note that the suppressive activity by the cell population did not depend on secretion of transforming growth factor β or interleukin 10.

Conclusions. HIV derives expansion of CD4+CD25 regulatory T cells. This regulatory T-cell subset in turn suppresses HIV-specific CD4+ T-cell responses in HIV-infected patients.

Reviewer’s Comments. HIV induces an immunodeficiency by depleting CD4+ T cells. However, demonstrable immunodeficiency occurs before the onset of severe peripheral T-cell depletion. A variety of mechanisms have been invoked to explain this process. The present study demonstrates an additional potential mechanism by which HIV subverts immune responses to both HIV-specific antigens and to those of other infectious agents. The expansion of HIV-induced Tregs suggests a mechanism by which HIV induces partial tolerance to its own antigens. Therapeutic strategies aimed at reducing HIV-specific Tregs might allow more effective control of HIV replication. Alternatively, species-specific simian immunodeficiency viruses seem to induce little disease caused by immune silence. Perhaps enhancement of HIV-specific Tregs rather than suppression of them might result in similar tolerance and lack of disease progression in HIV-infected humans.

Joseph A. Church, MD
Los Angeles, CA

CD4+ T CELL DEPLETION DURING ALL STAGES OF HIV DISEASE OCCURS PREDOMINANTLY IN THE GASTROINTESTINAL TRACT


Purpose of the Study. Mechanisms underlying T-cell depletion in HIV infection are not well understood. This depletion has been studied primarily in the peripheral blood and, to some extent, in peripheral lymphoid tissue. However, a large fraction of CD4+ T cells reside in the gastrointestinal tract. The purpose of this study was to identify the effects of HIV infection on activation and depletion of T cells in the peripheral blood, gastrointestinal tract, and lymph nodes.

Study Population. A total of 14 antiretroviral therapy-naive HIV-infected individuals and 7 HIV-uninfected individuals were recruited.

Methods. Peripheral blood mononuclear cells were obtained from venous blood, ileal Peyer’s patches and lamina propria samples were acquired by endoscopy and biopsy, and inguinal lymph nodes were obtained by percutaneous biopsy. Flow-cytometric analysis was conducted on specimens with standard techniques. HIV-specific T cells were analyzed for phenotypic markers. Additional studies were performed for HIV-specific CD8+ T cells and levels of collagen deposition within lymph nodes.

Results. During primary HIV infection, preferential depletion of mucosal CD4+ T cells occurs compared with peripheral blood and lymph nodes. At all stages of HIV disease, most CD4+ T-cell depletion occurs in the gastrointestinal tract. The primary targets for depletion are activated CD4+CCR5+ T cells. Finally, T-cell activation in lymph nodes is associated with abnormal collagen deposition.

Conclusions. These findings define the nature and extent of CD4+ T-cell depletion in lymphoid tissue, particularly that of the gastrointestinal tract. Most CD4+ T-cells in the effector sites of the gastrointestinal tract are activated and express CCR5. This circumstance creates a particularly attractive medium for HIV infection and replication, which occurs most efficiently in activated CCR5+CD4+ T cells. Additionally, it was shown that therapeutic suppression of HIV permits recovery of circulating CD4+ T cells but did not restore CD4+ T cells in the gastrointestinal tract.

Reviewer’s Comments. Intestinal CD4+ T cells are depleted selectively and rapidly in HIV-infected patients. These findings reflect earlier studies in simian immunodeficiency virus–infected macaque monkeys (Science. 1998; 280:142–431). All of these studies together demonstrate that HIV induces severe, organ-specific T-cell depletion in a much briefer time frame than previously identified. Although clinical immunodeficiency may not be apparent for
months to years after initial infection, it is clear that immune compromise occurs very early in the disease process. Of great importance is the failure of long-term (≥5 years) highly active retroviral therapy to reverse this site-specific T-cell depletion. Additionally, other studies have demonstrated that HIV is consistently detectable in the intestine of HIV-infected patients, even those with no detectable plasma virus. Current therapies are inadequate for clearing the virus from the intestine, a major reservoir of HIV. New therapies aimed at the mucosal immune system will be required to address this issue. Finally, because the intestine is the earliest target for virus infection and T-cell loss, enhancing mucosal immunity will be critical for any vaccine strategy to be effective.

JOSEPH A. CHURCH, MD
Los Angeles, CA

PREVENTION OF VAGINAL SHIV TRANSMISSION IN RHESUS MACAQUES THROUGH INHIBITION OF CCR5


Purpose of the Study. Topical agents that prevent transmission of HIV across mucosa during sexual activity are urgently needed, because the vast majority of HIV infections are acquired through transmission across mucosal surfaces. However, the mechanisms of HIV entry at vaginal sites of infection are poorly understood. The chemokine receptor CCR5 serves as an essential coreceptor for HIV entry into target cells. Individuals who lack surface CCR5 expression are highly resistant to acquiring HIV infection through the mucosal route. Because viruses that use CCR5 predominate in the early stages of mucosal transmission, it is likely that such transmission selectively involves CCR5. This suggests a strategy by which vaginal transmission might be prevented.

Methods. The chemokine RANTES is a specific ligand for CCR5. The investigators generated an analog of RANTES, PSC-RANTES, that has an N-terminal modification. In vitro PSC-RANTES inhibited propagation of SHIV, a chimeric simian/human immunodeficiency virus. Thirty adult female rhesus macaques were pretreated with varying concentrations of PSC-RANTES intravaginally. The animals were subsequently challenged with high-multiplicity (300 median tissue culture infectious doses) SHIV intravaginally and monitored for up to 24 weeks.

Results. All 5 animals treated with the highest dose of PSC-RANTES were protected from SHIV infection. Lower doses also proved protective to a lesser extent. Plasma levels of PSC-RANTES were not detectable, suggesting specific local protection against viral infection.

Conclusions. PSC-RANTES, a selective blocker of CCR5, protected rhesus macaques from intervaginal exposure to a highly infectious dose of SHIV, although the topical concentration of PSC-RANTES that was shown to be protective was many times higher than the concentration required to neutralize the same virus in vitro.

Reviewer’s Comments. A safe, simple, and affordable topical microbicide that would effectively prevent vaginal transmission of HIV is desperately needed, particularly in the developing world. This study provides proof of the concept that targeting the coreceptor for HIV entry into target cells, CCR5, is a viable strategy for the prevention of vaginal transmission of HIV. Cost, however, would be a major obstacle to the implementation of this strategy, but it is now clear that HIV can be stopped before it infects the vaginal mucosa.

JOSEPH A. CHURCH, MD
Los Angeles, CA

Infectious Disease

A SYNTHETIC CONJUGATE POLYSACCHARIDE VACCINE AGAINST HAEMOPHILUS INFLUENZAE TYPE B


Purpose of the Study. To demonstrate the safety and immunogenicity of synthetic glycoconjugate vaccine against Haemophilus influenzae type b (Hib).

Study Population. Adults, children, and infants in Camaguey, Cuba.

Methods. The authors established a large-scale good manufacturing protocol for the production of ~100-g batches of polyribosylribitol phosphate (PRP), the Hib capsular polysaccharide. Synthetic PRP (sPRP) conjugated to protein was shown to be capable of binding antibody from the serum of children immunized with commercial Hib conjugate vaccine. sPRP conjugated to tetanus toxoid (sPRP-TT) from 3 different lots was used for immunization experiments in animals and phase I and II clinical trials in humans. The vaccination dose given was 10 µg of sPRP (sPRP/TT ratio 1:2.6 by weight) via intramuscular injection. All clinical trials were double blind and randomized. Single-dose phase I trials of adults (n = 40) and unimmunized children (4–5 y; n = 133) were followed by single-dose phase II trials of 1041 children. PRP-specific IgG and bactericidal activity were measured from subject sera samples 4 weeks after immunization. A total of 139 infants were then enrolled in a multiple-dose phase I trial and received vaccine at 2, 4, and 6 months. Infants (n = 1141) then were enrolled in a double-blind phase II trial and randomized to receive either sPRP-TT, sPRP-TT with aluminum phosphate, or commercial conjugate vaccine (Vaxem-Hib) at 2, 4, 6, and 18 months. PRP-specific IgG was measured by enzymelinked immunosorbent assay at 7, 18, and 19 months.

Results. No adverse reactions were reported. From single-dose studies, average PRP-specific IgG levels and percent of patients achieving seroconversion were comparable when sPRP-TT was given with or without aluminum phosphate, and both were comparable to commercial Hib vaccine. Three different lots of sPRP-TT vaccine were tested, with no significant differences between them. In multiple-dose trials of infants, 99.7% reached levels of PRP-specific IgG that are considered to be protective (>1 µg/mL), and geometric mean concentrations of PRP-specific IgG were similar to those in infants immunized with commercial vaccine.

Conclusion. The synthetic vaccine was as safe and immunogenic as licensed commercial vaccines that incorporate native polysaccharide.

Reviewer’s Comments. This is the first report of the large-scale production and clinical testing of a synthetic polysaccharide vaccine. The production of conjugate vaccine from a large-scale culture of microorganisms is expensive, time consuming, and variable. The present work is likely to portend developments in other vaccines that are directed against polysaccharide capsular material (eg, Streptococcus pneumoniae, meningococcal group C). Clinical efficacy remains to be established. Some of the published data suggest lower responses in the youngest infants, which would be of concern.

WAYNE G. SHREFFLER, MD, PhD
New York, NY
Echinacea Purpurea Therapy for the Treatment of the Common Cold: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial


Purpose of the Study. Echinacea purpurea stimulates the immune response and is promoted to reduce symptom severity and the duration of upper respiratory tract infections. The researchers sought to determine the efficacy of a standardized preparation of E. purpurea in reducing symptom severity and duration of the common cold.

Study Population and Methods. A randomized, double-blind, placebo-controlled design was used. Patients received either 100 mg of E. purpurea (freeze-dried pressed juice from the aerial portion of the plant) or a lactose placebo 3 times daily until cold symptoms were relieved or until the end of 14 days, whichever came first. Symptoms (sneezing, nasal discharge, nasal congestion, headache, sore or scratchy throat, hoarseness, muscle aches, and cough) were scored subjectively by the patient and recorded daily in a diary. Kaplan-Meier curves were used to estimate the survival function of time to resolution in each group. The Wilcoxon rank-sum test was used to compare time to resolution between the 2 groups.

Results. One hundred twenty-eight patients were enrolled within 24 hours of cold-symptom onset. Group demographic distribution was comparable for gender, age, time from symptom onset to enrollment in the study, average number of colds per year, and smoking history. No statistically significant difference was observed between treatment groups for either total symptom scores (P = 0.90) or mean individual symptom scores (P = 0.90–0.93). The time to resolution of symptoms was not statistically different (P = 0.73).

Conclusions. The preparation of E. purpurea at these doses was not effective in relieving the severity or duration of the common cold.

Reviewer’s Comments. It is probably not a surprise that inconsistent results have been found in different studies, because there is no required standardization for potency or content of echinacea. We can thank the US Congress, who in the mid-1990s capitulated to the food-supplements industry and removed Food and Drug Administration regulation of echinacea and other similar products. Although we generally think of echinacea as fairly harmless, it can reduce the effectiveness of corticosteroids, which would be commonly used in viral-induced asthma. It also can cause hypersensitivity reactions to persons allergic to ragweed.

Allen Adinoff, MD
Denver, CO

Efficacy and Safety of Echinacea in Treating Upper Respiratory Tract Infections in Children: A Randomized Controlled Trial


Purpose of the Study. To determine if echinacea is effective in reducing the duration and/or severity of upper respiratory infection (URI) symptoms in children and assess its safety in this age group.

Study Population. Five hundred twenty-four healthy children, aged 2 to 11 years, were enrolled from a practice-based pediatric research network and an alternative-medicine institution in the Seattle, Washington, area. Each child was enrolled in the project for a 4-month period in 2 consecutive years during the peak rhinovirus season. Data were collected on up to 3 URIs per study patient. Twenty-three percent of the children in the active-treatment group were in a day care setting versus 13% in a placebo group.

Methods. This was a randomized, double-blind, placebo-controlled trial of echinacea for up to 3 URIs over the 4-month study period. Study medication was begun at the onset of symptoms and continued throughout the URI for a maximum of 10 days. Primary outcomes were duration and severity of symptoms and adverse events recorded by parents.

Results. Data were analyzed on 707 URIs that occurred in 407 study patients. Median duration of URIs was 9 days. There was no difference in duration between URIs treated with echinacea or placebo (P = 0.89). There was also no difference in the overall severity of URI symptoms between the 2 treatment groups (P = 0.69). There were no statistically significant differences between the 2 groups for peak severity of symptoms, number of days of peak symptoms, number of days of fever, or parental global assessment of severity of the URI. There was no difference in the rate of adverse events reported in the 2 treatment groups; however, rash occurred during 7.1% of the URIs treated with echinacea and 2.7% of URIs treated with placebo (P = 0.008).

Conclusions. Echinacea as used in this study was not effective in decreasing duration or severity of URI symptoms in healthy children 2 to 11 years old. Its use was associated with an increased risk of rash.

Reviewer’s Comments. Echinacea, derived from wildflowers from the daisy family (family Compositae), is one of the most commonly used herbal preparations in the United States, with reported sales of more than $300 million annually despite limited evidence of clinically beneficial effects in the treatment of viral respiratory infections. This study is one of the largest randomized, controlled trials of echinacea treatment in patients of any age. In addition to the large sample size, the validity of the results is strengthened because enrolled patients had sought care from both traditional and alternative providers in an attempt to negate the effects of preconceived biases about echinacea. These data provide additional information regarding lack of efficacy of echinacea in treating the 6 to 8 colds an average child has each year.

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