Section on Allergy and Immunology
American Academy of Pediatrics

Founded in 1948, the Section on Allergy and Immunology is dedicated to ensuring that children receive the highest quality of allergy and immunology care. To accomplish its mission, the Section provides a number of educational programs and training and research programs and continually advocates for improved allergy and immunology care and services.

The Section sponsors educational programs for both pediatric generalists and subspecialists at the American Academy of Pediatrics (AAP) National Conference and Exhibition (NCE) each fall and at the American Academy of Allergy Asthma & Immunology annual meeting each spring. The Section’s other educational endeavors include this annual “Best Articles in Pediatric Allergy, Asthma, and Immunology” supplement to Pediatrics, Visiting Professor Program, Pediatric Asthma Speaker’s Kit, online continuing medical education course on “asthma gadgets,” electronic quality improvement in practice program on asthma diagnosis and management (Education in Quality Improvement for Pediatric Practice [eQIPP]), which meets the American Board of Pediatrics maintenance-of-certification criteria, school nurse allergy tool kit, and a number of public education materials. The Section’s Speakers Bureau and Visiting Professor Program offer the public, pediatricians, and other health care professionals with pediatric allergist and immunologists to speak on various topics.

To support training and promote research in pediatric allergy and immunology, the Section awards travel grants to residents and training fellows to participate in and present cases at the AAP NCE and provides outstanding abstract awards for training fellows and junior faculty for presentation at the American Academy of Allergy Asthma & Immunology annual meeting. In close collaboration with other subspecialty societies, the Section is actively involved with initiatives to improve subspecialty education such as the American Board of Allergy and Immunology maintenance-of-certification requirements. Section members represent the AAP in national and government conferences and provide input on federal legislation on behalf of the AAP. For more information on all AAP allergy and immunology resources and initiatives, visit www.aap.org/sections/allergy.

ABOUT THIS SYNOPSIS BOOK
The reviews contained in the 2008 synopsis were written by Fellows of the American Academy of Pediatrics Section on Allergy and Immunology, guest reviewers, and fellows in allergy and immunology training programs who contributed reviews with their mentors.

The editor selected the journals to be reviewed on the basis of the likelihood that they would contain articles on allergy and immunology that would be of value and interest to the pediatrician. Each journal was assigned to a voluntary reviewer who was responsible for selecting articles and writing reviews of their articles. Only articles of original research were selected for review. Final selection of the articles to be included was made by the editor.


The editor and the Section on Allergy and Immunology gratefully acknowledge the work of the reviewers and their trainees who assisted. The reviewers were: Allen Adinoff, MD, Denver, CO; James R. Banks, MD, Arnold, MD; Francisco A. Bonilla, MD, PhD, Boston, MA; Bradley E. Chipp, MD, Sacramento, CA; Joseph A. Church, MD, Los Angeles, CA; John E. Duplantier, MD,
Indianapolis, IN; Casey Geaney, MD, Salem, OR; James E. Gern, MD, Madison, WI; Alan B. Goldsobel, MD, San Jose, CA; John M. James, MD, Fort Collins, CO; Kirs M. Järvinen, MD, PhD, New York, NY; Stacie M. Jones, MD, Little Rock, AR; Michael S. Kaplan, MD, Los Angeles, CA; John M. Kelso, MD, San Diego, CA; Anu Kewalramani, MD, Baltimore, MD; Jennifer S. Kim, MD, Chicago, IL; Mary V. Lasley, MD, Seattle, WA; Mitchell R. Lester, MD, Norwalk, CT; Harvey L. Leo, MD, Ann Arbor, MI; Joann H. Lin, MD, McKinney, TX; Todd A. Mahr, MD, La Crosse, WI; Jennifer M. Maloney, MD, New York, NY; Elizabeth C. Matsui, MD, Baltimore, MD; Cecilia P. Mikita, MD, MPH, Washington, DC; Anna Nowak-Wegrzyn, MD, New York, NY; Tamara T. Perry, MD, Little Rock, AR; Wanda Phipatanakul, MD, MS, Boston, MA; Michael Pistiner, MD, MMSc, West Nyack, NY; Christopher Randolph, MD, Waterbury, CT; Wayne G. Shreffler, MD, PhD, New York, NY; Scott H. Sicherer, MD, FAAP, New York, NY; Elinor Simons, MD, Albany, NY; Brian A. Smart, MD, FAAP, Glen Ellyn, IL; Jonathan M. Spergel, MD, PhD, Philadelphia, PA; Akaluck Thatayatikom, MD, St Louis, MO; David E. Tunkel, MD, Baltimore, MD; Julie Wang, MD, New York, NY; Larry W. Williams, MD, Durham, NC; and Robert A. Wood, MD, Baltimore, MD.

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In these pages you will find reports of advances and key observations that will impact the care of children with allergic and immunologic diseases now and in the near future. The pediatrician is poised to identify infants and children at risk for atopic disease and to intervene. A recent clinical report from the AAP Committee on Nutrition and the Section on Allergy and Immunology presented an update on the role of maternal and infant diet on atopy prevention (Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics, Committee on Nutrition and Section on Allergy and Immunology. Pediatrics. 2008;121[1]:183–191) highlighting the utility of breastfeeding and delaying whole proteins until 4 to 6 months of life. Presenting additional fuel to a growing appreciation of the nuances of dietary influence on atopy are articles reviewed here showing that infants do not develop allergen sensitization in utero, that breastfeeding may delay or prevent atopy (although this effect is modified by maternal atopic status and additional factors), and that delaying introduction of solid foods beyond 4 to 6 months does not necessarily provide additional protection from atopy. Factors apart from allergen exposure, whether in the diet or by inhalation, seem to play a role in the development of atopic disease, because studies have shown only a modest risk for developing new pet allergies when acquiring a new pet, and several studies support the “hygiene hypothesis,” indicating protection from atopy for those in less hygienic conditions and increased risks for those who received antibiotics in the neonatal period. However, several interesting articles have presented conflicting results regarding allergen exposures and the role of hygiene. One area that is not controversial is the adverse effect of tobacco smoke and air pollution on atopic disease. Articles reviewed here indicate increased respiratory allergy risks for children in homes with smokers and for those living near traffic and include data to elucidate possible mechanisms. Also reviewed are articles indicating that food allergy is common and significantly impacts quality of life, and unfortunately, data are showing a greater persistence of egg and milk allergies well beyond the first years of life. Therefore, pediatricians are increasingly required to diagnose and manage food allergy; several articles present pearls and pitfalls to avoid regarding testing. Exciting studies are showing interventions that may treat food allergy in the future. Treatments for anaphylaxis, however, have not changed in decades and are based on avoidance of the trigger, prompt use of injected epinephrine for symptoms, or the use of immunotherapy for insect-venom allergy. However, the identification of platelet-activating factor as a significant mediator in severe anaphylaxis presents a novel target for future therapies. Advances in atopic dermatitis include the recognition of important triggers and cofactors such as allergens and infection, and a key role of the skin barrier; several articles have presented potential therapeutic options to consider today. A variety of articles on asthma pathophysiology, diagnosis, and management were published shortly after the new National Heart, Lung, and Blood Institute Expert Panel 3 guidelines for the diagnosis and management of asthma and addressed evolving paradigms. For example, studies selected by our reviewers addressed the role of infection, social environment, and obesity, suggest aids in diagnosis, including pearls about testing and history-taking, and review global issues about adherence to asthma management plans, including special issues regarding adolescents. A milestone article revealed that a single dose of dexamethasone did not alter hospital admission rates for 2- to 12-month-olds presenting with a first episode of moderate-to-severe bronchiolitis. Articles about medication use for asthma explored outcomes of various approaches to using inhaled corticosteroids and/or a leukotriene antagonist and identified differential effects of β agonists depending on a child’s β2 adrenoreceptor genotype. There is increasing interest in, and evidence for efficacy of, immunotherapy and immunomodulators for treatment of allergies; future modalities of treatment may be more child-friendly (eg, oral administration rather than injection). Several articles on primary and secondary immunodeficiency have provided insight on disease pathogenesis, diagnosis, and emerging therapies, including a breakthrough report that identified the genetic basis of hyper-immunoglobulin E syndrome. On behalf of myself and our reviewers, we hope that this supplement stimulates and informs, giving you practical information to improve the care of children with allergic and immunologic diseases now and an exciting peek out of a window toward understanding therapies on the horizon. For additional information about our Section, please visit www.aap.org/sections/allergy.

Scott H. Sicherer, MD, FAAP
Chair, Section on Allergy and Immunology
Editor, Best Articles Relevant to Pediatric Allergy and Immunology
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URL: www.pediatrics.org/cgi/doi/10.1542/peds.2008-2139C
Eczema, but not wheeze, asthma, or rhinitis, in nonsensitized young children seems to be a risk factor for the development of subsequent allergen sensitization. Sensitization at a young age was a predictor of subsequent wheeze, asthma, and rhinitis but not eczema.

**CONCLUSIONS.** Eczema, but not wheeze, asthma, or rhinitis, in nonsensitized young children seems to be a risk factor for the development of subsequent allergen sensitization. Sensitization at a young age was a predictor of subsequent wheeze, asthma, and rhinitis but not eczema.

**REVIEWER COMMENTS.** Studies have shown that early allergic sensitization can be associated with later development of atopic diseases. This study confirms this observation with the small subpopulation of sensitized infants going on to develop wheeze, asthma, and rhinitis. Development of eczema in this subpopulation was not seen, but the “allergic march” usually begins in early infancy with atopic dermatitis and food allergy and then progresses to allergic rhinitis and asthma by 5 years of age. Less is known about early clinical predictors of sensitization developing later in childhood. This study concentrated on a group of nonsensitized 18-month-olds and found that eczema was a risk factor for the subsequent development of sensitization. It is important to remember that although sensitization (evidence of IgE antibodies to an allergen) was confirmed, clinical allergy was not. It also should be noted that this population of children was selected because of their positive family histories of asthma or current wheeze, so these results may not apply to the general population.

**Anu Kewalramani, MD**
Baltimore, MD
against single allergens was detected in 22 samples. IgA was detected in 98% of the samples. None of the specific IgE found in cord blood was detected at 6 months of age. Cord blood IgE was not detected in any infants whose mothers were not sensitized, and the infants who did have cord blood IgE detected displayed a “fingerprint match” to maternal IgE. In every case, the IgE for a specific allergen detected in cord blood was the same as that detected in maternal blood, and it was present in a relatively similar concentration to that found in maternal blood. The cord blood IgA level also showed a linear relationship to the IgE level, suggesting that more maternal contamination resulted in higher IgE levels in cord blood.

CONCLUSIONS. IgE in cord blood does not reflect in utero sensitization but seems to reflect maternofetal transfer of IgE.

REVIEWER COMMENTS. The questions rarely change, but our answers often do. In recent years, the American Academy of Pediatrics recommended that some parents avoid certain foods during pregnancy to reduce the chance of their child developing atopic disease. These recommendations were based on studies that showed that the human fetus is capable of producing IgE as early as the 20th week of gestation and that cord blood IgE seemed to be a predictor of future atopy. Now the evidence seems to suggest that although sensitization could theoretically occur in utero, it simply does not. This study provides convincing evidence that the IgE in cord blood does not come from the infant but, rather, from the mixing of maternofetal blood, probably at the time of delivery. This study, along with other evidence that has come to light recently, raises questions about whether maternal dietary restriction of allergens during pregnancy impacts allergy outcomes to the avoided food/foods.

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Joseph C. Turbyville, MD
Cecilia P. Mikita, MD, MPH
Washington, DC

Breast-feeding Duration and Infant Atopic Manifestations, by Maternal Allergic Status, in the First 2 Years of Life (KOALA Study)

PURPOSE OF THE STUDY. To investigate the potential effect of modification by maternal allergic status on the relationship between breastfeeding duration and infant atopic manifestations in the first 2 years of life.

STUDY POPULATION. Data from 2705 infants of the KOALA Birth Cohort Study (Netherlands) were analyzed.

METHODS. The data were collected by repeated questionnaires at 34 weeks’ gestation and 3, 7, 12, and 24 months postpartum. Total and specific immunoglobulin E measurements were taken on venous blood samples collected during home visits when the infants were 2 years of age. Relationships were analyzed by using logistic regression analysis.

RESULTS. Longer duration of breastfeeding was associated with a lower risk for eczema in infants of mothers without allergy or asthma ($P_{trend} = .01$) and slightly lower risk in those of mothers with allergy but no asthma ($P_{trend} = .14$). There was no such association for asthmatic mothers ($P_{trend} = .87$). Longer breastfeeding duration decreased the risk of recurrent wheeze independent of maternal allergy ($P_{trend} = .02$) or asthma ($P_{trend} = .06$) status.

CONCLUSIONS. The findings show that the relationship between breastfeeding and infant eczema in the first 2 years of life is modified by maternal allergic status. The protective effect of breastfeeding on recurrent wheeze may be associated with protection against respiratory infections.

REVIEWER COMMENTS. The role of diet in preventing and treating atopic disease has been and continues to be an active area of clinical research. Snijders et al found that a longer duration of breastfeeding was associated with a lower risk of eczema in infants of mothers without allergy or asthma. There was a slight effect in mothers with allergy but no asthma, yet no such relationship was observed for asthmatic mothers. It is interesting to note that no effect modification of maternal allergy/asthma on infant IgE or allergen sensitization was observed. Finally, longer breastfeeding reduced the risk of recurrent wheezing independent of maternal allergic or asthma status, which the authors speculated may be the effect of reduced numbers of respiratory infections. Overall, these findings do support the role of breastfeeding in prevention of atopy, and additional studies are needed to better define the influence of maternal and infant diets during this time frame.

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John M. James, MD
Fort Collins, CO

Effect of Prolonged and Exclusive Breast Feeding on Risk of Allergy and Asthma: Cluster Randomised Trial

PURPOSE OF THE STUDY. To evaluate if exclusive and prolonged breastfeeding reduces the risk of childhood asthma and allergy.
STUDY POPULATION. The Promotion of Breastfeeding Intervention Trial (PROBIT) is a birth cohort of 17,046 healthy, term infants enrolled from 31 maternity hospitals in the Republic of Belarus. Of this group, 13,889 (81.5%) had a follow-up evaluation at 6 years of age.

METHODS. The maternity hospitals were randomly assigned to the intervention or control group. The intervention hospitals adopted the infant-friendly initiative, which was developed by the World Health Organization and the United Nations Children’s Fund to promote and support breastfeeding, particularly among mothers who have chosen to start breastfeeding. The control hospitals continued the practices that were already in place. At follow-up at 6 years of age, subjects were evaluated for allergic symptoms and diagnoses by using the International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire and underwent skin-prick allergy tests.

RESULTS. The intervention led to an increase in duration of any breastfeeding as measured at 3, 6, 9, and 12 months of age. In addition, the prevalence of exclusive breastfeeding was higher in the intervention group at 3 months (43.3% vs 6.4%; \( P < .001 \)) and 6 months (7.9% vs 0.6%; \( P = .01 \)). At follow-up at 6 years of age, there were no differences found between the 2 groups for rates of atopic illness such as wheezing, asthma, hay fever, and eczema. In addition, there were no differences between the groups for the rates of positive skin-prick test results. Additional analysis, after the exclusion of 6 sites (3 experimental and 3 control) with suspiciously high rates of positive skin-prick test results, demonstrated significantly higher rates of positive skin-prick test results for those in the intervention group.

CONCLUSIONS. These results indicate that promoting breastfeeding did not reduce the risk of atopic illnesses at 6 years of age despite large increases in the duration and exclusivity of breastfeeding.

REVIEWER COMMENTS. Rates of pediatric atopic illnesses have increased in industrialized countries over the past several decades. Many studies have searched for reasons that explain this rise and ways to reverse the current trend. The PROBIT study group has focused on the association between breastfeeding and subsequent risk of asthma and other allergic diseases. Previous studies on this topic have demonstrated conflicting results. This study discovered that, despite large increases in the duration of breastfeeding, there was not a reduction in the risk of asthma, hay fever, eczema, or aeroallergen sensitivity. The researchers concluded that public health measures to increase breastfeeding are unlikely to assist in the reduction of atopic diseases. The authors acknowledged that one of the limitations of the study was the relatively low rates of allergic diagnoses among children in the study group. For example, the rates of asthma (1.2%), hay fever (4.6%), and eczema (1.0%) in the PROBIT children were lower than those generally seen in Western industrialized countries. Therefore, it may be difficult to extrapolate these results to countries in which atopic disease occurs more frequently.

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William J. Sheehan, MD
Wanda Phipatanakul, MD, MS
Boston, MA

Effect of Breastfeeding on Lung Function in Childhood and Modulation by Maternal Asthma and Atopy
Guillert TW, Stern DA, Morgan WJ, Martinez FD, Wright AL.
Am J Respir Crit Care Med. 2007;176(9):843–848

PURPOSE OF THE STUDY. Breastfeeding and its relationship to the development of subsequent asthma remain controversial. To clarify these complex issues, this study examined the association between lung function and infant-feeding practices.

STUDY POPULATION. A population-based cohort of healthy infants was enrolled at birth in the Children’s Respiratory Study in Tucson, Arizona (n = 1246); the analysis was of 679 study participants on whom lung-function testing was performed at ages 11 and/or 16 years and provided data regarding infant-feeding practices.

METHODS. In the Children’s Respiratory Study in Tucson, feeding practices were assessed prospectively on the basis of questionnaires completed at enrollment and well-child visits. Formula introduction was categorized as having occurred before 2 months (n = 143, “early formula introduction”), from 2 to before 4 months (n = 336), or at ≥4 months (n = 200, “longer breastfeeding”). Lung function was measured at ages 11 and 16 years. A random-effects model was used to assess the relationship of infant-feeding practices to measures of lung function.

RESULTS. Forced vital capacity (FVC) by age 16 was increased by 103 ± 40 mL (\( P = .01 \)), and the forced expiratory volume in 1 second (FEV1)/FVC ratio was lower (−1.9 ± 0.6%; \( P = .004 \)) in the longer-breastfed children compared with children with early formula introduction. This effect was modified after stratifying according to maternal asthma. Compared with children with early formula introduction, longer-breastfed children with asthmatic mothers had an FVC that was not increased (\( P = .7 \)) and an FEV1/FVC ratio (−5.7 ± 2.4%; \( P = .02 \)) that was significantly decreased by age 16. Longer-breastfed children with nonatopic, nonasthmatic mothers demonstrated an increased FVC (142 ± 71 mL; \( P = .047 \)) and no decrease in FEV1/FVC (\( P = .7 \)) compared with children with early formula introduction.
CONCLUSIONS. Longer duration of breastfeeding favorably influences lung growth in children. However, in the presence of maternal asthma, longer breastfeeding is associated with decreased airflows.

REVIEWER COMMENTS. There seems to be a differential effect of the relation of breastfeeding to lung function on the basis of the asthmatic background of the mother. Breastfed children with nonatopic, nonasthmatic mothers had an increased FVC and no decrease in their airflows. However, children of mothers with asthma with longer breastfeeding did not demonstrate any improvement in FVC but had a significant reduction in airflows, suggesting that the risk for increased asthma in this group may be partly a result of altered lung growth. Children with longer breastfeeding who had atopic but nonasthmatic mothers had intermediate findings, and they showed a similar increase in FVC compared with those with nonatopic, nonasthmatic mothers but a decrease in airflows similar to children with asthmatic mothers. These findings may support the speculation that the milk of mothers with atopy or asthma may differ with regard to immunologically active substances; thus, breastfeeding in these groups may have a different effect on growth and/or development of the airways. It goes without saying that the clinical significance of these findings is unknown. Human milk is uniquely suited to the feeding of infants. There are many well-documented benefits of breastfeeding. For children of nonasthmatic mothers, this study demonstrates a further benefit of breastfeeding. Additional study is needed to draw firm conclusions for other infants.

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Todd A. Mahr, MD
La Crosse, WI

Solid Food Introduction in Relation to Eczema: Results From a Four-Year Prospective Birth Cohort Study

PURPOSE OF THE STUDY. To assess the association between the introduction of solid foods in the first 12 months and the occurrence of eczema during the first 4 years of life in a prospective study of newborns.

METHODS. Data were taken from annually administered questionnaires from a large birth cohort (recruited 1995–1998) comprising an intervention and a nonintervention group. Outcomes were doctor-diagnosed and symptomatic eczema. Multiple generalized estimation equation models were performed for the 2 study groups.

RESULTS. From the 5991 recruited infants, 4753 (79%) were followed up. The 2 study groups were different in their family risk of allergies and feeding practices. No association was found between the time of introduction of solids or the diversity of solids and eczema. In the nonintervention group, a decreased risk was observed for avoidance of soybean/nuts, but an increased risk was seen in doctor-diagnosed eczema for the avoidance of egg in the first year.

CONCLUSIONS. The evidence from this study supports neither a delayed introduction of solids beyond the fourth month nor a delayed introduction of the most potentially allergenic solids beyond the sixth month of life for the prevention of eczema. However, effects under more extreme conditions cannot be ruled out.

REVIEWER COMMENTS. The dilemma of when to introduce solid foods during infancy continues. The data from this investigation support the notion that it is unnecessary to delay solid foods beyond the fourth month of life or allergenic solid foods beyond the sixth month of life to prevent eczema. Specifically, this investigation found no significant effect of timing or diversity of solid foods on eczema outcomes to 4 years of age. The duration of exclusive breastfeeding as compared with the timing of introduction of solid foods, including both formulas made with whole cow’s milk or soy proteins, as well as extensively hydrolyzed casein and partially hydrolyzed whey protein formulas, were examined. It is interesting to note that findings from this investigation seem to indicate that there may be a period of immunologic immaturity during which whole protein in large amounts, whether solid or liquid, may promote the development of atopic disease. These data should help to settle the argument of when to introduce solid foods during infancy for the prevention of eczema and will have a direct impact on global recommendations dealing with this clinical issue.

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John M. James, MD
Fort Collins, CO

Glutamine-Enriched Enteral Nutrition in Very Low-Birth-Weight Infants: Effect on the Incidence of Allergic and Infectious Diseases in the First Year of Life

PURPOSE OF THE STUDY. To determine the effect of glutamine-enriched enteral nutrition in very low birth weight infants on the incidence of allergic and infectious diseases during the first year of life. The authors hypothesized that glutamine may enhance maturation of the immune response by shifting the fetal T-helper 2 (Th2) response
toward Th1 cytokine responses in early infancy, leading to decreased allergic disease later in life.

**STUDY POPULATION.** Infants with a gestational age of <32 weeks and/or birth weight of <1500 g who were admitted to a level III NICU were randomly assigned to receive enteral glutamine or control (L-alanine) supplementation.

**METHODS.** Enteral glutamine supplementation (L-glutamine, 0.3 g/kg per day) was administered to the intervention group from 3 through 30 days of life. Validated questionnaires were later sent to the parents of all eligible children, when they were a corrected age of 1 year, to assess the incidence of allergic and infectious diseases during the child’s first year of life. Bronchial hyperreactivity was defined by report of at least 3 of the following physician-diagnosed symptoms: dyspnea, wheezing, humming/sawing breath sounds, or nightly dry cough without rhinitis.

**RESULTS.** Of 90 eligible infants, 77 participated (response rate: 86%). The risk for atopic dermatitis (AD) was lower in the glutamine-supplemented group (odds ratio: 0.13 [95% confidence interval: 0.02–0.97]). However, other outcomes did not differ between the intervention and control groups, such as incidence of bronchial hyperreactivity. Moreover, upper respiratory tract infections, lower respiratory tract infections, lower respiratory tract infections, and gastrointestinal infections.

**CONCLUSIONS.** Glutamine-enriched enteral nutrition in very low birth weight infants decreased the incidence of AD during the first year of life but had no effect on the incidence of bronchial hyperreactivity and infectious diseases during the first year of life.

**REVIEWER COMMENTS.** The sample size was relatively small and was not powered sufficiently, specifically to assess the incidence of bronchial hyperreactivity. Moreover, the corrected age of 1 year is too early for assessing the incidence of development of atopy and infections. Therefore, it is unclear as to whether AD was prevented or simply delayed in onset among this cohort.

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Jennifer S. Kim, MD
Chicago, IL

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A Prospective Study of Allergy Development in 158 Children and 128 Adults With New Extensive Exposure to Furred Animals


**PURPOSE OF THE STUDY.** To explore allergy development associated with new extensive exposure to furred animals in adults and children.

**STUDY POPULATION.** This was a prospective study of 128 parents (age range: 22.4–49.7 years) and 158 children (age range: 1.5–17.9 years) recruited from 68 families through newspaper advertisements in Sweden. These individuals reported that either they would be buying a dog or cat or that at least 1 child in the household would be starting to ride a horse.

**METHODS.** Subjects were examined before the new exposure and once per year thereafter for 5 years (6 occasions). At each visit, individuals were scored on allergy symptoms. General allergic sensitization was analyzed by Phadiatop (Pharmacia, Uppsala, Sweden), a screening test for allergy to cat, horse, dog, house dust mite, and a few pollen and mold spores. Radioallergosorbent (RAST) testing with relevant allergens was performed to detect allergen-specific immunoglobulin E if screening was positive. Home environmental analyses of furred animal allergens were performed.

**RESULTS.** Thirty subjects from 5 families dropped out of the study. Of the remaining 256 individuals, 248 were exposed to 1 new animal, whereas 8 were exposed to 2 new animals. At the start of the study, 219 participants (86% [122 children and 97 adults]) were nonsensitized, and 37 (15% [15 children and 22 adults]) were sensitized to ≥1 allergen. Among the 219 nonsensitized subjects, only 1 adult developed sensitization to his new animal. No adults developed sensitization to other animals, and no children developed a sensitization to any animals (their own or others). Ten children and 6 adults became sensitized to other allergens. Of the 37 sensitized participants, 4 children and no adults (4 of 37 [11%]) developed sensitization to their new animals. Four children and 2 adults (6 of 37 [16%]) developed sensitization to another animal, and 1 child developed sensitization to a nonanimal allergen. The relative risk (RR) for developing a new sensitization in presensitized children and children was 3.8, whereas the RR for developing new sensitization in presensitized children was 7.3. Because of the small sample size, a RR could not be calculated for developing new sensitization for one’s own animal. Baseline symptom scores were higher for the presensitized group compared with the nonsensitized group, but the scores did not significantly change over the 5-year period, and no individual developed asthma. The levels of animal dander in house dust were significantly higher at the end of the study for dog and horse.

**CONCLUSIONS.** For patients over 1 year of age, exposure to a new furred animal did not seem to increase the rate of new allergic symptoms or sensitization over the next 5 years. This result was not affected by the baseline sensitization status of the subjects. On the basis of this study, there is no strong evidence to recommend avoidance of new animals to prevent new allergy development.
REVIEWER COMMENTS. Currently, it is recommended that allergic patients not obtain new pets because of the concern that they may develop new allergies to those pets. This study seems to indicate that pet exposure after 1 year of age does not confer an increased risk of developing new allergy to the pet in presensitized or nonsensitized individuals. The presensitized participants did have a higher risk of developing sensitization in general, but symptom scores stayed the same, indicating no new allergy development within 5 years. It may be interesting to follow this group for a longer period of time to determine if the results stay the same.

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Anu Kewalramani, MD
Baltimore, MD

Decreased Markers of Atopy in Children With Presumed Early Exposure to Allergens, Unhygienic Conditions, and Infections

PURPOSE OF THE STUDY. To compare 2 populations of children with different risk and protective factors for the development of atopy.

STUDY POPULATION. The study group consisted of 415 children living in community foster homes in Lodz, a large industrial city in Poland. The reference group consisted of 500 children who were living with their parents at home and recruited from primary care centers.

METHODS. Questionnaires were completed by parents or guardians. The primary outcome measures were skin-prick test results to 14 environmental and 4 food allergens and specific immunoglobulin E (IgE) in serum. Secondary outcomes included symptoms of asthma and allergic diseases, lung function, parental allergy, and family history, including life conditions in early childhood, and markers of allergy, such as total IgE serum concentration and eosinophil blood cell count. Stool samples were analyzed for parasites.

RESULTS. The analysis included 408 study children and 402 reference children. Atopy was significantly more prevalent in the reference group (25.9%) than in the foster home children (11.3%). More positive skin-prick test results were observed in children from the reference group than in study children. Specific IgE was significantly higher to dust mites, timothy, and mugworth, as were asthma, rhinitis, and atopic dermatitis, in the reference group. To explain this phenomenon, the investigators selected 16 variables that differed in both groups in the first year of life and related them to atopy. They found that the more cumulative features characteristic of the foster home population (poor living conditions), the lower the risk of atopy.

CONCLUSIONS. Extremely unfavorable environmental circumstances, which are characteristic of the foster home population during early childhood, might prevent atopy.

REVIEWER COMMENTS. These data may suggest that many of our recommendations to parents (cleaning, reducing mold, prevention of infections) are not protective against development of atopy. The limitation of the study was lack of a search for the mechanism that is protective of atopy for those living in poor conditions. One factor could be endotoxin exposure in old homes, which was the case for 90% of those in foster homes. Furthermore, parasitic infections, prevalent in poor socioeconomic and poor hygienic conditions and further suggested by high eosinophil blood counts and serum total IgE concentrations in the nonatopic foster home children, were not fully evaluated.

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Kirsi M. Järvinen, MD, PhD
New York, NY

Infections in Child Day Care Centers and Later Development of Asthma, Allergic Rhinitis, and Atopic Dermatitis Infections in Child Day Care Centers: Prospective Follow-up Survey 12 Years After Controlled Randomized Hygiene Intervention
Dunder T, Tapiainen T, Pokka T, Uhari M. Arch Pediatr Adolesc Med. 2007;161(10):972–977

PURPOSE OF THE STUDY. To evaluate the effect of prevention of common infections in child day care centers (CDCCs) on the later development of allergic disease.

STUDY POPULATION. Children <2 years of age were recruited from 20 CDCCs in Finland for a 15-month randomized, controlled hygiene intervention trial conducted in 1991–1992. Among the children in the intervention CDCCs, there were 27% fewer episodes of acute otitis media and 24% fewer days of antimicrobial agents.

METHODS. Questionnaires were sent in 2003 (12 years later) to 1376 participants of the previous intervention trial; 928 participated (response rate: 68%). The main outcome measures were the number of respondents with a physician diagnosis of asthma, allergic rhinitis, and/or atopic dermatitis (AD) and those who reported symptoms of atopic disease.

RESULTS. No differences were found between the intervention and control groups with regard to rates of asthma, allergic rhinitis, or AD or with frequency of atopic symptoms.
CONCLUSIONS. The prevention of common respiratory tract and enteric infections during early childhood does not change later allergic morbidity.

REVIEWER COMMENTS. This particular hygiene intervention, aimed at decreasing the frequency of common childhood upper respiratory and gastrointestinal illnesses, was not successful in decreasing the development of asthma, allergic rhinitis, or AD among this cohort. The authors argued that the magnitude of the reduction in infections and duration of the intervention should have led to an increase in asthma rates as proposed by the hygiene hypothesis. However, the infection history was based on clinical symptoms and use of antibiotics rather than more definitive laboratory diagnostic measures for specific bacteria and/or viruses. In addition, the follow-up data were based solely on questionnaire findings, which have an inherent reporting bias. Regardless, additional studies are necessary to characterize the role of the hygiene hypothesis in the development of atopic disease.

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Jennifer S. Kim, MD
Chicago, IL

Neonatal Antibiotic Treatment Is a Risk Factor for Early Wheezing

PURPOSE OF THE STUDY. To analyze the risk factors for wheezing at 12 months of age with special reference to antibiotic treatment.

STUDY POPULATION. Participants were infants in western Sweden, which includes urban, rural, and coastal areas, who are participating in an ongoing study. Of the total birth cohort of 16,682 infants born in 2003, 50% (8,176) were randomly selected.

METHODS. Families of infants were sent an invitation to participate in the study. Respondents completed questionnaires regarding the infant and the family when the child was 6 and 12 months of age. Response rates were 68.5% at 6 months and 68.9% at 12 months. Factors significant in an initial univariate analysis were analyzed in a multivariate model.

RESULTS. At 12 months of age, 20.2% of infants had ≥1 episode of wheezing, and 5.3% had ≥3 episodes of wheezing during the first year of life. Overall, 41% received inhaled corticosteroids (ICSs). In the multivariate analysis, independent significant risk factors for “wheezing ever” and for wheezing disorder treated with ICSs were neonatal antibiotic treatment, male gender, gestational age (GA) of <37 weeks, having a mother with asthma, having a sibling with asthma or eczema, and breastfeeding for <5 months. Treatment with antibiotics was more common among extremely preterm infants. Neonatal antibiotic treatment increased the risk of later wheezing in both term and preterm infants. The odds ratio (OR) for infants with a GA of ≥33 weeks was 2.9 (95% confidence interval: 1.8–4.7) and for infants with a GA of ≥37 weeks was 2.9 (95% confidence interval: 1.7–4.9).

CONCLUSIONS. The authors found that treatment with antibiotics in the neonatal period is the most potent independent risk factor for wheezing treated with ICSs during the first year of life.

REVIEWER COMMENTS. Previous studies have suggested that antibiotics in the first year of life are a risk factor for developing asthma. It is difficult, however, to exclude the confounder that infants who wheeze may receive more antibiotics during the first year of life. The advantage of this large study is that administration of antibiotics in the neonatal period was evaluated as an independent risk factor. An obvious limitation, however, is that the study was conducted with a questionnaire that required parental recall. Additional limitations that were partly addressed included lack of determination of the type or duration of antibiotics given, the underlying diagnoses, and confirmation of asthma diagnoses. Nonetheless, this study supports the hygiene hypothesis and presents an opportunity to consider asthma/allergy prevention strategies.

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Mariah M. Pieretti, MD
Scott H. Sicherer, MD, FAAP
New York, NY

Atopic Sensitization and the International Variation of Asthma Symptom Prevalence in Children

PURPOSE OF THE STUDY. The International Study of Asthma and Allergies in Childhood (ISAAC I) found that the prevalence of asthma symptoms varies >15-fold among various countries. ISAAC II was designed to identify why such differences occur.

STUDY POPULATION. Studied were a random sample of 8- to 12-year-old children (n = 54,439) in 22 countries worldwide.

METHODS. Data were collected by parental questionnaires (n = 54,439) and skin-prick tests (n = 31,759). Economic development was assessed by gross national income per capita.

RESULTS. Prevalence of current wheeze (wheeze during the last year) ranged from 0.8% (Ecuador) to 25.6%.
The prevalence of skin-prick test reactivity ranged from 1.7% (Ghana) to 45.3% (Hong Kong). The association between current wheeze and skin-prick test reactivity was stronger in affluent countries (odds ratio: 4.0 [95% confidence interval: 3.5–4.6]) than nonaffluent countries (odds ratio: 2.2 [95% confidence interval: 1.5–3.3]). The population attributable fraction (PAF), or fraction of current wheeze attributable to skin-prick test reactivity, ranged from 0% (Turkey) to 59.6% (Hong Kong). Overall, the combined PAFs were substantially higher in affluent countries (40.7%) than in nonaffluent countries (20.3%).

CONCLUSIONS. The authors concluded that the link between atopic sensitization and asthma symptoms in children differs strongly between populations and increases with economic development.

REVIEWER COMMENTS. The variation in rates of asthma and allergy around the world are striking, and the fact that the relationship between allergy and asthma seems related to the level of economic development in any given country is fascinating. The authors speculated that this may be a result of exposures or other factors that are different for children in more or less affluent countries that make it more or less likely that allergy would lead to asthma. Such factors could include greater exposure to helminth infections or different commensal bacteria in poorer countries and higher rates of urbanization and obesity in wealthier countries.

Allergens and Environmental Exposures

Children’s Respiratory Health and Mold Levels in New Orleans After Katrina: A Preliminary Look


PURPOSE OF THE STUDY. To study indoor air mold levels, lung function, and respiratory symptoms in a sample of children returning to live in New Orleans, Louisiana, immediately after Hurricane Katrina.

STUDY POPULATION. Participants were children aged 7 to 14 years currently residing in greater New Orleans with no plans to move. All study participants were recruited from a private primary school in the Garden District of New Orleans.

METHODS. Parents of all study participants completed a respiratory health symptom questionnaire during February/March and April/May 2006. During these defined study points, the children performed spirometry, and indoor and outdoor air sampling was performed. All data were statistically analyzed to determine if indoor mold levels correlated to the children’s respiratory health.

RESULTS. Average indoor and outdoor mold concentrations decreased during the study, although only the reduction in outdoor mold levels reached statistical significance. Pulmonary function of all study participants was >80% of predicted at both study points. Participants were stratified according to asthma history and flooding status, but no lung-function decrements were observed with stratification. A trend was seen in which respiratory symptoms increased after the hurricane and seemed to improve during the study. This difference, however, was only statistically significant for lower respiratory tract symptoms.

CONCLUSIONS. Indoor mold levels were low and pulmonary function in a sample of children living in New Orleans was normal >6 months after Hurricane Katrina.

REVIEWER COMMENTS. The Children’s Respiratory Health Study is the first published study to evaluate pediatric respiratory health and indoor mold in the post–Hurricane Katrina environment. Although a small sample size was evaluated, this study provides practitioners with objective, reassuring findings. This study, however, included children who were exposed to limited flood damage. This possible selection bias should not allow us to ignore respiratory symptoms in the pediatric population returning to the more damaged neighborhoods. We look forward to further research studying this at-risk pediatric population.
sisted of nursing visits designed to decrease environmental allergen and tobacco-smoke exposure and improve the quality of maternal caregiving and illness management. Psychosocial information was used to individualize plans for behavior change.

RESULTS. The percentage of children with asthma at 4 years of age did not differ significantly between the 2 groups (intervention and control) \( (P = .33) \). However, among children with lower symptom severity at study entry, the odds of developing asthma were 3 times lower for those in the intervention group \( (P = .04) \). Caregiver quality of life was significantly better \( (P = .01) \) and symptom severity was lower \( (P = .03) \) for those in the intervention group. It is interesting to note that asthma rates did not differ significantly for children whose mothers had asthma or for those found to be atopic (\( \geq 1 \) positive skin-test result).

CONCLUSIONS. Multifaceted intervention was unsuccessful as a secondary intervention in decreasing the development of asthma in this cohort as a whole. However, asthma development was ameliorated in children with low symptom severity in infancy.

REVIEWER COMMENTS. The nonmedical interventions, performed in a relatively small cohort, were ineffective in altering the progression from infant wheezing to persistent asthma at 4 years of age. However, they did have a significant positive effect on the caregivers’ quality of life compared with those in the control group. The authors hypothesized that children with lower severity at baseline may be more susceptible to changes in environmental exposures or illness-related caregiving. However, the study did not ensure that children with more severe symptoms received appropriate treatment with inhaled corticosteroids or that the medications were administered appropriately. This may explain why only children with milder disease benefited from environmental interventions. The investigators plan to follow these children until the age of 7 years.

Tobacco and Air Pollution

Home Exposures to Environmental Tobacco Smoke and Allergic Symptoms Among Young Children in Singapore


PURPOSE OF THE STUDY. To investigate the association of environmental tobacco smoke (ETS) exposure among preschool-aged children with allergic symptoms in homes in Singapore.

RESULTS. The nonmedical interventions, per-

Cigarette Smoke Exposure Impairs Dendritic Cell Maturation and T Cell Proliferation in Thoracic Lymph Nodes of Mice


PURPOSE OF THE STUDY. Airborne antigens are processed and presented by respiratory tract dendritic cells (DCs). The purpose of this study was to determine the consequences of cigarette-smoke exposure on DC function in mice.

METHODS. Mice were exposed to cigarette smoke 5 days per week for 1 month. There was also a control group of

METHODS. This study used a cross-sectional design, adopt-

RESULTS. The response rate was 70.0%, and 4759 children from 97 centers participated. After adjusting for covariates, it was found that home ETS exposure was associated with increased rates of current symptoms of rhinitis (PR: 1.23 [95% CI: 1.01–1.50]) and rhinoconjunctivitis (PR: 1.79 [95% CI: 1.26–2.54]). These associations followed dose-response trends with respect to the number of cigarettes smoked or smokers in the home. Home ETS exposures were also associated with higher PRs of wheeze, nocturnal cough, and doctor-diagnosed asthma. Compared with paternal smoking, higher risks of the above-listed outcomes were found for maternal smoking.

CONCLUSIONS. Home ETS exposure is a risk factor associated with rhinitis and asthma among preschool-aged children.

REVIEWER COMMENTS. This article provides additional evidence that exposure to ETS is associated with asthma and rhinitis. These findings support the continued need to discuss the risks of ETS exposure when reviewing anticipatory guidance items with families.
Air Quality and Pediatric Asthma-Related Emergencies


PURPOSE OF THE STUDY. To examine the effects of seasonality, outdoor air quality, climatic factors, and presence of outdoor aeroallergens on emergency department (ED) visits for children with asthma.

STUDY POPULATION. Dates with “low” and “high” pediatric ED visits with a primary diagnosis of asthma (International Classification of Diseases, Ninth Revision code 493) were identified for children presenting to Alfred I. du Pont Hospital for Children from January 1, 2000, to December 31, 2003. Dates with zero ED visits for asthma were labeled as low, and dates with ≥7 ED visits for asthma were labeled as high.

METHODS. This was a retrospective review of ED visits for asthma and environmental factors, with 8-hour average ozone, 24-hour average nitrogen dioxide (NO2), and particulate matter with an aerodynamic diameter of <2.5 μm (PM2.5) levels, as well as tree pollen, weed pollen, grass pollen, and mold levels obtained. Monthly minimum, maximum, and mean temperatures and precipitation levels were obtained. Seasonal and environmental factors associated with high and low ED visits for asthma were compared with independent t tests.

RESULTS. Of 1460 dates reviewed over a 4-year period, 106 were classified as low-visit days and 103 were classified as high-visit days. Of high-visit days, 45.6% were in summer, 28.2% were in spring, 14.6% were in winter, and 11.7% were in summer. The greatest proportion of high-visit days occurred in September. Mean 8-hour average ozone for low-visit days was significantly higher than on high-visit days (0.047 vs 0.033 ppm). No differences were observed in mean 24-hour average NO2 levels on high- and low-visit days. The mean 24-hour average PM2.5 was higher on low-visit days (18.54 μg/m3) versus high-visit days (13.85 μg/m3). Trends were observed with higher weed and tree pollen on high-visit days. Mean temperature and precipitation were both significantly lower on high-visit days.

CONCLUSIONS. Asthma-related ED visits were associated with aeroallergens and climactic factors. Air pollutants seem to play a smaller role in asthma-related ED visits.

REVIEWER COMMENTS. This retrospective analysis has identified significant seasonal variation in high and low ED visits for pediatric asthma. The results suggest that the observed seasonal variation may be related to weed- and tree-pollen levels and climactic factors. However, the study may have been inadequately powered to identify minor differences between the high- and low-visit groups. Air pollutant levels were not associated with asthma-related ED visits in the expected direction (low-visit days had higher pollutant levels). Perhaps there is a
Effect of Exposure to Traffic on Lung Development From 10 to 18 Years of Age: A Cohort Study

PURPOSE OF THE STUDY. To investigate the association between residential exposure to traffic and 8-year lung-function growth in children.

STUDY POPULATION. Two cohorts of 4th-grade children with a mean age of 10 years were recruited from 12 southern California communities and were followed for 8 years. All eligible children were invited, and 3677 (82%) participated; 1445 children were followed for the full 8 years.

METHODS. Yearly pulmonary-function data were obtained for each participant by trained technicians using standard equipment. Indicators of residential exposure to traffic were determined by proximity of the child’s residence to the nearest freeway or major nonfreeway road and by dispersion-model estimates including residence distance to roadways, vehicle counts, vehicle emission rates, and meteorological conditions. Regional air pollution was monitored at a central site within each community. Baseline questionnaires were completed regarding demographic data, doctor-diagnosed asthma, in utero exposure to maternal cigarette smoke, and household exposure to air pollutants. Yearly questionnaires updated information on asthma and personal or environmental tobacco-smoke exposure. Regression models also included adjustment for height, BMI, and recent aerobic activity and respiratory illness.

RESULTS. Children living <500 m from a freeway had reduced 8-year lung-function growth compared with children living >1500 m from a freeway (forced expiratory volume in 1 second deficit: −81 mL [95% confidence interval: −143 to −18]). This effect was slightly greater after adjustment for socioeconomic status and indoor air pollution and after omission of children who changed residence within the study area and continued to participate. Reduced lung-function growth was independently associated with freeway distance and regional air pollutant levels, including nitrogen dioxide, acid vapor, elemental carbon, and particulate matter with aerodynamic diameters of <10 and 2.5 µm. At 18 years of age, lung function was decreased among children who lived <500 m from a freeway (forced expiratory volume in 1 second: 97.0% [95% confidence interval: 94.6 to 99.4]; P = .013).

CONCLUSIONS. The adverse effects of local exposure to freeway traffic on children’s lung development are independent of regional air quality and may result in lung-function deficits later in life.

REVIEWS COMMENTS. This well-designed study suggests a causal association between residential traffic exposure and adverse effects on children’s lung function, especially for children living closest to freeways. A number of other recent cohort studies in children have also suggested associations between traffic-pollution exposure and asthma, respiratory symptoms, and allergic sensitization. Future studies are needed to determine minimum safe distances from major roadways for homes and schools and to continue evaluation of the guidelines restricting levels of airborne pollutants. Concerns regarding the effects of traffic pollutants on children’s respiratory health should continue to be a focus of asthma research.

FOOD ALLERGY

Prevalence and Cumulative Incidence of Food Hypersensitivity in the First 3 Years of Life

PURPOSE OF THE STUDY. To investigate the prevalence and incidence of food hypersensitivity.

STUDY POPULATION. The authors studied a whole population-based birth cohort of 969 children (91% of the target population) born on the Isle of Wight (United Kingdom) between 2001 and 2002.

METHODS. At age 1, 2, and 3 years, all children/parents were invited to attend a clinic for a medical examination and to answer a questionnaire pertaining to food hypersensitivity (FHS), defined as any adverse reaction to food. In addition, all children were asked to participate in skin-prick testing (SPT) to milk, egg, wheat, peanut, sesame, fish, aero-allergens, and other allergens as
guiding by history. Children with a positive SPT result to a food that they have eaten without difficulty and children who had previous adverse reactions to specific foods were asked to undergo food challenges. With the exception of peanut and sesame, food challenges were performed after 6 months of age. Food challenges to peanut and sesame were held until the children were 3 years of age. Children with large SPT diameters considered to be >95% predictive of allergy did not undergo challenge. Frequency tables were produced at each time point, and comparisons between prevalence rates in this study and a historical reference population (Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. Pediatrics. 1987;79[5]:683–688) was made by using Fisher’s exact test.

RESULTS. Over the 3-year study period, 942 (97.2%) of the children were evaluated at 1, 2, or 3 years, whereas 83.3% were seen at 1, 2, and 3 years. Sensitization rates as determined by positive SPT results at 1, 2, and 3 years were 2.2%, 3.8%, and 4.5%, respectively. Of those who were evaluated at all visits, 33.7% reported food-related problems. FHS was reported in 8.3% of those who were evaluated at their 2-year visit and 8.3% at their 3-year visit. The cumulative incidence of FHS, according to open food challenges and a clinical history, was 6% (58 of 969; 95% confidence interval [CI]: 4.6–7.7), whereas the cumulative incidence according to double-blinded, placebo-controlled food challenges was 5% (48 of 969; 95% CI: 3.7–6.5). On the basis of those with a positive open food-challenge result and clear history, the prevalence of FHS at ages 2 and 3 years was determined to be 2.5% (21 of 858; 95% CI: 1.5–3.7) and 3.0% (27 of 891; 95% CI: 2.0–4.4), respectively. Nine children who were not invited to undergo food challenges were excluded because their SPT diameter was >95% of the positive predictive value. Also, 11 and 19 of the subject’s families that declined food challenges at ages 2 and 3, respectively, had histories and testing results that suggested FHS. In addition, the percentages of those diagnosed with FHS on the basis of positive food-challenge results and a clear history and were SPT-positive was 26% (age 1 year), 44% (age 2 years), and 71% (age 3 years).

CONCLUSIONS. The authors reported that the cumulative incidence of FHS, according to food challenges and a clinical history, by 3 years of age was 5% to 6%. They concluded that when comparing their findings with the 1987 US study performed by Bock, there were no significant differences in the cumulative incidence of FHS.

REVIEWER COMMENTS. A major strength of this study is that the authors used an unselected population that may be more representative of patients seen by pediatricians than those followed by subspecialists. Because the authors set the definition of FHS to depend on agreeing to participate and meeting criteria for participation in food challenges, the reported incidence and prevalence of true adverse reactions to food is likely to be underestimated. Additional bias could exist because many subjects did not participate in food challenges because they either had skin-testing results that suggested that they would have a clinical reaction or they had histories of recent reactions or clinical improvement with elimination of the offending food. The importance of this study is that using the authors’ very conservative definition of FHS, the reported incidence of FHS is conservatively 5% to 6%, which represents a significant pediatric health problem and underscores the need for appropriate evaluation and management of adverse reactions to food.

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Michael Pistiner, MD, MMSc
West Nyack, NY

The Impact of Food Hypersensitivity Reported in 9-Year-Old Children by Their Parents on Health-Related Quality of Life


PURPOSE OF THE STUDY. To examine the impact of reported food hypersensitivity (FHS) in 9-year-old children on parental perception of health-related quality of life (HRQoL).

STUDY POPULATION. A population-based birth cohort of 4089 Swedish children was used for a nested case-control study based on age 4 questionnaires (689 subjects, 689 controls). Parents completed questions pertaining to HRQoL at 9 years of age (~75% completion).

METHODS. FHS was defined as parental report of wheezing/prolonged cough, runny/stuffy nose in the absence of a cold, itchy/watery eyes, eczema, urticaria, vomiting/diarrhea, or other symptoms after ingestion of a specific food in the last year. Those with previous FHS but avoiding the food were considered to have FHS. Pronounced FHS was defined by wheezing/prolonged cough, >1 symptom, or symptoms occurring >1 time per month. A validated 28-item form was used to explore parental perceptions of their children’s HRQoL and was supplemented by a disease-specific nonvalidated questionnaire. Children with FHS at age 9 (212) were compared with those without FHS but with asthma, allergic rhinitis, or eczema (221) and to those with no allergic disease (581).

RESULTS. Primary analysis showed that compared with children with asthma, allergic rhinitis, or eczema but no FHS, those with FHS had significantly worse scores on physical functioning, limitations in school or social activities resulting from physical problems, and decreased

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perception of overall health (there were significant differences in additional subscale scores between those with FHS and those without any allergic disease). Even greater differences were observed for those with pronounced FHS and for those with high specific immunoglobulin E to foods. On the basis of the disease-specific questionnaire, parents reported significantly more feelings of sadness/restriction in everyday life and family conflicts for those with pronounced FHS compared with those with more mild or infrequent symptoms.

CONCLUSIONS. FHS had a significant impact on parentally reported HRQoL of 9-year-old children and their families.

REVIEWER COMMENTS. This study supports that there is a negative impact of adverse food reactions on perceived HRQoL. This unselected population may more accurately represent patients seen by pediatricians than populations used in previous QoL studies (tertiary care centers). The authors’ definition of FHS included a heterogeneous group of adverse food reactions (~40% not doctor diagnosed), but there was a significant negative impact on perceived HRQoL regardless of the etiology. It is interesting to note that the subjects with “physician-diagnosed food allergy” had significantly better scores in limitations in school or social activities resulting from emotional or behavioral problems and scored no worse than those without a diagnosis of food allergy on any subscale, which emphasizes the importance of appropriate management. The pediatrician plays a critical role in initiating the appropriate evaluation (eg, determining by history if there is a likely food allergy) and management (eg, avoidance instructions, prescription of self-injectable epinephrine, referral to an allergist, etc) that may improve HRQoL.

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Michael Pistiner, MD, MMSc
West Nyack, NY

The Natural History of IgE-Mediated Cow’s Milk Allergy

PURPOSE OF THE STUDY. Cow’s milk allergy (CMA) is generally reported to resolve in 85% of children by the age of 3 to 5 years. This study evaluated the rate of resolution of CMA in a food-allergy referral population with emphasis on factors predicting resolution.

STUDY POPULATION. Final selection of charts for review and abstraction were obtained from clinical records of 4117 patients seen by 1 of the authors over 14 years; 1368 patients had food allergy, and 1073 patients had CMA. After excluding non–immunoglobulin E (IgE)-mediated disease and fewer than 2 visits, 807 patients’ charts were reviewed.

METHODS. A retrospective chart review was conducted, and 3 definitions were applied regarding tolerance of cow’s milk. The strictest definition (1) was tolerating home introduction or a supervised food challenge, the second definition (2) included those with a milk-specific IgE level of <3 kU/L and no history of clinical reactions in 1 year, and the least stringent criteria (3) included a milk-specific IgE level of <15 kU/L and no history of clinical reactions in the preceding year.

RESULTS. When tolerance was defined by using the most stringent criteria, only 5% outgrew their allergy by 4 years of age, 21% by 8 years of age, 37% by 12 years of age, and 55% by 16 years of age. With criteria 2, the rates of resolution were 19% at 4 years of age, 42% by 8 years of age, 64% by 12 years of age, and 79% by 16 years of age. For the least stringent criteria (3), 26% were tolerant by 4 years of age, 56% by 8 years of age, 77% by 12 years of age, and 88% by 16 years of age. The higher the milk-specific IgE level noted per patient, the less likely was prompt resolution (P < .001). Coexisting asthma (P < .001) and allergic rhinitis (P < .001) were also significant predictors of delayed tolerance.

CONCLUSIONS. The prognosis for CMA in this population was worse than previously reported. However, some patients developed tolerance during adolescence, indicating that follow-up and reevaluation of patients with CMA is important in their care. Cow’s milk-specific IgE levels are highly predictive of outcome.

REVIEWER COMMENTS. It is depressing to see recent studies supporting a slower resolution of common food allergies (see also the following review on a study about egg allergy). However, the good news is that hope is not lost when an allergy persists into school age; these studies confirm that children may continue to “outgrow” allergies into adolescence and that repeated evaluations are helpful. It must be appreciated that this study represents a referral population that likely is enriched for children with a more persistent phenotype of milk allergy.


Scott H. Sicherer, MD, FAAP
New York, NY

The Natural History of Egg Allergy

PURPOSE OF THE STUDY. To estimate the proportion of children with egg allergy who develop egg tolerance and to identify predictors of tolerance development.

STUDY POPULATION. Subjects were 881 egg-allergic children identified by chart review from an academic allergy
practice. Egg allergy was defined as a clear history of immunoglobulin E (IgE)–mediated allergic reaction to egg ingestion or an egg-specific IgE level of $\geq 2$ kU/L without known tolerance.

**METHODS.** Information was collected and included demographics, symptoms at egg-allergy diagnosis, presence of other atopic diseases and food allergies, dietary history, age/symptoms with egg exposure, egg skin-prick tests, egg-specific IgE, oral food challenge results, and outcome of egg and other food allergies. Three definitions were used to define oral tolerance to egg in all 881 subjects: definition 1 included those children who passed a formal oral food challenge or had successful home introduction of egg; definition 2 included children who met definition 1 and had an egg-specific IgE level of $<2$ kU/L and no reaction within the previous year; and definition 3 included children who met definition 2 but had an egg-specific IgE level of $<6$ kU/L.

**RESULTS.** Of the 881 subjects, the median age at the initial visit was 14 months, and median follow-up was 4.9 years with 68% male subjects. Most (93%) had at least 1 other food allergy, 54% had asthma, 55% had allergic rhinitis, and 81% had eczema. Of 881 subjects, 375 (43%) had a documented history of allergic reaction to rhinitis, and 81% had eczema. Of 881 subjects, 375 (43%) had a documented history of allergic reaction to egg and evidence of egg sensitization. The other 506 subjects were included on the basis of an egg-specific IgE level of $\geq 2$ kU/L and no reaction within the previous year; and definition 3 included children who met definition 2 but had an egg-specific IgE level of $<6$ kU/L.

The primary study group comprised children with a peak IgE level of $<2$ kU/L who outgrew their egg allergy by 4 years of age, 26% by 8 years of age, 48% by 12 years of age, and 68% by 16 years of age. Using definition 2, 11% were tolerant at 4 years of age, 41% by 8 years of age, 65% by 12 years of age, and 82% by 16 years of age. Using definition 3, 19% developed tolerance by 4 years of age, 55% by 8 years of age, 76% by 12 years of age, and 91% by 16 years of age. When the relationship of peak egg IgE levels and the development of tolerance was examined, children with a peak IgE level of $<2$ kU/L had the fastest rate of tolerance development, those with a peak IgE level between 2 and 49.9 kU/L developed tolerance at a much slower rate, and those with a peak IgE level of $\geq 50$ kU/L were the slowest and generally did not develop tolerance. The median time to tolerance was higher in children with other atopic disease (eg, 13.5 years for asthmatic children versus 8.5 years for nonasthmatic children [$P < .001$]; 12.6 years with rhinitis versus 11.8 years without rhinitis [$P < .001$]; 12.3 years with eczema versus 11.1 years without eczema [$P = .055$]).

**CONCLUSIONS.** This study supports the general idea that most children with egg allergy will eventually outgrow their allergy, but at an older age than previously implicated. Egg-specific IgE levels are predictive of tolerance development, and the presence of other atopic disease delays the process.

**Clinical Characteristics of Peanut-Allergic Children: Recent Changes**


**PURPOSE OF THE STUDY.** To determine if patients seen in a referral clinic are experiencing initial allergic reactions to peanuts earlier, compared with a similar population profiled at a different medical center 10 years earlier.

**STUDY POPULATION.** The primary study group comprised children evaluated and diagnosed as having peanut allergy in the Duke University pediatric allergy and immunology clinic in North Carolina between July 2000 and April 2006.

**METHODS.** This was a retrospective chart review with some follow-up telephone calls to determine missing data. Food-allergy diagnoses were based on clinical and laboratory data or oral food-challenge results. Results were compared with those previously published from a referral practice at Johns Hopkins Hospital in Baltimore, Maryland, from a decade earlier.

**RESULTS.** One hundred forty patients (70 born between 1988 and 1999 and 70 born between 2000 and 2005) were included in the study. Eighty-three percent reacted on their first known exposure to peanut. The median age of first peanut exposure was 14 months, and median age at first reaction was 18 months. This contrasts to the study at Johns Hopkins Hospital between 1995 and 1997, in which the median age at first reaction was 22 months. Within the Duke University patient group, those born before 2000 were first exposed to peanuts at a median age of 19 months and reacted at a median age of 21 months, compared with first exposure at 12 months and first reaction at 14 months for those born in or after 2000. Most (68%) patients demonstrated sensitization or clinical allergy to other foods (53% to eggs, 26% to cow’s milk, 20% to tree nuts, 11% to fish, 9% to shellfish, 7% to soy, 6% to wheat, and 6% to sesame seeds).
CONCLUSIONS. The ages of first peanut exposure and reaction have declined among peanut-allergic children seen in a referral clinic. The decline in the age of first peanut reaction seems to be attributable to earlier exposure.

REVIEWER COMMENTS. Assuming there is not a referral bias driving these results between the 2 sites or within the Duke University site over time, there are 2 ways to interpret these data: either peanut-allergic reactions are occurring earlier because we are feeding peanut earlier, or peanut reactions will occur in those disposed to it whenever they are fed it, whether at age 1 or 2 years. I am going to argue for the latter explanation on the basis of there being no difference in the percentage who reacted at first exposure or in the time between first exposure and first reaction. We have much more to learn regarding the influence of timing of feeding an allergenic food such as peanut; studies on this unresolved issue are underway. Many factors may play a role, but it is intriguing that, counter to what is implied in this study (that early exposure may be bad and related to an apparent rise in peanut allergy), peanut allergy is uncommon in countries that feed peanut earlier (e.g., Israel). Other important messages in this study are that (1) sesame allergy is prominent, and (2) if you see egg or milk allergy, consider the possibility that peanut allergy is lurking.

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Scott H. Sicherer, MD, FAAP
New York, NY

Sensitization to Human Milk

PURPOSE OF THE STUDY. To analyze the specificity and possible biological relevance of immunoglobulin E (IgE) reactivity to human milk antigens in milk-allergic patients.

STUDY POPULATION. Milk-allergic children and adults from different European countries with a positive case history, positive skin-prick reactions, and specific IgE to cow’s milk extract were selected.

METHODS. The specificity of IgE reactivity to cow’s milk and human milk antigens was analyzed with sera from milk-allergic children and adults by immunoblotting. IgE cross-reactivity between milk antigens was studied by immunoblot inhibition experiments. To demonstrate that IgE reactivity to human milk antigens is not caused by alloseactivity or transmission of foreign antigens, genetically unrelated mothers’ milk samples were analyzed before and after intake of dietary milk products. Skin-prick tests were performed with cow’s, sheep’s, mare’s, and human milk samples.

RESULTS. IgE antibodies to human milk were found in >80% of the tested milk-allergic patients (n = 17). Cross-reactive IgE-reactive human antigens such as α-lactalbumin and non–cross-reactive human milk an-
METHODS. A normal pattern and extent of collagen and elastin fiber composition in the esophageal lamina propria was established in the control specimens. Extent of fibrosis was determined on trichrome-stained specimens. Fibrosis was defined as abnormally increased collagen deposition. Hematoxylin and eosin staining, and immunohistochemical staining for tryptase and major basic protein and were used to determine intraepithelial and lamina propria maximum eosinophil counts and extent of eosinophilic degranulation at 400 high-power field as well as mast cell presence and extent of degranulation. Basal thickness and lymphocyte and plasma cell infiltration were also determined.

RESULTS. Subepithelial fibrosis was present in 57% of the patients with EE, 1 patient with eosinophilic gastroenteritis, 0 patients with gastroesophageal reflux disease, and 1 control patient. Dysphagia was present in 42% of the patients with fibrosis. Dysphagia was not observed in the absence of fibrosis. Fibrosis was not influenced by increasing eosinophil or mast cell counts; however, fibrosis was significantly associated with eosinophilic degranulation in the epithelium.

CONCLUSIONS. Subepithelial fibrosis is both common in EE and specific for this disease in children. There is a strong association between dysphagia and fibrosis in children with EE. The extent of eosinophilic activation seems to be influenced by the degree of fibrosis.

REVIEWER COMMENTS. This article provides additional insight into the pathology of EE, an inflammatory disorder that is often associated with food allergy. Although a strong relationship was seen between fibrosis and dysphagia in this study, its impact on motility in this specific disease would be an interesting additional determination. Nevertheless, fibrosis preceded the dysphagia in this study, and it may serve as an early marker of more-severe disease. Fibrosis was associated with eosinophilic activation, which may also serve as a maker for more-severe disease. The presence of 1 or both may indicate a need for more aggressive treatment.

Patterns of Quantitative Food-Specific IgE-Antibodies and Reported Food Hypersensitivity in 4-Year-Old Children

PURPOSE OF THE STUDY. To investigate the probability of parentally reported food hypersensitivity (FHS) in relation to levels of food-specific immunoglobulin E (IgE) by using a birth cohort at 4 years of age.

STUDY POPULATION. The researchers studied a population-based birth cohort of 4089 Swedish children. Parents...
completed questionnaires pertaining to allergy-related symptoms at 2 months, 2 years, and 4 years of age. Those with questionnaire data at 4 years (3742) were invited for specific IgE testing.

**METHODS.** FHS was defined as parental report of “symptoms such as eczema, vomiting/diarrhea, urticaria, facial edema, itchy eyes/runny nose or asthma related to ingestion of a specified food between ages 2 and 4 years.” Allergen-specific IgE levels (ImmunoCAP [Pharmacia, Uppsala, Sweden]) were measured for a panel of 6 foods (cow’s milk, egg white, cod, peanut, soy, and wheat). Plasma IgE concentrations of ≥0.35 kU/L were considered sensitive/positive. Analyses were performed on children with completed questionnaire data at 2 months of age and 4 years of age and for those whom complete data on IgE were available (n = 2336).

**RESULTS.** At 4 years, 284 (12%) subjects met criteria for FHS and, compared with those without FHS, were more likely to have doctor-diagnosed food allergy (44% vs 3%). The most common symptoms were eczema (50%), vomiting/diarrhea (39%), urticaria (30%), facial edema (26%), itchy eyes and nose (18%), and asthma (6%). Of all children tested, 13% (305) were sensitized to at least 1 food, whereas 31% of those with FHS and 11% of those without FHS were sensitive to at least 1 food. The prevalence of FHS in the setting of sensitivity to that food was 11% for milk, 29% for egg, 41% for cod, 38% for peanut, 10% for soy, and 6% for wheat. The levels of specific IgE that correlated with the 90% probability of reporting FHS to that food were 22 kU/L for milk, 13 kU/L for egg, and 4.7 kU/L for cod (small sample size). A 90% probability of FHS with IgE was not reached for peanut, soy, or wheat.

**CONCLUSIONS.** Quantitative IgE to milk, egg, and cod can be useful for evaluating IgE-associated FHS in 4-year-old children, but such testing may be of limited value for soy and wheat.

**REVIEWER COMMENTS.** This unselected population may more accurately represent patients seen by the pediatrician than those followed at tertiary care allergy facilities, which more often generate reports regarding relationships of IgE test results to food-allergy outcomes. However, there are several caveats. A major limitation and caution is that food allergy was not confirmed by physicians and oral food-challenge tests. Also, keep in mind that the findings about food-specific IgE levels were reported for 4-year-old children and may have been different at other ages. A major take-home point of this study is that there was a high rate of sensitivity (IgE > 0.35 kU/L) to foods that were not causing FHS. In clinical practice, such a high rate of false-positive results can cause confusion and unnecessary dietary restrictions if tests are performed without a clinical reason. Thus, it is important to consider which tests, if any, should be performed when evaluating adverse food reactions.

**Correlation Between Specific Immunoglobulin E Levels and the Severity of Reactions in Egg Allergic Patients**


**PURPOSE OF THE STUDY.** To determine if specific immunoglobulin E (IgE) antibody titers to egg were predictive of the severity of reaction during a standardized food challenge.

**STUDY POPULATION.** The study was a retrospective review of children who underwent oral food challenges to egg over a 2-year period. Median age of patients was 3.9 years (range: 16 months to 11.9 years). Children with high egg-specific IgE titers and those with a severe reaction <2 years earlier were not tested.

**METHODS.** Children with immediate-type reactions were tested by open food challenge, and those with atopic dermatitis or equivocal reactions were tested by double-blind, placebo-controlled food challenge. Graded challenges were performed with pasteurized raw egg, cooked egg, or egg hidden in a chocolate testing preparation. The challenge was terminated when the patient reached a total dose of 45 g of egg or if there was unambiguous clinical reactivity and reaction severity was graded.

**RESULTS.** Of the 51 challenges performed during the study period, 35 (69%) were positive. Thirteen (37%) of the positive challenges were considered severe. An egg radioallergosorbent (RAST) assay result of ≥17.4 kU/L was associated with 95% probability of having a positive challenge; 8.2 kU/L was associated with a 90% probability. For all challenges, egg-specific IgE titers ranged from <0.35 to 14.9 kU/L. The negative challenge group had a median egg-specific IgE titer of 1.17 kU/L (range: 0.35–6.41 kU/L); the mild-to-moderate group median was 2.47 kU/L (range: 0.35–14.9 kU/L); and the severe group median was 3.70 kU/L (range: 1.18–11 kU/L). The differences of median egg-specific IgE levels were statistically significant (P = .006). Children with a positive challenge who received cooked egg were found to have a higher specific IgE level versus those who received raw egg (P = .016), but there was no statistically significant difference between severity of reactions between these groups. The median dose that caused a mild-to-moderate reaction was 6 g (range: 2.5–20 g) and was the same median dose that caused severe reactions (range: 0.5–15 g).
CONCLUSIONS. There is a correlation between median egg-specific IgE levels and the severity of reaction during oral food challenge to egg. These levels may be helpful in predicting a potential reaction to egg.

REVIEWER COMMENTS. It is often assumed that reaction severity correlates with the food-specific IgE level, but most studies have refuted this notion. Here, a relationship was determined. However, it is difficult to assess the clinical utility of these results, because there was considerable overlap of the ranges of egg-specific IgE levels between groups. These findings may be more relevant to the controlled setting of a diagnostic food challenge rather than to the community setting in which a large or uncontrolled dose of egg might be ingested. In a real-life setting, a severe reaction may occur even with a low egg-specific IgE level, particularly if one considers patient-dependent factors such as concurrent diagnosis of asthma or personal history of a previous severe reaction.

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Correlation of Serum Allergy (IgE) Tests Performed by Different Assay Systems

PURPOSE OF THE STUDY. To compare the allergen-specific immunoglobulin E (IgE) testing performed on 3 different assays (Turbo-MP [Aglient Technologies Co, Santa Clara, CA], Immulite 2000 [Siemens Medical Solutions Diagnostics, Tarrytown, NY], and ImmunoCAP [Pharmacia, Uppsala, Sweden]) to determine if IgE levels derived from different assays are equivalent.

STUDY POPULATION. The study was a prospective analysis of serum from 50 atopic patients (median age: 7.25 years) using the 3 different allergen-specific assays (ImmunoCAP, Turbo-MP, and Immulite 2000).

METHODS. Patients being seen at the Mount Sinai pediatric allergy and immunology practice who were already having blood drawn for routine management were eligible, and the additional serum was aliquoted into 3 samples and sent to 3 different commercial laboratories, each of which used a different assay system. Of the 50 patients enrolled, 42 were diagnosed with food hypersensitivities, 5 avoided specific foods because of a history of positive skin-prick tests or serum-specific IgE, and 3 had no history of food hypersensitivity. Samples were evaluated for specific IgE to egg white, milk, peanut, cat, birch pollen, and dust mite (Dermatophagoides farinae). The results were analyzed by using the ImmunoCAP as the reference system, because published data regarding decision points for the major food allergens used this assay system. Values that fell outside of the 20% limits of agreement were determined for each allergen.

RESULTS. Significant differences were found in the measurement of allergen-specific IgE levels in identical serum samples when using these 3 assays. Immulite 2000 values were consistently higher than the reference standard for all allergens measured; however, levels for D. farinae were not statistically significant. Turbo-MP showed variability without a trend toward overestimation or underestimation for milk and peanut, overestimated egg-specific IgE levels, and underestimated specific IgE levels for birch pollen. Although all 3 have a similar distribution of results consistent with the population studied, minor differences in the sources of allergens used may have contributed to the different IgE levels observed.

CONCLUSIONS. Clinicians cannot substitute a commercial allergen-specific IgE assay for another when making clinical decisions about whether to proceed to an oral food challenge or in monitoring IgE levels of an individual patient over time. The published data that are widely used are based on the ImmunoCAP assay, and the IgE levels obtained by 2 other assays (Turbo-MP and Immulite) are not equivalent.

REVIEWER COMMENTS. Most published data concerning relationships of food allergy to food-specific IgE test results were determined by using the ImmunoCAP assay. Although the IgE measurements between the different assays may correlate well on a statistical basis, the study considered the differences in absolute values, particularly around decision points widely used by clinicians. The article shows that applying decision points determined by 1 assay to test results obtained from a different assay could lead to erroneous advice about management. The authors indicated that additional studies should be performed to examine reproducibility of the results and determine assay-specific decision points for these different testing assays. This study highlights the fact that knowing what assay is used, in addition to obtaining a careful clinical history, is an important part of the evaluation of a child with possible food allergies.

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Safety of Open Food Challenges in the Office Setting

PURPOSE OF THE STUDY. To examine the safety of open food challenges (OFCs) administered in an office setting.
STUDY POPULATION. A total of 109 patients aged 18 years who underwent OFCs at the Duke University pediatric allergy-immunology clinic, excluding patients with a history of severe symptoms with previous reactions, were studied. Patient-selection criteria were based on the clinical history, results of skin-prick tests, and food-specific immunoglobulin E (IgE) levels that were much lower than those previously published levels predictive of a high likelihood of a clinical reaction.

METHODS. The authors performed a retrospective medical chart review of OFCs.

RESULTS. Among a total of 150 OFCs, most of which were to milk (n = 39), peanut (n = 37), and egg (n = 29), there were 40 positive test results (27% of all challenges) in 33 patients. Reactions were mild-to-moderate in 92% of the positive challenges. Cutaneous reactions occurred in 68% of the positive challenges, followed by gastrointestinal tract reactions (45%) and upper respiratory tract reactions (38%), excluding laryngeal symptoms. No patient had cardiovascular involvement, received epinephrine, or required hospitalization. Interventions included observation or antihistamine only for 92% of the positive challenges. Food-specific IgE values did not correlate with reaction severity. Of the 23 OFCs to milk, egg, and peanut without a history of clinical reactions, 8 were positive. For negative challenges, median prechallenge food-specific IgE levels approached previously published negative predictive values for these foods (1.22 kUA/L for milk, 0.96 kUA/L for peanut, and 0.65 kUA/L for egg). Negative challenge results for patients allowed the introduction of 19 different foods into the diets of 88 patients.

CONCLUSIONS. The authors concluded that OFCs are a safe procedure in the office setting for patients selected on the basis of food-specific IgE levels that approach negative predictive values and a lack of adverse reactions within the previous year.

REVIEWER COMMENTS. This nice report suggests that open OFCs performed by experienced practitioners in a clinic setting on carefully selected patients can be of significant benefit for patients who are tolerant to a food to avoid unnecessarily restrictive diets. Keeping in mind that the authors detected positive challenges in 4 patients with an undetectable food-specific IgE level and that there was a lack of association between the food-specific IgE level and severity of a reaction, prechallenge skin-prick tests and careful review of the clinical history should be used. Every challenge should be approached with appropriate precautions (emergency medications and equipment readily available) to treat potentially severe reactions.

Specific Oral Tolerance Induction in Food Allergy in Children: Efficacy and Clinical Patterns of Reaction


PURPOSE OF THE STUDY. To evaluate the efficacy of oral tolerance induction as a treatment for cow’s milk and egg allergies.

STUDY POPULATION. Forty-seven children aged 0.6 to 12.9 years with positive double-blind, placebo-controlled food challenges to milk or hen’s egg were included in this German study. Children with severe eczema were excluded.

METHODS. Subjects were randomly assigned to specific oral tolerance induction or continued avoidance. Treatment involved home escalation over at least 67 days from a dose of 1 drop of cow’s milk to 250 mL or from 5 mg of lyophilized hen egg powder to 3500 mg. Subjects continued home dosing for a median of 21 months total, after which time they underwent a secondary period of avoidance for 2 months followed by a food challenge.

RESULTS. At follow-up challenge, 9 (36%) of 25 children in the specific-oral-tolerance-induction group showed permanent tolerance, 3 (12%) of 25 were tolerant with regular intake, 4 (16%) of 25 were partial responders, and 9 (36%) of 25 did not complete the treatment because of adverse effects. In the control group, 7 (35%) of 20 children were tolerant at the study end. Allergen-specific IgE levels decreased in children who developed tolerance both in the control (P < .05) and treatment (P < .001) groups.

CONCLUSIONS. Specific oral tolerance induction may be a valid treatment option for patients with persistent food allergy. However, only a minority of patients had evidence of persistent tolerance once treatment was stopped, with some unable to tolerate the therapy and others seeming to be only transiently desensitized.

REVIEWER COMMENTS. Allergen-specific immunotherapy with injected extracts has proven too dangerous to be a viable treatment method for food allergy. Sublingual or oral immunotherapy, as described here, is a promising alternative to strict avoidance. Although one third of the patients in this study had to withdraw because of adverse effects, the remaining patients were able to incorporate the allergen into their diet at some level. This treatment modality is highly promising, but it is still experimental, carries the potential for significant risk, and requires close monitoring by experienced physicians. Several studies of oral and sublingual immuno-
Specific Oral Tolerance Induction in Children With Very Severe Cow’s Milk-Induced Reactions


PURPOSE OF THE STUDY. To evaluate the safety and efficacy of specific oral tolerance induction for children with severe cow’s milk protein (CMP) allergy.

STUDY POPULATION. The study included 97 children (aged 5 to 17 years) with a history of severe allergic reactions and CMP-specific immunoglobulin E (IgE) levels of >85 kU/L.

METHODS. All subjects underwent a double-blind, placebo-controlled food challenge (DBPCFC) starting with very low amounts of diluted milk. Children were considered eligible for random assignment only if they had symptoms during the DBPCFC to the lowest doses (0.8 mL of whole milk). Sixty had positive test results and were randomly assigned to 1 of 2 groups: group A started the specific-oral-tolerance-induction protocol immediately after the DBPCFC; and group B maintained a milk-free diet for 1 year and then underwent another DBPCFC. CMP-specific IgE levels were obtained at enrollment and at 6 and 12 months. Subjects in group A were monitored as inpatients for 10 days during rapid, daily increases in milk dosage and then discharged from the hospital with instructions for increasing milk ingestion to a final goal of 150 mL per day. Once on 150 mL, subjects were instructed to add dairy products to their diet.

RESULTS. After 1 year, 11 (36%) of 30 children in group A were tolerant to the highest dose of 150 mL of cow’s milk per day with some ingesting additional dairy products, thus allowing them an unrestricted diet. Sixteen (54%) could take limited amounts of milk (5–150 mL), and 3 (10%) were not able to complete the protocol because of persistent respiratory and abdominal complaints. CMP-specific IgE levels measured in group A at 6 and 12 months showed a significant decrease in 15 of 30 subjects. In subjects in group B, DBPCFC results were positive with only minimal amounts of milk in all 30 cases, and only 2 subjects showed a decrease in specific IgE levels. Clinical differences between the groups were significant ($P < .001$). Adverse reactions were common among the subjects in group A, with multiple subjects requiring treatment throughout the protocol. It is interesting to note that 20% of the subjects in group B had adverse reactions after accidental exposure to CMP.

CONCLUSIONS. Specific oral tolerance induction is effective in a significant number of patients with severe cow’s milk allergy.

REVIEWER COMMENTS. Oral desensitization is a novel form of immunotherapy that is under investigation for food allergy, with benefits noted in several clinical studies. Unlike previous studies, this study addressed oral desensitization in children with very severe cow’s milk allergy. The authors noted their success among the subjects studied but were also quick to point out the number of adverse events that occurred when using their protocol. These results are encouraging for patients who suffer from food allergy but highlight the need for additional studies before implementation in clinical practice and the need for close monitoring in highly controlled settings.

ANAPHYLAXIS

Platelet-Activating Factor, PAF Acetylhydrolase, and Severe Anaphylaxis


PURPOSE OF THE STUDY. To characterize the roles of platelet-activating factor (PAF) and PAF acetylhydrolase, the enzyme that inactivates PAF, in humans.

STUDY POPULATION. The population was a variety of pediatric and adult patients with different levels of allergic disease along with nonallergic controls.

METHODS. Serum PAF levels and activity of PAF acetylhydrolase were measured in 41 patients with anaphylaxis and in 23 control patients. Serum PAF acetylhydrolase activity was also measured in 9 patients with fatal anaphylaxis and compared with that in 26 nonallergic pediatric control patients, 49 nonallergic adult control patients, 63 children with mild peanut allergy, 24 patients with nonfatal anaphylaxis, 10 children who died of nonanaphylactic causes, 15 children with life-threatening asthma, and 19 children with non–life-threatening asthma.

RESULTS. Mean serum PAF levels were significantly higher in patients with anaphylaxis than in patients in the control groups and were correlated with the severity of anaphylaxis. The proportion of subjects with elevated
PAF levels increased from 4% in the control groups to 20% in the group with grade 1 anaphylaxis, 71% in the group with grade 2 anaphylaxis, and 100% in the group with grade 3 anaphylaxis. There was an inverse correlation between PAF levels and serum PAF acetylhydrolase activity. The proportion of patients with low PAF acetylhydrolase activity increased with the severity of anaphylaxis. Serum PAF acetylhydrolase activity was significantly lower in patients with fatal peanut anaphylaxis than in control patients.

CONCLUSIONS. Serum PAF levels were directly correlated and serum PAF acetylhydrolase activity was inversely correlated with the severity of anaphylaxis. PAF acetylhydrolase activity was significantly lower in patients with fatal anaphylactic reactions to peanuts than in patients in any of the control groups. Failure of PAF acetylhydrolase to inactivate PAF may contribute to the severity of anaphylaxis.

REVIEWER COMMENTS. PAF is 1 of the proinflammatory mediators that are released systemically by the degranulation of mast cells and basophils. Although PAF is not the only mediator that plays a role in anaphylaxis, these results suggest that PAF is very important. Therefore, it may be useful to develop new pharmaceutical agents that block its actions. Additional research is also needed to determine if PAF and PAF acetylhydrolase measurements may be used as a screening tool to select patients at highest risk for fatal anaphylaxis.

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Brian A. Smart, MD, FAAP
Glen Ellyn, IL

DRUG HYPERSENSITIVITY

Drug Allergy Claims in Children: From Self-reporting to Confirmed Diagnosis

PURPOSE OF THE STUDY. To assess the prevalence of self-reported adverse drug reactions and drug allergy in a pediatric population and confirm the diagnosis in children with suspected drug allergy.

STUDY POPULATION. Patients (n = 1426) responded to an initial cross-sectional survey. A total of 60 of 67 patients with reported drug allergy were evaluated at an allergy clinic.

METHODS. The first phase included a cross-sectional survey that assessed the life occurrence of adverse drug reactions and self-reported drug allergy in the outpatient clinic of a pediatric hospital. The second phase involved a diagnostic workup in children with parent-reported drug allergy, including detailed clinical history and in vitro and in vivo investigations. Specific immunoglobulin E (IgE) level determination for β-lactams, prick and intradermal skin testing for β-lactams, local anesthetics and sulfonamides, and patch tests (if a delayed reaction was reported) were performed. If all other investigations were inconclusive and a provocation test was not contraindicated, this test was performed.

RESULTS. The prevalence of self-reported adverse drug reactions and drug allergy were 10.2% and 6.0%, respectively. The frequency of a medical diagnosis of drug allergy was 3.9%. The majority of the suspected allergic reactions were nonimmediate cutaneous events attributed to β-lactam antibiotics in younger children. Of 60 patients evaluated in the allergy clinic, 39 patients had a plausible clinical history, and additional investigation including a skin test, IgE-level measurement, and possible provocation tests were conducted. Drug allergy was diagnosed in 3 children on the basis of positive responses in skin (n = 1) and oral provocation (n = 2) tests.

CONCLUSIONS. Although adverse drug reactions and suspected drug allergy are frequently reported in children, after a complete evaluation, only a few of these reactions can be attributed to immediate and nonimmediate drug allergy. Overall, 94% of the patients could tolerate the initially suspected drug.

REVIEWER COMMENTS. This study underscores a serious problem: patients who experience or perceive a drug reaction are often classified as being truly allergic when this may not be the case. Such overdiagnosis and misdiagnosis may result in suboptimal medication choices. These results show that only 6% of the patients with initially suspected drug allergy were truly allergic. This study demonstrates the importance of a complete and detailed history, with consideration of additional testing including skin-prick tests, specific IgE-level determination, and provocation tests. It should be noted that for nonimmediate drug allergy, an oral provocation test may require prolonged treatment to observe for symptoms. Such provocation tests would not be undertaken for severe previous reactions (eg, toxic epidermal necrolysis).

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Faith Huang, MD
Anna Nowak-Wegrzyn, MD
New York, NY

HLA-B*5701 Screening for Hypersensitivity to Abacavir

PURPOSE OF THE STUDY. Abacavir is associated with severe and potentially life-threatening hypersensitivity reactions in up to 8% of the white population. In 2002, HLA-B*5701
was noted to be highly associated with this hypersensitivity reaction. The purpose of this study was to evaluate the effectiveness of prospective HLA-B*5701 screening to avoid these reactions.

STUDY POPULATION. A total of 1956 HIV-infected patients from 19 countries who had not previously received abacavir were enrolled.

METHODS. Individual patients were randomly assigned to undergo prospective HLA-B*5701 screening, with exclusion of previously known HLA-B*5701 positive patients from abacavir treatment, or to undergo a standard approach of abacavir use without screening. All subjects who started abacavir were observed for 6 weeks, the time frame in which a large majority of hypersensitivity reactions occur. The clinical diagnosis of hypersensitivity reaction to abacavir was assessed further by epicutaneous patch testing.

RESULTS. The prevalence of HLA-B*5701 was 5.76% (109 of 1956 subjects) of the subjects assigned to receive abacavir. Seventy-two percent were men, 84% were white, and 18% had not received antiretroviral therapy previously. Screening effectively eliminated patch-test–confirmed hypersensitivity. None of the subjects in the prospectively screened group had reactions, compared with 2.7% in the control group. This yielded a negative predictive value of 100% and a positive predictive value of 47.9%. Hypersensitivity reactions to antiretroviral therapy were clinically diagnosed in 93 patients, with a significantly lower incidence in the prospectively screened group (3.4%) than in the control group (7.8%) (P < .001).

CONCLUSIONS. HLA-B*5701 screening dramatically reduced the risk of immunologically confirmed hypersensitivity to abacavir. This pharmacogenetic test is useful for reducing the incidence of immunologically mediated hypersensitivity reactions to abacavir.

REVIEWER COMMENTS. This expansive study demonstrated the clinical usefulness of pharmacogenomics testing for immunologically mediated hypersensitivity to a particular drug. This is the first such demonstration for reactions to antiretroviral agents. A major limitation in the use of abacavir has been the concern for a severe hypersensitivity reaction. The availability of this inexpensive test (approximately $80 at our institution) substantially reduces that potential and allows antiretroviral therapy selection to be based on the drug’s merit as an effective antiretroviral agent. A unique feature of hypersensitivity to this particular drug is that it is a true T-cell–mediated reaction. Patch testing has been used for many decades to identify offending contact hypersensitivity allergens (eg, nickel). The search for additional biomarkers that would reflect a potential for adverse reactions to other drugs is ongoing. This type of study leads the way in demonstrating clinical effectiveness of such an approach.
such as pollens can exacerbate atopic eczema in susceptible individuals. Physicians should remember to discuss this with their atopic patients before the start of pollen season.

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Jennifer M. Maloney, MD
New York, NY

Severe Atopic Dermatitis Is Associated With a High Burden of Environmental Staphylococcus aureus

PURPOSE OF THE STUDY. It has been established that Staphylococcus aureus worsens atopic dermatitis (AD) by a variety of mechanisms. The purpose of this study was to quantify S aureus burden in the homes of participants with AD of varying severity.

STUDY POPULATION. There were 62 volunteers aged 1 to 40 years. Participants were categorized as having mild (n = 18), moderate (n = 14), severe (n = 15), or no (n = 15) AD.

METHODS. Participants completed questionnaires about their asthma, allergies, and home environment. Patients with AD completed a Lung-Browder diagram, documenting the area and intensity of erythema, excoriation, papulation, and lichenification. From these diagrams, AD severity was calculated by using the Eczema Area and Severity Index (EASI). Subjects collected dust samples from their bed, the floor next to their bed, and the home vacuum bag and sent them to the laboratory for analysis. S aureus DNA was extracted, and quantitative reverse-transcription polymerase chain reaction for the femB gene (an S aureus–specific genomic marker) was performed. Data were log-transformed and then analyzed with analysis of variance, student’s t test, and Spearman’s r.

RESULTS. Bed dust yielded the highest S aureus concentrations. Participants with severe AD had significantly more S aureus DNA (14.67 pg/mg dust) in bed dust than those with moderate (0.41 pg/mg dust; P < .0001), mild (1.42 pg/mg; P = .0051), and no (0.09 pg/mg; P < .0001) AD. The concentration of S aureus DNA in bed dust strongly correlated with EASI scores. Similar patterns were observed for dust from bedroom floors for both DNA concentrations and EASI scores. The quantity of S aureus DNA from the vacuum samples was significantly higher in participants with severe AD versus moderate, mild, and no AD. However, there was no correlation between EASI scores and concentrations of S aureus DNA from vacuum dust samples.

CONCLUSIONS. S aureus is ubiquitous and was detected in dust samples from almost all homes regardless of disease state. However, house dust from participants with severe AD contained the most S aureus DNA. The correlation between S aureus DNA levels and AD severity is driven by proximity to the patient, as shown by the fact that the bed and bedroom floors from the patients with AD yielded the highest levels of S aureus DNA. In the home and especially the bedroom, higher levels of S aureus may contribute to disease severity and persistence in patients with AD.

REVIEWER COMMENTS. This is the first study to examine the environmental burden of S aureus in the homes of participants with AD. This study concludes that patients with severe AD have higher environmental burdens of S aureus. The source of the S aureus may be shed bacteria from the skin of the patient with AD, and if live organisms persist in house dust, then they may be the source of recolonization of patients’ skin. However, to prove whether the relationship between high environmental load of S aureus and severe AD is cause or effect, additional studies need to be performed, including quantification of bacterial load on the patient’s skin as correlated with home environmental burden and quantification of live bacteria in house dust.

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Mariah M. Pieretti, MD
Scott H. Sicherer, MD, FAAP
New York, NY

IgE Food Sensitization in Infants With Eczema Attending a Dermatology Clinic

PURPOSE OF THE STUDY. Because community-based studies, which report immunoglobulin E food sensitization (IgE-FS) in >80% of infants with moderate atopic eczema, may be influenced by referral bias, the researchers assessed the prevalence of IgE-FS in a cohort of infants with moderate atopic eczema who were attending a dermatology department clinic.

STUDY POPULATION. Consecutive infants (n = 51 [39 boys]; median age: 34 weeks [range: 20–51 weeks]) with moderate atopic eczema severity were studied prospectively.

METHODS. Clinical history and eczema severity were documented. IgE-FS was assessed by the skin-prick test (SPT) (n = 51) and food-specific serum IgE antibody levels (CAP-FEIA test; n = 41). IgE-FS was diagnosed if the SPT or CAP-FEIA level exceeded the >95% predictive reference cutoff for positive food-challenge results.

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RESULTS. On the basis of the SPT, 44 (86% [95% confidence interval (CI): 74%–95%]) of 51 infants had IgE-FS (cow’s milk, 16%; egg, 73%; peanut, 51%). Using age-specific 95% predicted cutoff values, CAP-FEIA identified 34 (83% [95% CI: 68% to 93%]) of 41 infants with IgE-FS (cow’s milk, 23%; egg, 90%). Forty-six (90%) infants had IgE-FS to at least 1 food item according to either the SPT or CAP-FEIA test.

CONCLUSIONS. Atopic eczema was found to be closely associated with IgE-FS in infants attending a dermatology department.

REVIEWER COMMENTS. These data should continue to fuel the ongoing debate, especially between allergists and dermatologists, regarding the role of food allergy in infants with atopic dermatitis (AD). This study addressed IgE-FS in infants who already had moderate-to-severe AD and who presented to a dermatology clinic for evaluation and management. These patients had test results (ie, skin testing or in vitro–specific IgE measurements) demonstrating likely clinical allergy to eggs, cow’s milk, and/or peanuts on the basis of previous studies correlating test results with oral food-challenge outcomes. The vast majority (90%) of these infants with AD were sensitive to at least 1 of these foods, demonstrating a very strong association between infants with AD and IgE sensitization to common food allergens. Despite extensive data from this study and previous investigations demonstrating a relationship, the specific role of food allergy in AD remains a “hotly contested” area of clinical research and debate. At this point in time, the balance of clinical evidence favors a specific role of IgE-FS in the pathogenesis of AD.

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John M. James, MD
Fort Collins, CO

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Pathophysiology of Nocturnal Scratching in Childhood Atopic Dermatitis: The Role of Brain-Derived Neurotrophic Factor and Substance P


PURPOSE OF THE STUDY. To determine if brain-derived neurotrophic factor (BDNF) and substance P are associated with disease severity, quality of life, and nocturnal scratching in atopic dermatitis (AD).

STUDY POPULATION. This was a prospective study of 28 children with AD (mean age: 11.1 ± 3.3 years) recruited from a pediatric dermatology clinic at a university teaching hospital in Hong Kong. Eighty-nine percent had moderate-to-severe AD on the basis of Scoring Atopic Dermatitis (SCORAD) scores.

METHODS. AD severity, as well as pruritus and sleep loss (in the preceding 3 days), was evaluated by using the SCORAD index. The Children’s Dermatology Life Quality Index (CDLQI) was used to measure the quality of life over the preceding 7 days. Serum BDNF, substance P, AD-associated chemokine (cutaneous T-cell–attracting cytokine [CTACK] and thymus and activation-regulated chemokine [TARC]), total immunoglobulin E (IgE), and eosinophil counts were measured. Patients wore a Digi-Trac monitor (IM Systems, Baltimore, MD) on their dominant wrist while sleeping to record limb motion from 10 PM to 8 AM the following morning. On the basis of the group’s previous work showing that the wrist activities between 1 and 3 Hz for the first 3 hours of sleep were indicators of AD severity of children, the same parameters were used for analyses of correlations.

RESULTS. The mean SCORAD score was 48.1 ± 21.5, and mean CDLQI score was 8.7 ± 5.4. The mean plasma concentrations of BDNF, substance P, CTACK, and TARC were 1798 ± 935, 94 ± 42, 1424 ± 719, and 824 ± 1000 pg/mL, respectively. BDNF correlated significantly with both the SCORAD (P = .010) and CDLQI (P = .004) scores, whereas substance P had a significant correlation only with the CDLQI score (P = .019). Both BDNF and substance P were highly significantly correlated with average (P < .001) and frequency-specific (P < .001) wrist activities measured by the DigiTrac. In contrast, the chemokine (CTACK and TARC), serum total IgE, and eosinophil counts did not correlate with scratching. It is interesting to note that there was no correlation between BDNF or substance P level and pruritus or sleep-loss scores reported by the parents in the SCORAD.

CONCLUSIONS. Serum levels of BDNF and substance P were significantly linked to disease activity, quality of life, and levels of nocturnal scratching.

REVIEWER COMMENTS. Pruritus can be very distressing for children with AD. Unfortunately, the pathophysiology of nocturnal itching and the mediators involved have not been well elucidated. This article is the first to demonstrate that BDNF and substance P levels are significantly linked to nocturnal scratching. Certainly additional studies are needed to show that these neuropeptides are the causative factors in itching. Inclusion of control groups and those with other dermatologic conditions that also cause pruritus would be helpful. However, this article also suggests that perceived symptoms of itch, especially by parents of those with AD, may not be precise and that perhaps the extent of nocturnal itching has been underappreciated.

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Audrey Y. Park, MD, PhD
Jonathan M. Spergel, MD, PhD
Philadelphia, PA

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Linoleic Acid Metabolites and Transepidermal Water Loss in Children With Atopic Dermatitis

PURPOSE OF THE STUDY. To investigate whether n-6 essential fatty acid (EFA) deficits account for atopic dermatitis (AD) by affecting transepidermal water loss (TEWL).

STUDY POPULATION. Children between the ages of 2 and 17 years with AD (n = 35), asthma or allergic rhinitis (AS/AR group, n = 35), or no atopic disease (n = 31) were studied. The AD group did not have allergic airway disease.

METHODS. Synthesis of the n-6 EFA from linoleic acid (LA) involves alternating steps of desaturation and elongation with serial conversion to γ-linoleic acid (GLA), dihomo-γ-linoleic acid (DGLA), and arachidonic acid (AA). Fasting blood samples were obtained with immediate serum separation and freezing to prevent changes in fatty acid composition of serum lipids. Analysis of lipid metabolism was performed by gas chromatography/mass spectrometry. Measurement of TEWL on the right volar forearm was reported as loss of grams of water per square meter of skin per hour. Nonparametric tests were used to evaluate differences between the groups.

RESULTS. Although not statistically significant, patients in the AD and AS/AR groups had higher LA and lower AA levels than controls. Patients with AD but not AS/AR had statistically lower GLA (P = .04) and DGLA (P = .03) levels than control subjects. There were no differences between the 2 groups of atopic patients. Ratios of GLA/LA, DGLA/LA, and AA/LA were lower in the AD group than controls (P < .01 for each). However, in the AS/AR group, only the GLA/LA and DGLA/LA ratios were statistically lower than in controls. TEWL had a significant negative correlation with GLA and DGLA (P < .001) and near-significant negative correlation with AA (P = .06). In subjects with AD, TEWL and the Scoring Atopic Dermatitis (SCORAD) index were correlated (P < .001). The SCORAD index had a significant correlation with GLA and DGLA (P < .001) but not AA (P = .06).

CONCLUSIONS. AD is associated with a defect in n-6 EFA metabolism. LA metabolites are involved in the maintenance of the epidermal water barrier.

REVIEWER COMMENTS. Antimicrobial protein defects, filaggrin defects, and fatty acid defects are among the newer areas of research on the underlying pathogenesis of AD. Because human epidermis lacks the capacity to convert LA to GLA or DGLA to AA, it is likely that those LA metabolites are synthesized elsewhere and transported to the epidermis. Serum levels of n-6 EFAs, as reported here, presumably reflect epidermal concentrations. It follows, therefore, that dietary supplementation of GLA or topical application of LA metabolites may have therapeutic benefit.

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Randomized, Placebo-Controlled Trial of Lactobacillus rhamnosus GG as Treatment of Atopic Dermatitis in Infancy

PURPOSE OF THE STUDY. To investigate the efficacy of Lactobacillus rhamnosus GG (LGG) as a food supplement for children with mild-to-moderate atopic dermatitis (AD).

STUDY POPULATION. One hundred two children aged 3 to 12 months with mild-to-moderately severe AD who were not taking antiinflammatory medications were included in this German study.

METHODS. Subjects were randomly assigned to receive LGG (5 × 10⁹ colony-forming units twice per day) or placebo for 12 weeks. Severity Scoring Atopic Dermatitis (SCORAD) index and use of hydrocortisone 1% ointment as a rescue medication were recorded at 4, 8, and 12 weeks of treatment.

RESULTS. One hundred two subjects were randomly assigned and completed the treatment period (54 in the treatment group, 48 in the placebo group). Initial symptom load was similar in both groups (SCORAD index: 24.6 ± 8.8 in the LGG group and 23.6 ± 7.8 in the placebo group) and improved over time. There were no statistically significant differences between the groups at any of the analysis times (SCORAD index for LGG versus placebo: 23.8 ± 12.4 vs 20.6 ± 9.9 at 4 weeks, 22.5 ± 14.6 vs 17.9 ± 13.1 at 8 weeks, and 19.6 ± 15.4 vs 15.1 ± 12.1 at 12 weeks, respectively). No statistically significant differences were found when the data were stratified according to age, eczema severity, or use of rescue medications, and no differences were found in the use of rescue medications, total immunoglobulin E level, or newly developed allergic sensitization to hen’s egg or cow’s milk.

CONCLUSIONS. This study showed no therapeutic effect of LGG for the treatment of mild-to-moderate AD in infancy.

REVIEWER COMMENTS. In our practice, parents of children with AD frequently inquire about whether they should supplement their children’s diets with lactobacilli. Previous studies have shown some possible benefit of supplementation with lactobacilli for prevention of AD in
Infants at risk but even less-promising results regarding its use in the treatment of AD. This study adds to the literature, finding no utility of lactobacilli supplementation for the treatment of established AD.

**Intermittent Therapy for Flare Prevention and Long-term Disease Control in Stabilized Atopic Dermatitis: A Randomized Comparison of 3-Times-Weekly Applications of Tacrolimus Ointment Versus Vehicle**


**PURPOSE OF THE STUDY.** To examine the usefulness of regular intermittent therapy instead of treating flares for the approach of atopic dermatitis (AD).

**STUDY POPULATION.** A total of 383 patients were randomly assigned to the stabilization phase, and 288 patients were controlled on tacrolimus ointment. There were 68 children (aged 2–16 years) and 57 adults (≥16 years) in the tacrolimus arm and 37 children and 35 adults in the vehicle arm. Eighty-five percent had moderate AD, and 15% had severe AD.

**METHODS.** Adult and pediatric patients with moderate-to-severe AD who were clear of disease after up to 16 weeks of treatment with tacrolimus ointment were randomly assigned in a double-blind fashion to 3-times-weekly treatment with either tacrolimus ointment (0.03% or 0.1%) or vehicle for 40 weeks. The primary end point was the number of flare-free treatment days. Relapses were treated with open-labeled tacrolimus.

**RESULTS.** There were 288 patients who entered the randomization phase. The largest reasons for not finishing the stabilization phase were voluntary patient withdrawal for 95 patients and loss to follow-up for 55 patients. Only 16 (4.2%) patients were withdrawn for lack of efficacy. A total of 125 patients were randomly assigned to tacrolimus, and 72 patients were assigned to vehicle. The mean number of flare-free treatment days was 177 for the tacrolimus group and 134 for the vehicle group (*P* = .003). Median time to first relapse was 169 days for the tacrolimus group and 43 for the vehicle group (*P* = .037).

**CONCLUSIONS.** Maintenance therapy with tacrolimus ointment was associated with significantly more flare-free days compared with vehicle and a significantly longer time until first disease relapse.

**REVIEWER COMMENTS.** This article examined the possibility of proactive treatment of AD instead of reacting to flares. The principle is similar to the use of maintenance medication for asthma. Similar results were seen with topical fluticasone propionate (Berth-Jones J, Damstra RJ, Golsch S, et al. *BMJ.* 2003;326(7403):1367). One significant limitation is that the study only included patients who responded to topical tacrolimus. The question now is whether it can be generalized to all patients with AD or patients not controlled with daily topical therapies.

**Sustained Efficacy and Safety of Pimecrolimus Cream 1% When Used Long-term (up to 26 Weeks) to Treat Children With Atopic Dermatitis**


**PURPOSE OF THE STUDY.** To evaluate the efficacy and safety of pimecrolimus cream 1% (Elidel [Novartis, East Hanover, NJ]) used for 26 weeks in children with atopic dermatitis (AD)

**STUDY POPULATION.** This was a prospective study of 403 children aged 2 to 17 years with AD (mean age at enrollment: 6.7 years) recruited from multiple academic centers in the United States.

**METHODS.** Pooled data were assessed from 20-week, open-label (OL) extensions of 2 previously reported 6-week, double-blind (DB) phase studies in which patients were randomly assigned 2:1 to pimecrolimus or vehicle. During the OL phase, all patients were treated with pimecrolimus. During the DB phase, no other AD treatments except emollients were allowed. The efficacy parameters included the Investigator’s Global Assessment (IGA), Eczema Area and Severity Index, and severity of pruritus scores. Safety assessment consisted primarily of monitoring adverse events. Patients were evaluated on days 8, 15, 22, 29, 43, 71, 99, 141, and 183.

**RESULTS.** Overall, 60.3% of the patients had moderately severe AD (IGA: 3) at study entry. Twice as many in the control group discontinued during the DB phase compared with the treated group (25% vs 11.4%). The main reason for the higher discontinuation rate in the control group was unsatisfactory therapeutic effect (15.4% vs 2.6%). Eighty-four percent completed the OL phase with similar rates of completion between the groups. At day 43, 34.8% of the pimecrolimus-treated patients versus 18.4% in the vehicle groups (*P* < .001) had clear or almost clear (IGA: 0 or 1) disease. Pimecrolimus was significantly more effective (*P* < .0001) in treating the
face and neck compared with the body during both DB and OL phases. In the pimecrolimus group, 56.5% of the patients had mild or absent pruritus by day 43 compared with 33.8% of those in the control group. The incidence of adverse events, including infections and complaints of a burning sensation with application, was not statistically different between groups during either phase of the study.

CONCLUSIONS. Treatment of AD with pimecrolimus was effective, particularly for the face and neck areas, and well tolerated.

REVIEWER COMMENTS. Given the black-box warning and concern with using topical calcineurin inhibitors, this article reemphasized that pimecrolimus is efficacious for children with AD. Particularly, it should be considered for use on the face and neck, which are difficult to treat with higher potency topical corticosteroids because of the risk of local adverse effects such as atrophy. The minimal adverse events associated with pimecrolimus support previous studies that had longer durations of treatment (up to 2 years).

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Jonathan M. Spergel, MD, PhD
Philadelphia, PA

H1-Antihistamine Treatment in Young Atopic Children: Effect on Urticaria

PURPOSE OF THE STUDY. To evaluate the effect of long-term treatment with levocetirizine on urticaria in young children with atopic dermatitis (AD).

STUDY POPULATION. The group studied 510 children with severe AD disease (mean Scoring Atopic Dermatitis [SCORAD] index: 30) aged 12 to 24 months at enrollment. This study is from the Early Prevention of Asthma in Atopic Children (EPAAC) study.

METHODS. This was a multicenter, randomized, double-masked, parallel-group, placebo-controlled study. Enrolled children were followed for 18 months on treatment with levocetirizine 0.125 mg/kg or placebo twice daily. The occurrence of urticaria was recorded on diary cards by parents or caregivers and “validated” by study investigators (validation was not explained).

RESULTS. During the 18 months of treatment, 27.5% (70 of 255) of the children receiving levocetirizine experienced urticaria in contrast to 41.6% (106 of 255) of the children receiving placebo (P < .001). The mean number of episodes of urticaria was 0.71 ± 0.11 and 1.71 ± 0.25 in the levocetirizine and control groups, respectively (P < .001). Urticaria was noted on a mean of 4.43 days in levocetirizine-treated patients and 5.36 days in placebo-treated patients (P < .001). For 85% of the children, the urticaria lasted ≤7 days. In 77% of the children with urticaria, the outbreak was associated with food ingestion. No significant adverse effects or long-term adverse effects were noted with active treatment.

CONCLUSIONS. Forty-two percent of highly atopic young children in the EPAAC study had acute urticaria, predominantly associated with food ingestion. Levocetirizine was effective at preventing urticarial outbreaks and had a modest effect treating urticaria, as demonstrated by the decrease in the duration of the episodes.

REVIEWER COMMENTS. In a previous, similar trial (Early Treatment of the Atopic Child [ETAC]) in young children with AD treated with cetirizine, acute urticaria was reported in 16% of the patients treated with placebo and 6% of the patients treated with the antihistamine (Simons FE. J Allergy Clin Immunol. 2001;107[4]:703–706). These patients were less highly atopic than the present study. The current EPAAC study is hindered by the lack of explanation of validation of urticarial episodes. This study has extended knowledge on the safety of cetirizine/levocetirizine for young children with AD and their efficacy in preventing acute urticaria resulting from food allergy.

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Alan B. Goldsobel, MD
San Jose, CA

Attenuation of Allergic Contact Dermatitis Through the Endocannabinoid System

PURPOSE OF THE STUDY. To assess the role of cannabinoid receptors in allergic contact dermatitis.

STUDY POPULATION AND METHODS. The study was conducted in an animal model for cutaneous contact hypersensitivity using wild-type mice and also those lacking cannabinoid receptors (CB1 and CB2).

RESULTS. Mice lacking both known cannabinoid receptors display exacerbated allergic inflammation. In contrast, fatty acid amide hydrolase–deficient mice, which have increased levels of the endocannabinoid anandamide, displayed reduced allergic responses in the skin. Cannabinoid receptor antagonists exacerbated allergic inflammation, whereas receptor agonists attenuated inflammation.

S200  BEST ARTICLES RELEVANT TO PEDIATRIC ALLERGY AND IMMUNOLOGY
CONCLUSIONS. These results demonstrate a protective role of the endocannabinoid system for contact allergy in the skin and suggest a target for therapeutic intervention.

REVIEWER COMMENTS. This very clever study was based on an observation that mice lacking cannabinoid receptors tended to develop an itchy dermatitis at the site of nickel-containing ear tags. From this simple observation, the authors conducted a series of well-designed experiments that demonstrated that the cannabinoid receptors help to regulate cell recruitment to sites of inflammation in the context of contact dermatitis. These results have led to new insights to the pathogenesis of this disorder and may lead to a new treatment for contact dermatitis. I wonder if cannabinoid receptors are involved in other forms of skin allergy.

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James E. Gern, MD
Madison, WI
The Upper Airway/Allergic Rhinitis

Seasonal Allergic Rhinitis Is Associated With a Detrimental Effect on Examination Performance in United Kingdom Teenagers: Case-Control Study


PURPOSE OF THE STUDY. Symptoms of seasonal allergic rhinitis (SAR) have been shown to impair learning ability in children under laboratory conditions. These investigators sought to study the effect of seasonal allergic rhinitis on actual examination performance in United Kingdom teenagers.

STUDY POPULATION. State schools in the United Kingdom with relatively large numbers of English-speaking students were invited to participate. These schools held practice examinations in the winter for the General Certificate of Secondary Education (GCSF). All students aged 15 to 17 years in the last year of study for their GCSF were invited to participate.

METHODS. Case status was defined by comparison of the performance of each student in winter practice with that of the final GCSF examination in May/June, which coincided with the grass-pollen season. GCSF examinations are critical for United Kingdom adolescents. Winter practice examinations are structured similarly to the final examinations. Both sets of examinations are marked on an 8-point scale. Any drop in grade on the final examination is unexpected. Students who dropped at least 1 grade in any of the 3 core subjects (math, English, and science) were considered cases. Controls were students whose grades in their final examinations were at least as good as those in their practice examinations in all 3 subjects. Two questionnaires were administered, 1 in April before the grass-pollen season and 1 on the day of each relevant examination. The first questionnaire determined if students had ever received a diagnosis of SAR. Information on potential confounders (eg, medication use, smoking status, history of asthma, etc) was also collected. The questionnaire administered immediately before the final examinations in May and June asked about SAR symptoms and treatment. The primary comparison was of the proportions of cases and controls with SAR symptoms and treatment, especially with sedating antihistamines. Pollen counts were reported daily.

RESULTS. A total of 1834 students (57% of the available population) agreed to participate. Between 38% and 43% of students reported SAR symptoms on any 1 of the examination days. There were 662 cases (36% of the students). Cases were significantly more likely than controls to have had allergic rhinitis symptoms during the examination period (odds ratio [OR]: 1.4 [95% confidence interval (CI): 1.1–1.8]; P = .002), to have taken any allergic rhinitis medication (OR: 1.4 [95% CI: 1.1–1.7]; P = .01), or to have taken sedating antihistamine (OR: 1.7 [95% CI: 1.1–2.8]; P = .03).

CONCLUSIONS. Current symptomatic allergic rhinitis and medication use were associated with a significantly increased risk of unexpected grade drop in summer examinations. These findings carry significant implications in clinical practice.

REVIEWER COMMENTS. The effects of uncontrolled SAR on school performance are most often insidious, and adolescents often have prolonged symptoms before proper medical intervention occurs. It is clear that proactive drug therapy and allergen avoidance can go a long way toward lessening symptoms of SAR. It is essential that the clinician educate parents on the value of intervening preseasonally and to then consider immunotherapy if avoidance and medication fail.

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

Failures of Adenoidectomy for Chronic Rhinosinusitis in Children: For Whom and When Do They Fail?

Ramadan HH, Tiu J. Laryngoscope. 2007;117(6):1080–1083

PURPOSE OF THE STUDY. To determine which children who undergo adenoidectomy for chronic rhinosinusitis will subsequently undergo endoscopic sinus surgery.

STUDY POPULATION. Children who had adenoidectomy for treatment of refractory chronic rhinosinusitis over a 10-year period at a tertiary pediatric facility were included in the study. Excluded children were those with immunodeficiency, cystic fibrosis, or previous sinus surgery. All patients had an extensive preoperative workup to rule out allergy, immunodeficiency, and cystic fibrosis.

METHODS. Charts were reviewed, and data were collected retrospectively. All patients underwent adenoidectomy via the suction electrocautery technique. Children were followed monthly for 3 months after adenoidectomy and then every 3 months. Data collected included age, presence of allergy or asthma, severity of sinusitis as indicated on computed tomography (CT) scans, and dates of adenoidectomy and subsequent sinus surgery. Endoscopic sinus surgery was performed for persistent symptoms despite adenoidectomy and medical management with radiographic evidence of sinusitis on CT scans.
RESULTS. A total of 143 children had adenoidectomy for sinusitis, and follow-up data were available for 121 children. Adenoidectomy failed for 61 (50%) children, with data available from 55 who had subsequent endoscopic sinus surgery. The mean time between adenoidectomy and endoscopic sinus surgery was 24 months (range: 4.4–77.4 months). Children with asthma had a mean of 19 months between surgeries, whereas those without asthma had an interval of 28 months \((P = .04)\). Children younger than 7 years of age had sinus surgery a mean of 15 months after adenoidectomy, compared with an interval of 27.5 months between surgeries for children \(\geq 7\) years \((P = .01)\). The presence of allergy, severity of sinusitis as indicated by CT scans, and gender did not seem to affect the time of failure of adenoidectomy.

CONCLUSIONS. At least 50% of children with rhinosinusitis will benefit from an adenoidectomy without the need for subsequent sinus surgery. Children who have persistent sinusitis that requires endoscopic sinus surgery after adenoidectomy tend to be younger children and/or children with asthma, with a mean of 24 months between surgeries.

REVIEWER COMMENTS. Adenoidectomy is a simple procedure that is effective for treating children with rhinosinusitis whose conditions fail medical therapy, but a number of children do go on to have more extensive surgical procedures. The retrospective nature of this study and limited information on how sinusitis symptoms were stratified, as well as how treatment failure was defined, affect our ability to generalize the conclusions of this study. The shorter interval between adenoidectomy and endoscopic sinus surgery in children with asthma may reflect a more aggressive approach to surgical management of sinusitis in the presence of pulmonary disease rather than an actual difference in the natural history of sinusitis in these children. The shorter interval between adenoidectomy and endoscopic sinus surgery in the younger children suggests more severe sinus symptoms in this group, although it may just reflect the natural history of sinusitis and upper respiratory infections in children, with eventual resolution expected for many older children regardless of treatment.

PURPOSE OF THE STUDY. To compare the outcomes of adenoidectomy with adenoidectomy combined with maxillary sinus wash for the treatment of children with medically refractory sinusitis.

STUDY POPULATION. Studied were children treated at a tertiary otolaryngology referral center with chronic (>6 months) or recurrent (>6 episodes) rhinosinusitis diagnosed by both clinical criteria and computed tomography (CT) who did not improve with 6 months of treatment with oral antibiotics, decongestants, and allergy management when appropriate. Children with cystic fibrosis, immunoglobulin deficiency, ciliary dysfunction, or a history of previous adenoid or sinus surgery were excluded.

METHODS. Patients were assigned to adenoidectomy alone or adenoidectomy in combination with maxillary sinus wash in a nonrandomized manner on the basis of surgeon and parental preference. A questionnaire was administered 12 months after surgery to evaluate changes in symptoms of nasal obstruction/congestion, purulent drainage, cough, and headache after surgery. Univariate and multivariate analyses were performed to compare results of the 2 procedures.

RESULTS. Sixty patients were enrolled in this study: 32 (53%) underwent adenoidectomy with sinus wash, and 28 (47%) had adenoidectomy alone. The adenoidectomy/wash group had more severe sinus disease on the basis of the Lund-Mackay scoring of CT scans (mean score: 7.9 vs 3.0; \(P = .001\)) and had more boys \((P = .04)\). Overall, 87.5% of the patients who had adenoidectomy/sinus wash were improved on the basis of questionnaire results, compared with 60.7% of the subjects who had adenoidectomy alone \((P = .017)\). Children with more severe sinusitis on the basis of CT scans were more likely to improve with both adenoidectomy/sinus wash than with adenoidectomy alone \((93\%\ vs 60\%; \ P = .03)\).

CONCLUSIONS. This study demonstrates a benefit of maxillary sinus wash at the time of adenoidectomy for refractory sinusitis, particularly for children with more extensive sinus disease as indicated on preoperative CT scans.

REVIEWER COMMENTS. The role of surgery for treatment of children with sinusitis remains controversial. Who should have surgery, and which child should have adenoidectomy, endoscopic surgery, or maxillary lavage? The role of maxillary sinus wash or nasoantral windows for children has been discouraged in the past 2 decades with the recognition of key anterior ethmoid windows that might best be treated by endoscopic surgery when medical treatments fail. This article shows a benefit of maxillary wash when added to adenoidectomy, particularly for severe disease. This benefit may be from the method of irrigation through the natural ostium of the maxillary sinus rather than via the inferior meatus or the canine ostium.
fossa. Unfortunately, this article is sparse with the details of measured outcomes criteria and the definition of improvement of symptoms. Although statistical analysis was used to control for nonrandom assignment of treatment, unrecognized bias may still exist. With these limitations, maxillary sinus wash through the middle meatus seems to be a conservative surgical option in the treatment of refractory childhood sinusitis, a disease with a favorable natural history.

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Carole Fakhry, MD
David E. Tunkel, MD
Baltimore, MD
Asthma

PATHOPHYSIOLOGY

Transient Tachypnea of the Newborn May Be an Early Clinical Manifestation of Wheezing Symptoms

PURPOSE OF THE STUDY. To identify risk factors associated with transient tachypnea of the newborn (TTN) and its possible association with wheezing symptoms in early childhood.

STUDY POPULATION. Data were collected from the Population Health Research Data Repository at the Manitoba Centre for Health Policy. This was a retrospective evaluation of 12,763 children who were born at term. In this cohort, children with physician-determined bronchiolitis, acute bronchitis, chronic bronchitis, asthma, or need for prescription asthma medications were identified as having wheezing syndromes.

METHODS. Children diagnosed with TTN at birth were identified, and Cox proportional hazards regression analysis for time to first event of hospitalization, physician visit, or prescription for an asthma medication up to 7 years of age was performed. Hazard ratios were compared with those of healthy newborns.

RESULTS. A total of 308 (2.4%) of the study children developed TTN. Risk factors for development of TTN included maternal asthma, birth weight of ≥4500 g, male gender, and urban location. Infants with TTN at birth had a significantly increased risk of having a wheezing disorder in early childhood (adjusted hazard ratio: 1.17 [95% confidence interval: 1.02–1.34]).

CONCLUSIONS. TTN is associated with the development of wheezing syndromes in early childhood.

REVIEWER COMMENTS. TTN is generally believed to resolve in 2 to 5 days with no increased risk of pulmonary complications. The findings in this study suggest otherwise, with maternal asthma a risk factor for development of TTN. Nevertheless, the spectrum of wheezing disorders is broad, especially in this study where they evaluated onset of symptoms before 7 years of age, and not every young child with wheezing eventually develops childhood asthma. Additional studies to examine the association between TTN and wheezing before the age of 3 years may help determine if TTN plays a critical role in early pulmonary development.

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Early Detection of Airway Wall Remodeling and Eosinophilic Inflammation in Preschool Wheezers

PURPOSE OF THE STUDY. Eosinophilic airway inflammation and epithelial reticular basement membrane (RBM) thickening, absent in wheezy infants, may be present in preschool-aged children with severe, recurrent wheeze. This study compared RBM thickness and inflammation in endobronchial biopsies from wheezy preschool-aged children and age-matched control subjects.

STUDY POPULATION. Tissue for endobronchial biopsy was obtained from wheezy preschool-aged children (aged 3 months to 5 years) who were undergoing a clinically indicated fiber-optic bronchoscopy. Nonasthmatic controls were subjects undergoing fiber-optic bronchoscopy to investigate stridor.

METHODS. There were 16 children (median age: 29 months) with wheezing confirmed by video questionnaire (confirmed wheezers), 14 children (median age: 17 months) with reported wheeze (reported wheeze), and 10 (median age: 10 months) control subjects. Biopsy specimens were examined to compare eosinophilic inflammation (volume fraction of immunologically distinct inflammatory cells) and RBM thickness between the groups.

RESULTS. Median RBM thickness was 4.6 μm in children with confirmed wheezing compared with 3.5 μm in those with reported wheezing and 3.8 μm in controls. Median values for eosinophil density were 1.07% in confirmed wheezers, 0.72% in reported wheezers, and 0.0% in controls. Eosinophilic inflammation was significantly greater in confirmed wheezers compared with control subjects (P < .05). There were no between-group differences for any other inflammatory cell phenotype.

CONCLUSIONS. The characteristic pathologic features of asthma in adults and school-aged children develop in preschool-aged children with confirmed wheeze between the ages of 1 and 3 years, a time when intervention may modify the natural history of asthma.

REVIEWER COMMENTS. This study reconfirms that pathologic evidence of asthma can be found as early as 1 to 3 years of age. This also seems to relate to the time when lung-function abnormalities appear in preschool-aged persistent wheezers. Treatment during this critical period may affect the natural history of asthma.

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The Presence of Rhinovirus in Lower Airways of Patients With Bronchial Asthma

Wos M, Sanak M, Soja J, Olechnowicz H, Busse WW, Szczeklik A. Am J Respir Crit Care Med. 2008;177(10):1082–1089

PURPOSE OF THE STUDY. To determine if there was identifiable rhinovirus in the bronchi of stable asthmatic subjects and whether there is a difference in the prevalence of bronchial rhinovirus in asthmatic subjects versus nonasthmatic controls.

STUDY POPULATION. Adult asthmatic subjects having bronchoscopy for clinical indications were enrolled if they had a forced expiratory volume in 1 second of <80% of predicted and had >12% improvement with bronchodilator or airway hyperreactivity to methacholine. Subjects must have had stable symptoms for at least 2 weeks and no upper airway infection in the previous 3 weeks. Control subjects were nonasthmatic patients who were undergoing diagnostic bronchoscopy for symptoms such as dyspnea, hemoptysis, or tumor or having lobectomy or pulmonectomy for tumor. Controls must not have had upper airway infection within 3 weeks.

METHODS. Mucosal biopsies and lung tissue samples were analyzed by immunohistochemical staining using monoclonal antibody to rhinovirus and by in situ reverse-transcription polymerase chain reaction to identify rhinoviral RNA.

RESULTS. Immunohistochemical staining showed rhinovirus in 64% (9 of 14) of the bronchial biopsies from asthmatic subjects and in 33% (2 of 6) of the controls. With the polymerase chain reaction method, 73% of biopsies from asthmatic subjects and 22% of the controls had evidence of rhinovirus RNA. Asthmatic subjects who tested positive for rhinovirus had worse pulmonary function and increased serum and tissue eosinophilia and increased tissue leukocytes compared with subjects in the virus-negative group.

CONCLUSIONS. Rhinovirus is more often present in the lower airways of asthmatic patients, and its presence is associated with worse lung function and increased eosinophilic inflammation.

REVIEWER COMMENTS. Traditional teaching has been that rhinovirus does not replicate at 37°C but instead only at the nasal temperature of 35°C. However, our local experience indicates that this may not be an absolute; we have followed an infant with severe combined immunodeficiency with persistent pulmonary infiltrates and respiratory failure who had only rhinovirus grow from bronchoscopy several times and from lung-biopsy tissue. In hosts with supposedly normal immune systems, this study is intriguing and provides a possible therapeutic opening if agents for enterovirus (which includes the rhinovirus group) are eventually available. The studied asthmatic subjects are not a representative population of asthmatic people, because they are a convenience sample with illness for which bronchoscopy was indicated, but the data certainly should stimulate further investigation in better characterized asthmatic people who do not otherwise have an indication for bronchoscopy.

Childhood Asthma After Bacterial Colonization of the Airway in Neonates


PURPOSE OF THE STUDY. To investigate a possible association between bacterial colonization of the hypopharynx in asymptomatic neonates and later development of recurrent wheeze, asthma, and allergy during the first 5 years of life.

STUDY POPULATION. The subjects were children from the Copenhagen Prospective Study on Asthma in Childhood who were born to mothers with asthma. Samples were obtained from 321 subjects at the age of 1 month when the infants were asymptomatic.

METHODS. Aspirates from the hypopharyngeal region were cultured for Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus. Wheeze was monitored prospectively on diary cards during the first 5 years of life. Peripheral eosinophil count, total immunoglobulin E (IgE) levels, and specific IgE levels were measured at 4 years of age. Lung function was measured and asthma was diagnosed at the age of 5.

RESULTS. Overall, 21% of the infants were colonized with S pneumoniae, M catarrhalis, H influenzae, or a combination of these organisms. Colonization with ≥1 of these organisms, but not S aureus, was significantly associated with persistent wheeze, acute severe exacerbation of wheeze, and hospitalization for wheeze. Eosinophil counts and total IgE levels at age 4 were significantly increased in children colonized at age 1 month with S pneumoniae, M catarrhalis, or H influenzae, but the specific IgE level was not significantly affected. Children who had been colonized neonatally with S pneumoniae, M catarrhalis, or H influenzae also had, at age 5, increased prevalence of asthma, increased risk for hospitalization for wheeze, and increased reversibility of airway resistance after the administration of a bronchodilator.

CONCLUSIONS. Neonates colonized in the hypopharyngeal region with S pneumoniae, M catarrhalis, H influenzae, or a combination of these organisms are at increased risk for recurrent wheeze and asthma early in life.
The Role of the Social Environment in Children and Adolescents With Asthma

PURPOSE OF THE STUDY. To test associations of neighborhood, peer, and family factors with asthma outcomes in youth and to determine the pathways through which these social factors operate.

STUDY POPULATION. Seventy-eight youths aged 9 to 18 years who were diagnosed with asthma by a physician were recruited.

METHODS. Youths completed questionnaires about neighborhood problems, peer support, and family support. Biological (immunoglobulin E level, eosinophil count, production of interleukin 4) and behavioral (youth smoking, exposure to smoke, adherence to medications) pathways were measured. Asthma symptoms and pulmonary function were assessed in the laboratory and at home for 2 weeks.

RESULTS. Lower levels of family support were associated with greater symptoms (β coefficients: −.26 to −.33; P < .05) and poorer pulmonary function (β: 0.30; P < .05) via biological pathways (z statistics: 1.19–1.51; P < .05). Higher levels of neighborhood problems were associated with greater symptoms (β: .27–.33; P < .05). Peer support was not associated with symptoms or pulmonary function.

CONCLUSIONS. This study indicates that family factors may affect youths’ asthma via physiologic changes, whereas community factors may help shape the health behaviors of youths with asthma.

REVIEWER COMMENTS. Previous studies also have shown that dysfunctional family interactions predicted persistent atopic symptoms in children. This study is intriguing because it raised the possibility that family factors may affect youths’ asthma through direct biological mechanisms such as allergic inflammation rather than through medication adherence and other health behaviors such as smoking. Neighborhood factors were related to asthma outcomes through behavioral rather than biological pathways, possibly because neighborhoods set up norms for what type of behaviors are acceptable and because people tend to mirror the behaviors of those around them. This may better explain why community-wide asthma education and sponsoring health fairs have shown promising results. Limitations of this study include the sample size and the cross-sectional observational design.

 CHILDHOOD OVERWEIGHT INCREASES HOSPITAL ADMISSION RATES FOR ASTHMA

PURPOSE OF THE STUDY. To determine if childhood overweight increases the risk of hospitalization for asthma among children presenting to an emergency department with an asthma exacerbation.

STUDY POPULATION. Children who were >2 years old and presented to the emergency department of a Connecticut children’s hospital with an asthma exacerbation in 2005 were included in the study.

METHODS. A retrospective chart review was completed. Children were classified as overweight (>95th weight-for-age percentile) or nonoverweight (=95th weight-for-age percentile). Children with chronic medical conditions other than asthma were excluded.

RESULTS. There were 884 visits for 813 children. Overall, 238 (27%) were admitted to the hospital, and 33 (4%) were admitted to the ICU. Overweight children (202 [23%]) were significantly more likely to be older (8.5 ± 4.4 vs 7.3 ± 4.3 years) and to inhabit an impoverished area (37% vs 28%). Overall, hospital admission was associated with higher clinical asthma score but not with age, gender, or poverty status. Despite similar asthma scores and therapeutic management in the emergency department, hospital and ICU admission was significantly more likely for overweight than nonoverweight children (odds ratio: 1.76 [95% confidence interval: 1.23–2.51]; P = .002).

CONCLUSIONS. Overweight children with an acute episode of asthma seen in an emergency department are significantly more likely to be admitted than their nonoverweight counterparts. Overweight status clearly impacts asthma management and health in children.
Relationship of Body Mass Index With Asthma Indicators in Head Start Children


PURPOSE OF THE STUDY. To examine the relationship of BMI and asthma in children in the Head Start program in Arkansas.

STUDY POPULATION. A group of 213 children aged 3 to 5 years with physician-diagnosed asthma were compared with 816 age-matched peer control subjects from the sample of the National Health and Nutrition Examination Survey (NHANES) and with 1024 children in prekindergarten in Arkansas public schools.

METHODS. Caregivers of the children with asthma from the Head Start program were interviewed with a structured questionnaire including the Juniper Asthma Quality of Life Survey, and the children’s medical charts were reviewed. One hundred forty-one of the 213 children underwent skin-prick testing. One hundred forty-five of the children had urine cotinine levels measured to determine exposure to environmental tobacco smoke. These data were compared with the 2 reference groups in a cross-sectional analysis.

RESULTS. The prevalence of obesity (BMI > 95th percentile) was significantly higher in the Head Start children with asthma compared with the NHANES children (P < .001) and the prekindergarten children (P < .05). Compared with Head Start children with a BMI at 85th percentile, Head Start asthmatic patients with a BMI at >85th percentile reported significantly more school days missed, lifetime hospitalizations, emergency department visits, activity limitations, and oral corticosteroid bursts. No significant differences were observed in rescue and controller medications, environmental tobacco smoke exposure, prick-puncture allergy testing, quality of life, or nighttime symptoms.

CONCLUSIONS. Obesity (BMI > 95th percentile) was associated with increased asthma prevalence and morbidity. There was no association with the number or type of asthma medications or atopic status.

REVIEWER COMMENTS. This is another study showing the association of obesity and asthma. In this study, 18.8% of the Head Start children with asthma had a BMI at >95th percentile, compared with 10.8% of the NHANES and 14.4% of the prekindergarten general-population children. The mechanisms of association have not been clearly established. Both conditions are characterized by chronic inflammation.

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Christopher Randolph, MD
Waterbury, CT

Alan B. Goldsobel, MD
San Jose, CA

DIAGNOSIS AND MANAGEMENT

Pulse Oximetry Coupled With Spirometry in the Emergency Department Helps Differentiate an Asthma Exacerbation From Possible Vocal Cord Dysfunction


PURPOSE OF THE STUDY. These investigators sought to determine if they could find evidence for vocal cord dysfunction (VCD) in asthmatic adolescents whose condition failed to respond adequately to treatment in the emergency department (ED) for a presumptive asthma exacerbation.

STUDY POPULATION. Subjects with wheezing presenting to the ED of an urban children’s hospital were recruited. Inclusion criteria were age 12 to 21 years, failure to respond to treatment for wheeze sufficiently to allow discharge, and pulse oximetry reading of ≥97%. Exclusion criteria were having other cardiac or pulmonary disease, inability to perform spirometry, or need for endotracheal intubation.

METHODS. Spirometry with standard techniques was performed by using a computer-linked pneumotachograph and appropriate software to capture both inspiratory and expiratory flow volume curves. Spirometric results were classified as small airway obstruction, variable extrathoracic airway obstruction (consistent with VCD), a combination of the 2 previous findings, or normal airflow.

RESULTS. Twenty ED encounters with 17 subjects were studied. Only 5 (25%) of the encounters included spirometric evidence of small airway obstruction, but 12 of 20 had evidence for VCD (ie, variable extrathoracic airway obstruction on the inspiratory loop). These 12 in-
cluded 3 that also had evidence for small airway obstruction. There were 6 encounters with no abnormality on spirometry.

CONCLUSIONS. Spirometry may identify presumptive refractory asthma exacerbations that, instead, are episodes of VCD.

REVIEWER COMMENTS. Several years ago we treated an 8-year-old boy who had been admitted to the hospital for status asthmaticus 4 times in 1 month but never had an oxygen requirement. A videotape of the boy when he was symptomatic (provided by the parents) showed obvious stridor, not wheezing. Similarly, in this study the cardinal observation was refractory “wheeze” without arterial desaturation. Computerized spirometry is not universally available in the ED, and in addition, not all such units have software capable of displaying the inspiratory limb of the flow-volume loop. However, in busy ED environments with large asthmatic populations, availability of this measurement should greatly aid the classification of wheezing events. Pediatricians need to be more aware that VCD may present symptoms that mimic asthma.

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Larry W. Williams, MD
Durham, NC

Value of the Bronchodilator Response in Assessing Controller Naive Asthmatic Children

PURPOSE OF THE STUDY. To define the bronchodilator response (BDR) cutoff point that best identified asthma to determine the frequency of abnormal spirometry results across severity.

STUDY POPULATION. Children with asthma (n = 346) and 51 children without asthma, aged 4 to 17 years, who met entry criteria for spirometry were identified.

METHODS. Controller-naive children were evaluated with clinical criteria alone to establish a diagnosis of asthma and severity classification and then compared with the BDR, which was calculated as the percentage change from the initial forced expiratory volume in 1 second (FEV1). Receiver operator characteristic analysis determined the cutoff point for asthma diagnosis that gave the best combination of sensitivity and specificity.

RESULTS. The mean BDR in asthmatic subjects was 8.6% (95% confidence interval: 7.5%–9.8%), compared with 2.2% (95% confidence interval: 0.2%–4.3%) for the nonasthmatic subjects (P < .001). A BDR of ≥9% best differentiated these populations with a sensitivity rate of 42.5% and a specificity rate of 86.3%. Abnormal spirometry results, defined as a BDR of ≥9%, an FEV1 of <80% predicted, or both, ranged from 44.4% for mild intermittent bronchial asthma to 57.0% for severe persistent bronchial asthma.

CONCLUSIONS. Spirometric criteria that include BDR can potentially identify children who have clinically mild asthma and might benefit from controller therapy.

REVIEWER COMMENTS. What a breath of fresh air (pardon the pun). Establishing a firm diagnosis of asthma in pediatric patients can be, at times, a real challenge. Clinical history, physical examination, and a low FEV1 are all very useful in the diagnosis, but there are convincing data in children showing that an isolated, baseline FEV1 is not a good measure of the presence of asthma or its severity. The findings from this investigation demonstrate that detecting bronchodilator responsiveness (ie, 9% cutoff value for improvement in FEV1 after inhaled albuterol by metered-dose inhaler or nebulizer) can certainly aid in the diagnosis of asthma in children. A prospective assessment of this cutoff value in an unselected cohort of subjects, as well as the use of a single delivery system for the inhaled albuterol, will need to be investigated further to establish this measure as a useful diagnostic test for asthma in pediatric patients. Ultimately, use of the BDR in combination with baseline FEV1 should help clinicians detect a population of children with asthma and which children would benefit the most from therapeutic interventions such as inhaled corticosteroids.

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John M. James, MD
Fort Collins, CO

Achieving and Maintaining Asthma Control in an Urban Pediatric Disease Management Program: The Breathmobile Program

PURPOSE OF THE STUDY. This observational study evaluated the asthma control achieved in children from a lower socioeconomic urban setting with regular participation in a disease-management guideline-based program.

STUDY POPULATION. Patients aged 3 to 18 years with asthma were a self-selected, predominately Hispanic group recruited from lower socioeconomic areas of Los Angeles, California, served by the Pediatric Asthma Disease Management Program. Enrollment was from January 1, 1998, through June 30, 2006.

METHODS. The primary measure was physician-assessed asthma control based on National Heart, Lung, and Blood Institute guidelines from parent and/or patient recall. This included symptom frequency of <2 days per week and <2 nights per month for the 4-week period.
before the visit, no severe flare-ups of asthma since the last visit, normal lung function, and no reported limitations on the patient’s activities or exercise. Other data collected included physician estimate of compliance with the management plan, indicators of asthma morbidity, and severity assessments based on guideline criteria. Cox regression analysis was conducted to determine the cumulative probability that a new patient will achieve asthma control with each subsequent visit.

RESULTS. A total of 2185 patients were eligible for evaluation of time to first achieve control, and 1591 patients were eligible to evaluate subsequent control maintenance. Of these patients, 70% to 87% achieved control by visit 3, and 89% to 98% achieved control by visit 6. Subsequent control maintenance was variable. Thirty-nine percent displayed well-controlled asthma (control at >90% of subsequent visits), and 13% had difficulty-control asthma (control at <50% of subsequent visits). Maintenance of control was influenced by physician-estimated compliance with the treatment plan, baseline severity, and the interval between clinic visits.

CONCLUSIONS. Asthma control can be achieved in the majority of children in an urban setting if they participate in a structured disease-management program. Long-term maintenance of asthma control was variable, and physician-rated compliance was the factor most closely associated with the probability of controlled asthma in all severity groups.

REVIEWER COMMENTS. This study reported remarkably similar rates of initial asthma control across a broad severity spectrum in a lower socioeconomic urban setting. Equally noteworthy is the observation that maintaining such control was challenging across the severity spectrum, too. These findings reinforce the importance of routine monitoring of patients with persistent asthma, which is the cornerstone of recent revisions in the National Heart, Lung, and Blood Institute guidelines. This self-selected group of patients was more likely to be motivated and compliant with asthma-management plans. Nonetheless, this study shows what can be achieved, often with some difficulty, with a systematic approach in this patient population.

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Assessment of Inhalation Technique in Children in General Practice: Increased Risk of Incorrect Performance With New Device


PURPOSE OF THE STUDY. To assess the inhalation technique of asthmatic children with varying inhalation devices over time.

STUDY POPULATION. The study included children between the ages of 6 and 7 years who were prescribed at least 2 β agonists or controller medications by a general practitioner during 2000–2003 in the Netherlands.

METHODS. Inhalation technique was evaluated twice by using a standardized checklist first at enrollment in the study (n = 530) and 1 year later (n = 362). If children used >1 device, they were asked to demonstrate (with a placebo) their inhalation technique for the different inhalers. The study was observational, and no inhalation instructions were given. At enrollment, parents were questioned on previous inhalation instructions.

RESULTS. A total of 131 (24%) children made ≥1 essential error with their inhaler devices initially. Children with a longer duration of asthma showed significantly more frequent incorrect inhaler performance. Incorrectly performing children with a metered-dose inhaler (MDI) with a spacer received less inhalation instruction by a health care worker as reported by the child or parent. The poor performance in children with a pressurized MDI was only slightly and not significantly better if they had received inhalation instruction (P = .2). Children who kept the same device more often demonstrated correct technique compared with the year before. This was irrespective of the type of inhaler and only significant for children with an MDI (without spacer). Despite this improvement after 1 year, children with an MDI again performed worse compared with all of the other inhaler types. Moreover, Discus and other dry-powder–inhalation devices were more often demonstrated correctly compared with MDIs with or without a spacer. Of the children who were prescribed a new device, 21% (24 of 114) demonstrated an incorrect technique compared with 11% (26 of 241) of the children who kept the same device (P = .01). Furthermore, 41% (37 of 91) of incorrect performances appeared to be correct 1 year later. Conversely, 4% (11 of 300) of the correct performances were incorrect at the end of the study. The MDI was still significantly and strongly associated with incorrect technique.

CONCLUSIONS. Children are prone to use inhalation devices incorrectly if they are not monitored closely in correct use. Pressurized MDIs with and without a spacer were more prone to errors compared with dry-powder inhalers. Children prescribed a new device were more prone to usage errors.

REVIEWER COMMENTS. Although MDIs and dry-powder–inhaler devices offer convenient and effective means of controller- and rescue-medications delivery, proper instruction and reinforcement of technique is essential to
Health Plan Notification and Feedback to Providers Is Associated With Increased Filling of Preventer Medications for Children With Asthma Enrolled in Medicaid

PURPOSE OF THE STUDY. To determine if children enrolled in Medicaid managed care that provides asthma-specific communication to providers would be more likely to have adequate asthma-medications filling.

STUDY POPULATION. The study included 4498 children between the ages of 2 and 17 years with moderate-to-severe asthma enrolled in Medicaid in Tennessee and Washington State from 2000 and 2002.

METHODS. Study subjects had (1) an asthma hospitalization or asthma emergency department (ED) visit, (2) high use of asthma medications in the 6 months before their hospitalization or ED visit, and (3) stayed in the same Medicaid health plan from study entry through follow-up. Interviews were conducted with health plans to identify communication strategies used to improve asthma care by providers in the plan. The main outcome measure was guideline-recommended filling of asthma-preventer medications.

RESULTS. In the 365-day follow-up period, children in plans that provided specific feedback to providers about asthma quality and notified providers when children had an asthma-related event had higher rates of filling medications than children in plans with neither (164.6 ± 13 vs 135.3 ± 10.8 days; P < .05). For children with the greatest asthma severity, enrollment in a plan with both features was associated with 27.1 additional days of filling (95% confidence interval: 0.7–53.4 days) during the follow-up period.

CONCLUSIONS. Health plan communication to providers was associated with increased preventer filling in children with moderate-to-severe asthma in 2 state Medicaid programs.

REVIEWER COMMENTS. The children with the higher preventer fill rates only used their medications for less than half of the year. Identification of patients at high risk and frequent follow-up are needed to ensure more regular use of preventer medications. Health plans could assist providers by providing quarterly updates of fill rates for these patients at high risk so that intervention could occur before the patient ends up in the hospital or ED.
Impact of Interview Mode on Accuracy of Child and Parent Report of Adherence With Asthma Controller Medication

Bender BG, Bartlett SJ, Rand CS, Turner C, Wamboldt FS, Zhang L. Pediatrics. 2007;120(3). Available at: www.pediatrics.org/cgi/content/full/120/3/e471

PURPOSE OF THE STUDY. To examine the effect of different modes of reporting adherence on the accuracy of self-administration of inhaled corticosteroids in asthmatic children under conditions mimicking a clinical trial.

STUDY POPULATION. A total of 104 asthmatic children, 8 to 18 years old, who were being treated for asthma with regular use of inhaled corticosteroids were studied. One parent was required to participate with each child.

METHODS. Each parent/child pair was assigned to 1 of 3 self-reporting modes: audio computer-assisted self-interview (ACASI), face-to-face interview with a member of the study staff, or self-administered paper-and-pencil questionnaire. The same mode was administered at each study visit for any given parent/child pair; baseline and at 1, 2, 3, and 4 months. Corticosteroid metered-dose inhalers were fitted with an electronic chronometer that captured the time and date of metered-dose inhaler dispensing, freshly initialized at baseline and at each study visit. Adherence was determined by dividing the number of puffs recorded by the number of puffs prescribed. Self-assessment of adherence was determined similarly for the 3 modes. The recall time frames were 1 week and 1 day. The primary outcome was self-reporting discrepancy (percent adherence recorded minus percent self-adherence self-reported). A positive discrepancy score represented underreporting, a negative score represented overreporting, and zero represented exact reporting. Adequate accuracy was considered when the discrepancy score was ±25%.

RESULTS. Children and parents overrepresented adherence for both the 1-week and 1-day monitoring periods. Adherence discrepancy was the greatest in the ACASI mode (adequate accuracy for children and parents, respectively, was 32% and 27% for 1-day recall and 47% and 38% for 1-week recall). The best accuracy was for the 1-day recall in children interviewed face-to-face (50% adequate). Larger discrepancies were observed in both children and parent with the other modes.

CONCLUSIONS. Self-reporting of adherence was insufficient even under the best of circumstances regardless of the mode of self-reporting used in this study.

Early Rattles, Purrs and Whistles as Predictors of Later Wheeze


PURPOSE OF THE STUDY. To determine how different respiratory sounds in 2-year-olds (whistles, purrs, and rattles) characterized as wheeze by parents predicted wheeze and asthma diagnosis at 5 years of age. A better understanding of parental descriptions of respiratory symptoms may lead to a more accurate diagnosis of asthma.

STUDY POPULATION. The study subjects were children followed at 2 time points: at ages 2 and 5 years. They were recruited randomly before birth irrespective of history of parental asthma and allergy.

METHODS. Two thousand pregnant women were recruited randomly at 12 weeks' gestation, initially as part of a longitudinal birth cohort designed to relate dietary exposure in early life to asthma outcomes in childhood. Parents filled out questionnaires by mail regarding respiratory symptoms when their children were aged 2 and 5 years. Questions included, “Has your child ever suffered from asthma?” and “Has this been diagnosed by a doctor?” Current wheeze was defined as wheezing that has occurred over the last 12 months. If present, parents were asked to categorize the wheeze by sound, describing it as a whistle, rattle, purr, or other sound. If “other sound” was designated, the subjects were excluded from the analysis.
RESULTS. A total of 210 children wheezed as determined by the questionnaire at 2 years of age, and 77% (162) of the parents of these children also returned a questionnaire when the child was 5 years old. Wheeze persisted in 62 of these subjects. At 5 years of age, children with “whistle” at age 2 were more likely to have current wheeze (73% [11 of 15]) with physician-confirmed asthma (67% [10 of 15]). They were also more likely to be on asthma treatment (40% [6 of 15]). This was compared with “rattle,” which only translated to a 34% (33 of 97) incidence of current wheeze at age 5 and 42% (43 of 97) with physician-confirmed asthma, with 11% (11 of 97) on asthma therapy. A description of “purr” at age 2 had similar outcomes to that of rattle. Children with whistle at 2 years of age were more likely to have mothers with asthma, whereas children with rattle and purr were more likely to be exposed to environmental tobacco smoke.

CONCLUSIONS. Parents often interpret any respiratory sound as “wheeze.” When respiratory sounds are further characterized as whistle, rattle, or purr, a parent using the terminology “whistle” to describe his or her child’s wheeze was a good predictor of persisting symptoms and was associated with future asthma treatment. Use of terms “rattle” and “purr” did not predict future wheeze particularly well.

REVIEWER COMMENTS. In pediatric medicine, physicians must rely on parents for the history. For children with respiratory symptoms, parents often do not understand or know what “wheeze” means. Having parents use terms such as whistle, rattle, or purr to characterize the noise they hear may help physicians make a diagnosis of asthma, especially if the term whistle is used.

Anjuli Mehrotra, MD
Mary V. Lasley, MD
Seattle, WA

Pediatric Prescribing of Asthma Drugs in the UK: Are We Sticking to the Guideline?

PURPOSE OF THE STUDY. Similar to those in the United States, there are asthma-treatment guidelines in the United Kingdom, which were published in 1993 and updated in 1995, 1997, 2003, and 2005. The authors wondered whether the prescribing habits of physicians reflect recommendations in these guidelines.

STUDY POPULATION. The population studies was persons in the United Kingdom National Health Service Information database, which includes all prescriptions dispensed by community pharmacists and dispensing doctors.

METHODS. Prescriptions for children were reviewed for the years 2000–2006.

RESULTS. From 2000 to 2006, the number of prescriptions for bronchodilator syrups decreased 60% from 302 500 to 121 000. The use of steroid-alone inhalers declined 22% from 1 968 000 to 1 525 000, whereas the use of combination steroid/long-acting β-agonist (LABA) inhalers increased sevenfold from 50 000 to 350 000. The percentage of total steroid inhalers prescribed as combination inhalers increased from 2% to 20%.

CONCLUSIONS. The authors concluded that the increase in the number of combination inhalers prescribed is not consistent with the guideline recommendations that combination inhalers should only be introduced in those patients with asthma that is not controlled on adequate doses of inhaled steroids.

REVIEWER COMMENTS. The authors noted that inhaled bronchodilators have fewer adverse effects and that, although the use of the oral bronchodilators has declined, there are still a large number of prescriptions being written for them. On the basis of other studies, they estimated that only 5% to 10% of children with asthma would qualify for treatment with combined inhaled-steroid/LABA inhalers, yet 20% are prescribed such medications. I suspect that these findings would be the same in the United States. It is useful to reinforce that there is virtually no indication for treatment with oral bronchodilators, and only children whose condition has failed to respond to treatment with low- to medium-dose inhaled steroids alone should be treated with inhaled-steroid/LABA combinations.

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The Impact of Parents’ Medication Beliefs on Asthma Management
Conn KM, Halterman JS, Lynch K, Cabana MD. Pediatrics. 2007;120(3). Available at: www.pediatrics.org/cgi/content/full/120/3/e521

PURPOSE OF THE STUDY. To evaluate how parents’ beliefs about asthma medications can influence their adherence to their child’s prescribed therapy and assess whether race/ethnicity is an independent predictor of medication adherence.

STUDY POPULATION. The authors conducted a cross-sectional survey of parents of children with asthma in southeast Michigan who were on ≥1 preventive asthma medication between April 2004 and February 2005. Parents (n = 1858) were selected from rural, suburban, and urban areas from 40 primary care pediatric offices, of which 1322 agreed to participate in the telephone sur-
STUDY POPULATION. The 2005 Youth Risk Behavior Survey (YRBS) was administered to 13,917 students in grades 9 through 12. Students from 159 high schools in 21 cities and 40 states produced a nationally representative distribution according to grade, gender, and race/ethnicity.

METHODS. The YRBS includes 2 questions about asthma. Only students with a physician diagnosis of asthma and symptoms within the previous year were considered to have asthma. The YRBS inquires about many health risk behaviors, and this study focused on substance-abuse queries including the use of cigarettes, smokeless tobacco, marijuana, cocaine, and ≥5 drinks within a couple of hours during the previous 30 days. The YRBS includes 5 questions that follow a progression of seriousness from sadness to suicide-attempt–induced injury. The report of suicidal thoughts was chosen as an indication of probable depression.

RESULTS. Of 13,917 questionnaires completed for the items studied, 2,427 (17.4%) respondents had been diagnosed with asthma. A total of 720 students (5.2%) indicated asthma symptoms within the previous year, comprising the asthma group. All others were placed in the no-asthma group. All 5 risk behaviors occurred at least as often in students with asthma as not. Cocaine use (5.8% vs 3.7%; P = .004) and cigarette smoking (23.3% vs 20.5%; P = .02) occurred significantly more frequently in asthmatic respondents. Long-term smokers with asthma smoked more cigarettes than their nonasthmatic counterparts. Marijuana use and binge drinking exceeded 20% in both groups. Depressive feelings (45.3%) and suicidal thoughts (31.0%), plans (24.2%), actions (17.9%), and injuries (6.7%) occurred significantly more often in the asthma group (P < .001 for all). As expected, the frequency of each reported event decreased as the severity indication increased. In the youth with asthma, use of all 5 health-endangering substances was higher in those with depression (P = .004 for alcohol use, P < .001 for all others).

CONCLUSIONS. High school students with asthma reported much higher rates of depressive ideation and used health-endangering substances at a rate equal to or greater than their nonasthmatic peers. These risk behaviors signal a heightened need for intervention.

REVIEWER COMMENTS. The rates of substance abuse and depression in the cohort as a whole are staggering. That high school students with asthma are an especially at-risk group indicates our need for vigilance in identifying depressed or substance-abusing teens with asthma. In addition to some of the risk behaviors (eg, cigarette smoking) that lead to poorer asthma control, the behaviors themselves have a great impact on the students’ overall health and well-being. It is well known that depression and other psychological disorders are risks for fatal asthma, which provides another incentive for us to

Depression Symptoms and Substance Abuse in Adolescents With Asthma


PURPOSE OF THE STUDY. To determine the frequency of substance abuse and examine rates of depression in youth with asthma.
Transition to Adulthood: Delays and Unmet Needs Among Adolescents and Young Adults With Asthma

**PURPOSE OF THE STUDY.** To examine the effect of the transition to adulthood on financial and nonfinancial barriers to care in youths with asthma.

**STUDY POPULATION.** Studied were adolescents and young adults with asthma. Public-use data from the National Health Interview Survey conducted by the National Center for Health Statistics were analyzed. Data from the years 2000–2005 were pooled to provide a sample of 26,597 adolescents (12–17 years) and 19,998 young adults (18–124 years).

**METHODS.** Subjects were classified as having delayed care because of financial barriers when during the previous 12 months they had delayed seeking medical care because of concerns about affordability. Similarly, an unmet need because of a financial barrier was identified when during the previous 12 months the respondents indicated that they had failed to receive needed medical care or prescription medication because they could not afford it.

**RESULTS.** More young adults than adolescents encountered financial barriers that resulted in delays (18.6% vs 8%; *P* < .05) and unmet needs (26.6% vs 11.4%; *P* < .05). Delays caused by nonfinancial barriers were similar (17.3% vs 14.9%; *P* was not significant).

**CONCLUSIONS.** Delays and unmet needs caused by financial reasons were significantly higher for young adults with asthma compared with adolescents with asthma.

**REVIEWER COMMENTS.** It is crucial for everyone who treats children with asthma to recognize the potential vulnerability of these patients as they transition to adulthood. Appropriate counseling and written materials regarding health insurance might be helpful, as might providing lists of resources for free or reduced-cost care that are available in the local community.

MEDICAL THERAPIES

A Multicenter, Randomized, Controlled Trial of Dexamethasone for Bronchiolitis

**PURPOSE OF THE STUDY.** To evaluate the efficacy of a single dose of oral dexamethasone (1 mg/kg) compared with placebo in the treatment of acute bronchiolitis.

**STUDY POPULATION.** A total of 600 children (aged 2–12 months) with a first episode of wheezing diagnosed in the emergency department as moderate-to-severe bronchiolitis were included.

**METHODS.** Patients were enrolled at 20 emergency departments during the months of November through April over a 3-year period. The primary outcome was respiratory assessment and score change during the first 4 hours. Later outcomes evaluated included length of hospital stay, medical visits, and adverse events.

**RESULTS.** Baseline characteristics were similar for both groups. The admission rate was 39.7% for children assigned to dexamethasone compared with 41% for those assigned to placebo. Both groups had improvement during the observation period with similar mean changes in respiratory assessment score. For the patients admitted to the hospital, there was no difference in mean hospital stay (2.55 vs 2.27 days), subsequent hospital admissions, or adverse events.

**CONCLUSIONS.** Single-dose dexamethasone did not prevent hospital admission for bronchiolitis.

**REVIEWER COMMENTS.** This study finally allows for a definitive statement that no significant benefit can be seen with the use of corticosteroid for first episodes of wheezing. It should be noted that bronchodilator treatment was not regulated but seemed not to affect outcomes because treatment was equally distributed between the groups. This continues to strengthen the notion that supportive therapy with good hydration and preventing hypoxia are the most important interventions for a first episode of bronchiolitis.

Anti-inflammatory Effects of High-Dose Inhaled Fluticasone Versus Oral Prednisone in Asthma Exacerbations

**PURPOSE OF THE STUDY.** There have been reports that parenteral corticosteroids have no bronchodilator effect within
the first few hours of an acute asthma exacerbation and that their effect occurs within the first 6 to 8 hours after administration. Inhaled corticosteroids have been suggested to work faster than oral or parenteral corticosteroids in the emergency setting. This study was undertaken to investigate the mechanism through which inhaled steroids may act faster than oral steroids for acute asthma.

STUDY POPULATION. The study included patients aged 16 to 65 years who were treated in the emergency department for moderate asthma exacerbations. Inclusion criteria included a previous diagnosis of asthma and no use of intravenous or oral steroid in the 4 weeks preceding the study.

METHODS. This study was a randomized, double-blind, placebo-controlled prospective trial. There were 39 patients aged 16 to 65 years assigned to receive fluticasone and placebo prednisone (19 patients) or prednisone and placebo fluticasone (20 patients). The medication was administered via a metered-dose inhaler and spacer (16 puffs, 4000 μg/day or placebo) plus 1 pill (prednisone 30 mg/day or placebo). Spirometry and induced sputum for differential cell counts and albumin, α1-macroglobulin and blood eosinophil, interleukin 5, and granulocyte-macrophage colony-stimulating factor levels were obtained before treatment and 2, 4, 6, and 24 hours after treatment.

RESULTS. Clinical symptoms (moderate-to-severe dyspnea) improved after 24 hours in both groups. Airway obstruction was similar between groups at baseline in peak expiratory flow and forced expiratory flow in 1 second, improving progressively during the first 6 hours and decaying slightly after 24 hours. There were no significant differences between treatment groups. Eosinophil counts in sputum also improved over time in both groups. The effect was faster with fluticasone than with prednisone but was partially lost at 24 hours. In contrast, prednisone reduced blood eosinophil counts more strongly than fluticasone, although no more rapidly. Plasma protein in sputum and eosinophil count in blood both decreased until 24 hours, with no significant differences between the groups.

CONCLUSIONS. Both treatments resulted in improved symptoms, airway obstruction and inflammation, and plasma protein leakage at 24 hours. Prednisone seemed to have reduced blood eosinophil counts, whereas fluticasone reduced airway eosinophils, suggesting a less systemic antiinflammatory effect of inhaled fluticasone.

REVIEWER COMMENTS. The role of inhaled steroids during an acute asthma exacerbation is unclear. There is insufficient evidence that inhaled steroids alone are as effective as systemic corticosteroids for treatment of acute asthma. The authors showed that there was no significant difference between high-dose fluticasone and oral prednisolone in reducing airway obstruction and treatment of symptoms. This is particularly interesting, because inhaled steroids are less systemically active as compared with either intravenous or oral steroids and may confer fewer adverse effects. Of note, however, is the tremendously high dose of fluticasone used in the study. All study subjects had a 3-week follow-up visit, yet the authors failed to mention any relapses or continued morbidity of the subjects’ asthma symptoms. It would be of great importance to observe whether patients treated only with inhaled steroids are able to regain control of their asthma symptoms in the same manner as those patients treated with systemic steroids. Moreover, further investigations are warranted to elucidate whether lower doses of fluticasone can produce similar effects on symptoms of asthma exacerbations and airway obstruction.
Effect of ADRB2 Polymorphisms on Response to Longacting β2-Agonist Therapy: A Pharmacogenetic Analysis of Two Randomised Studies


PURPOSE OF THE STUDY. To determine if polymorphisms at amino acid 16 of the β2-adrenergic receptor (ADRB2) affect response to long-acting β2-agonists in combination with inhaled corticosteroids (ICSs).

STUDY POPULATION. The study included individuals at least 12 years old (2225 in study 1 and 405 in study 2) who had asthma for at least 6 months and used ICSs.

METHODS. In study 1, individuals with at least 12% reversibility of their forced expiratory volume in 1 second received 6 months of double-blind treatment with budesonide plus formoterol for maintenance and reliever therapy, fixed-dose budesonide plus formoterol, or fixed-dose fluticasone plus salmeterol. The primary outcome was the time to first severe asthma exacerbation. In study 2, participants received 7 months of open-label treatment with an adjustable regimen of budesonide plus formoterol, fixed-dose budesonide plus formoterol, or fixed-dose fluticasone plus salmeterol. Primary outcomes included the number of asthma exacerbations, time to first exacerbation, and percentage of participants with at least 1 exacerbation. Participants were stratified according to ADRB2 genotype, and the relation between genotype and asthma outcome was determined.

RESULTS. Baseline characteristics were similar among all Gly16Arg genotypes, and the genotypes were equally distributed across treatment groups. A combination of the 3 treatment groups showed a similar likelihood of having ≥1 severe asthma exacerbation for each genotype in study 1 (Gly/Gly, 12%; Gly/Arg, 11%; and Arg/Arg, 9%) and study 2 (Gly/Gly, 9%; Gly/Arg, 8%; and Arg/Arg, 9%). The time to first exacerbation was similar among genotype groups (study 1 P = .31, study 2 P = .94). In study 1, there was no interaction among treatment group, genotype, and time to first severe exacerbation (P = .88). Improvement of morning peak expiratory flow and other secondary end points was similar for all genotypes in both studies. In study 2, differences in response according to genotype were not seen between participants with and without baseline reversibility of forced expiratory volume in 1 second.

CONCLUSIONS. Individuals with asthma may continue to receive ICSs plus long-acting bronchodilators regardless of their Gly16Arg genotype.

REVIEWER COMMENTS. Study results have varied regarding the effectiveness of long-acting β2-agonists, with or without

David Jeong, MD
Harvey L. Leo, MD
Ann Arbor, MI

12–15, severe). An age-specific score of 1 to 3 was assigned to 5 variables (oxygen saturation, respiratory rate, work of breathing, auscultation, and ability to talk). Response to inhaled β2 agonist was measured by determining the time taken to reduce the frequency of β2 agonists from 20-minute intervals to administration at 1, 2, and 4 hourly intervals, with longer times indicating poorer response to treatment. Polymerase chain reaction was used on peripheral blood samples to amplify the 2 polymorphisms of interest (Arg16Gly and Gln27Glu).

RESULTS. There were 58 (39.2%) patients who were homozygous Gln27Gln, 69 (46.6%) patients who were heterozygous Gln27Glu, and 21 (14.2%) patients who were homozygous Gln27Glu. Subjects homozygous for Gln were slowest to respond to inhaled β2 agonist therapy. Homozygotes for Glu had the most rapid response (time to 1 hourly: 2.0 ± 2.8 hours; time to 2 hourly: 10.7 ± 18.1 hours; time to 4 hourly: 28.5 ± 26.2 hours). Homozygotes for Gln had the most rapid response (time to 1 hourly: 1.4 ± 1.2 hours; time to 2 hourly: 6.8 ± 8.9 hours; time to 4 hourly: 24.3 ± 22.2 hours). No significant associations were found between Arg16Gly and response to treatment. After controlling for asthma severity score, previous use of asthma medications, age, gender, and concurrent upper respiratory infection symptoms, homozygotes for Gln were still more likely to have the slowest response to treatment. No associations were found between β2-adrenergic receptor genotype and asthma severity scores or asthma patterns.

CONCLUSIONS. This study demonstrates an association between single-nucleotide polymorphisms and response to β2-agonist treatment for children during an acute asthma exacerbation as compared with stable nonacute disease. Children who are homozygous for β2-adrenergic receptor Gln27Gln respond less effectively to inhaled β2-agonist therapy.

REVIEWER COMMENTS. As the authors pointed out in the report, most children are treated effectively during an acute asthma exacerbation. The length of treatment with inhaled β2 agonists, however, can be variable and unpredictable. The results of this study explain, at least in part, this variability. In the future, knowledge of a patient’s β2-adrenergic receptor genotype can possibly guide decisions about duration and need for additional therapies during an acute asthma exacerbation.
Montelukast as Add-on Therapy to ß-Agonists and Late Airway Response


PURPOSE OF THE STUDY. To evaluate montelukast’s ability to inhibit the late-phase airway response after allergen exposure in adults with house dust mite–induced asthma.

STUDY POPULATION. Thirty-five adults (19 men, 16 women) aged 18 to 31 with mild, stable asthma and sensitivity to house dust mites were included.

METHODS. This study was designed as a randomized, double-blind, single-dose, placebo-controlled, crossover trial. Subjects underwent serum testing for antigen-specific immunoglobulin E (IgE) to house dust mite. Sensitized subjects were then examined for airway infections and underwent spirometry and determination of their fraction of nitric oxide in exhaled air (FeNO). They were then challenged with increasing concentrations of inhaled Dermatophagoides farinae via a nebulizer system. Testing was stopped when the patient’s forced expiratory volume in 1 second (FEV₁) decreased at least 20% (early airway response [EAR]), they experienced significant clinical symptoms, or they received a cumulative dose of 1270 mg. Patients were then given 1 puff of salbutamol (0.1 mg) and either montelukast (10 mg) or a placebo. FEV₁ was measured for the following 8 hours with a decrease of at least 20% demonstrating a late airway response (LAR). Formoterol (12 μg) was then given to treat those patients. Subjects returned at least 2 weeks later and were crossed-over into the other group.

RESULTS. Of the 35 subjects in the study, 12 showed no significant EAR on 1 or both study days, 11 showed only an EAR, and 12 demonstrated both an EAR and LAR. This last group was analyzed further. The difference in FEV₁ from baseline values 3 to 8 hours after challenge was expressed as the area under the FEV₁ time-response curve (FEV₁-AUC). The FEV₁-AUC of patients on placebo was −2.47 ± 1.32 vs −0.768 ± 1.68 for the patients on montelukast (P < .005). Subjects with a dual response had a significantly higher baseline FeNO than those with no response (56.4 vs 21.0 ppb; P < .05).

CONCLUSIONS. Montelukast was able to block the late-phase airway response in subjects who responded dually to the allergen challenge. In addition, patients with a higher baseline FeNO seemed more likely to develop an LAR than those with lower ones.

REVIEWER COMMENTS. The results of this study implicate a role for montelukast as an “add-on,” therapeutic option for symptomatic relief after allergen exposure in subjects with mild asthma. It also suggests a rapid onset of action that allows for its usage in such a setting. This study supports existing ones that have demonstrated the effect of montelukast within 2 to 3 hours for up to 24 hours. There was also a “trend toward significance” showing subjects on montelukast with higher FEV₁ values than those on placebo. However, this study was limited in its sample size and should be expanded to fully elicit montelukast’s role in acute exacerbations. It would also be worthwhile to investigate its effects on subjects with moderate-to-severe asthma in the same setting. Last, this study also alluded to the fact that a patient’s baseline FeNO may be a predictor of whether he or she develops an LAR. This should also be explored further in expanded studies and in children.

Attenuation of the September Epidemic of Asthma Exacerbations in Children: A Randomized, Controlled Trial of Montelukast Added to Usual Therapy


PURPOSE OF THE STUDY. To evaluate whether montelukast, when added to usual asthma therapy, would affect the asthma symptoms experienced during the annual asthma epidemic occurring each year when school resumes after summer vacation.

STUDY POPULATION. Participants included 194 subjects from 2 to 14 years of age with physician-diagnosed asthma. More than 90% of the children had prescriptions for an inhaled corticosteroid (ICS).

METHODS. Children were randomly assigned to receive either an age-appropriate dose of montelukast (n = 98) or the concomitant use of ICSs, in individuals with the Arg/Arg genotype relative to the Gly/Gly genotype. This large and long-term randomized study, including participants taking different long-acting β₂-agonists, adds to the evidence suggesting that combination ICS/long-acting bronchodilator therapy may be equally effective in people with the Arg/Arg genotype. Given the overall effectiveness and prevalence of ICS/long-acting bronchodilator use and the increasing focus on individualization of asthma management, responses of subgroups of people with asthma to these medications will continue to be an important area of research.
and 14 years. The first tablet was taken the evening of September 1 and continued nightly for 45 days. Asthma symptoms, cold symptoms, use of oral prednisone, and unscheduled physician visits resulting from asthma were recorded daily. Subjects were instructed to take the tablet in addition to their usual asthma therapy.

RESULTS. Children who received montelukast experienced 53% fewer days with “worse asthma symptoms” compared with children who received placebo (3.9% vs 8.3%; P < .02). In addition, there was a 78% reduction in the number of unscheduled visits to a physician for asthma (4 vs 18; P = .011). These improvements were seen in patients with and without cold symptoms. Among boys, the greatest benefit from montelukast was seen in those aged 2 to 5 years. Girls benefited most from montelukast when they were between the ages of 10 and 14 years.

CONCLUSIONS. Montelukast, when added to usual asthma therapy, reduced the risk of worsening asthma symptoms and unscheduled physician visits during the annual September asthma epidemic.

REVIEWER COMMENTS. It has long been recognized that epidemics of asthma exacerbations occur annually after students return to school after summer vacation. This study demonstrates that montelukast, a leukotriene-receptor antagonist, could be used in conjunction with usual asthma medications to attenuate some of these annual symptoms. The study population enrolled in this study was composed largely of persistently asthmatic children, based on the fact that >90% were prescribed ICSs. Additional studies are needed to investigate whether a similar reduction in asthma symptoms would be seen in subjects with less-severe asthma. In addition, compliance with the use of prescribed ICS in this study was relatively poor, with only 47% of subjects using an ICS routinely. This is in agreement with other studies that have shown that ICS prescription filling is at its lowest just before the return to school. It remains to be seen whether simply improving compliance with prescribed ICSs at the start of the academic school year would also lead to a significant reduction in asthma symptoms.

PURPOSE OF THE STUDY. To evaluate the efficacy of budesonide inhalation suspension (Pulmicort respules) compared with montelukast (Singulair) for controlling asthma symptoms in young children with mild persistent asthma.

STUDY POPULATION. This was a prospective study of 395 children, aged 2 to 8 years, diagnosed with mild persistent asthma recruited from 55 US centers. Approximately 12% of the subjects had previous histories of inhaled corticosteroid (ICS) use.

METHODS. Subjects were randomly assigned to receive either budesonide 0.5 mg or montelukast 4 to 5 mg daily and were followed for 52 weeks. Compliance was assessed by daily electronic diary review. For mild asthma exacerbations, step-up therapy consisted of the addition of a morning dose of budesonide 0.5 mg in both arms. For severe asthma exacerbations, subjects received a 3- to 10-day standardized course of oral steroids. The primary end point was evaluated by using the intention-to-treat population and was defined as time to first additional medication for asthma worsening at 52 weeks. Secondary end points included the time to additional asthma medication and rates of occurrence of mild and severe asthma exacerbations. Changes in symptom scores, peak flows, rescue-medication use, and pulmonary-function test results were also evaluated.

RESULTS. Kaplan-Meier probability curves showed that the primary outcome measurement, time to the first additional asthma medication, was not significantly different between the 2 groups at 52 weeks (P = .3). There was a significant increase in the time to first additional asthma medication in the budesonide group compared with the montelukast group at 12 weeks (P = .05). The percentage of subjects requiring step-up therapy in the budesonide group versus the montelukast group at 12 weeks was 29.1% versus 38.6% (not significant [NS]), at 26 weeks was 41.3% versus 48.2% (NS), and at 52 weeks was 52% versus 56.9% (NS), respectively. The budesonide group achieved significantly improved morning and evening peak flow values compared with the montelukast group at 12 weeks (P = .005-.007). The rate of mild and severe asthma exacerbations per subject per year in the budesonide and montelukast groups was 1.23 and 1.63, respectively (P = .034). There was no significant difference in the number of severe asthma exacerbations between the 2 groups. Both treatment groups showed nonsignificant improvements in changes from baseline asthma scores, 24-hour rescue-medication use, and medication- and asthma-free days.

CONCLUSIONS. Both budesonide and montelukast are effective and well-tolerated as controller medications in children aged 2 to 8 years with mild persistent asthma. Results favored budesonide for several secondary outcome measures.
Effect of Different Antiasthmatic Treatments on Exercise-Induced Bronchoconstriction in Children With Asthma


PURPOSE OF THE STUDY. To compare the effectiveness of different patterns of antiasthmatic treatments to protect children from exercise-induced bronchospasm (EIB).

STUDY POPULATION. This was a randomized, double-blind, placebo-controlled study of 100 children aged 6 to 18 years with atopic asthma sensitive only to house dust mites and EIB. Subjects must have had a resting forced expiratory volume in 1 second (FEV₁) of ≥70% predicted and at least a 20% drop in FEV₁ after exercise to qualify for the study.

METHODS. Participants were randomly assigned to a 4-week double-blind, placebo-controlled trial to receive 1 of the following treatments: (1) budesonide 100 µg + formoterol 4.5 µg twice daily; (2) budesonide 100 µg twice daily + montelukast 5 or 10 mg at bedtime; (3) montelukast 5 or 10 mg at bedtime; (4) budesonide 100 µg twice daily; or (5) placebo alone. All study arms had matching placebo medications from which active drugs were omitted (eg, group 1 had placebo tablets in place of montelukast, etc). At randomization and after 4 weeks on the study medication(s), a treadmill exercise test was performed to evaluate the effectiveness of treatment.

RESULTS. Ninety-one subjects with a median age of 11.3 to 12.2 among the groups completed the study. Preexercise FEV₁ and EIB, as represented by the area under the curve of time-response curve and by maximum percentage decrease in FEV₁ after exercise, did not differ at baseline between the groups. EIB was diminished with all treatments when compared with placebo. The effect of treatment with budesonide plus montelukast and with montelukast alone were greater than budesonide alone or budesonide plus formoterol (P < .001). The budesonide-plus-formoterol group was also better than budesonide alone, but these results did not reach significance (P = .59).

CONCLUSIONS. Budesonide plus montelukast or montelukast alone were the most effective treatments for EIB in children.

Adverse Effects of Inhaled Corticosteroids in Funded and Nonfunded Studies


PURPOSE OF THE STUDY. Evidence regarding the safety profile of drugs may vary depending on study sponsorship. The authors aimed to evaluate differences between studies funded by the pharmaceutical manufacturer of the drug (PF) and those with no pharmaceutical funding (NoPF) regarding the finding and interpretation of adverse effects of inhaled corticosteroids.

METHODS. The authors assessed the safety reporting of inhaled corticosteroids in 275 PF and 229 NoPF studies identified by a Medline search using prespecified criteria.

RESULTS. Overall, the finding of statistically significant differences for adverse effects was significantly less frequent in PF (34.5%) than in NoPF (65.1%) studies (prevalence ratio [PR]: 0.53 [95% confidence interval (CI): 0.44–0.64]). This association became nonsignificant (PR: 0.94 [95% CI: 0.77–1.15]) after controlling for design features (such as dose or use of parallel groups) that tended to be associated with less-frequent findings of adverse effects and were more common in PF studies. Among studies that found a statistically significant increase in adverse effects associated with the study drug, the authors of PF articles concluded that the drug was “safe” more frequently than the authors of NoPF studies (PR: 3.68 [95% CI: 2.14–6.33]).
CONCLUSIONS. The type of funding may have determinant effects on the design of studies and on the interpretation of findings: funding by the industry is associated with design features less likely to lead to finding statistically significant adverse effects and with a more favorable clinical interpretation of such findings. Disclosure of conflicts of interest should be strengthened for a more balanced opinion on the safety of drugs.

REVIEWER COMMENTS. Okay, so maybe this is not a real big shock to most of us. What was surprising to me was the extent that this bias exists with a variety of other drugs including hypertensive agents, pain medications, and cancer treatments. This seems to be related to the study design of the protocols, suggesting that the whole system is “rigged.” The investigator physicians have no clue how the studies are set up or how the data are manipulated. So where is the Food and Drug Administration in all of this?

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Allen Adinoff, MD
Denver, CO
Immunotherapy and Immunomodulation

Efficacy of Long-term Sublingual Immunotherapy as an Adjunct to Pharmacotherapy in House Dust Mite-Allergic Children With Asthma


PURPOSE OF THE STUDY. To evaluate the effect of 3 years of dust mite sublingual immunotherapy (SLIT) on clinical and laboratory outcome measurements.

STUDY POPULATION. This was a prospective study of 90 children aged 4 to 16 years who were followed for 4 years from the time of enrollment. Inclusion criteria were mild-to-moderate persistent asthma requiring an inhaled steroid, monosensitization to dust mite, and no previous history of immunotherapy.

METHODS. Participants were randomly assigned to treatment for 3 years with dust mite SLIT plus standard pharmacotherapy or pharmacotherapy alone. The prescribed SLIT solution consisted of 50% Dermatophagoides pteronyssinus and 50% Dermatophagoides farinae. Doses were increased gradually to a maintenance dose, which was taken 2 times per week. All participants were initially started on 800 µg/day of inhaled budesonide. Follow-up visits were performed every 2 to 3 months, at which times the inhaled corticosteroid (ICS) dose was decreased until either it was discontinued or the minimum dose allowing for control of symptoms was reached. Pulmonary-function testing was performed at each visit. Skin-prick testing to 15 aeroallergens and a serum total immunoglobulin E measurement were performed annually.

RESULTS. A total of 90 children were randomly assigned: 62 to SLIT plus pharmacotherapy and 28 to pharmacotherapy alone. There were 19 drop-outs (31%) in the SLIT group after 3 years compared with 5 (18%) in the pharmacotherapy group. The number of months per year in which the children required ICS, as well as mean dose per day of budesonide, was significantly lower in the SLIT group compared with pharmacotherapy group during all 3 years. By the end of the 3 years, 52.4% in the SLIT group versus 9.1% in the pharmacotherapy group were able to successfully discontinue ICSs for at least 6 months. Both forced expiratory volume in 1 second and forced expiratory flow, midexpiratory phase, were significantly increased from baseline in the SLIT group after 3 years, whereas the pharmacotherapy controls showed no change. Total immunoglobulin E levels were significantly decreased only in the SLIT group after 3 years. Finally, there were no serious adverse reactions during the study.

CONCLUSIONS. Three years of SLIT as an adjunct to pharmacotherapy in house dust mite–allergic children with asthma resulted in a reduction of the necessity for ICS usage along with improvement in lung functions.

Cutting Edge: Immunosuppressant as Adjuvant for Tolerogenic Immunization


PURPOSE OF THE STUDY. Immunosuppressive agents are used frequently for the treatment of allergy, autoimmune disease, and transplant rejection but are thought to provide only temporary benefit. The authors of this study sought to determine if dexamethasone, a glucocorticoid with potent immunosuppressive properties, could promote long-term antigen-specific tolerance when administered with a peptide immunogen.

METHODS. The authors used a model of delayed-type hypersensitivity (DTH) to hen ovalbumin by subcutaneously injecting ovalbumin twice during a 2-week interval into BALB/c mice. Mice with established DTH to ovalbumin were then immunized with an ovalbumin-derived MHCII-restricted peptide in the presence or absence of dexamethasone. All mice were retested for DTH at 2-week and 4- to 5-month time points after completion of immunization by injecting ovalbumin into the footpad and measuring the increase in footpad thickness. Blood-derived CD4+CD25+Foxp3+ regulatory T cells (Tregs) were quantitated by labeling peripheral white blood cells with carboxyfluorescein diacetate succinimidyl ester (CFSE), stimulating the cultures with ovalbumin peptide, and analyzing for CFSE dilution (indicating cell division). Dendritic cells (DCs) in draining lymph...
nodes (LNs) were assessed for maturity by staining for CD11c, CD83, and CD86, as well as interleukin 10 (IL-10) in some experiments. Transgenic mice containing large numbers of ovalbumin-specific CD4+ T cells were studied also. A similar set of experiments was performed with nonobese-diabetic mice, a mouse model of autoimmune diabetes, by using dexamethasone and an insulin-derived MHCII-restricted peptide. Primary outcomes measured were median time to development of diabetes (as defined by glycosuria) and measurement of Treg numbers and antigen-specific proliferation.

RESULTS. Treatment with dexamethasone induced long-term desensitization (as long as 4–5 months) in mice with preestablished DTH to hen ovalbumin as evidenced by a decrease in foot-pad swelling after ovalbumin challenge. This finding was accompanied by an expansion of CD4+CD25+Foxp3+ Tregs, which largely had specificity for ovalbumin. Dexamethasone, in the presence of ovalbumin, seemed to block DC maturation in draining LNs and facilitated differentiation of IL-10+ DCs. Furthermore, treatment of nonobese-diabetic mice with dexamethasone hindered development of spontaneous diabetes and was associated with the development of long-term antigen-specific persistent Tregs.

CONCLUSIONS. Dexamethasone, when applied together with peptide, can promote long-term tolerance. The underlying mechanism may involve dexamethasone’s effect on inhibiting DC maturation and promoting development of persistent antigen-specific Tregs.

REVIEWER COMMENTS. Development of long-term tolerance, as opposed to transient desensitization, is the end goal of immunotherapy protocols, and this study suggests that glucocorticoids may be effective adjuvants in achieving this goal. The authors of this article speculated that other small-molecule immunosuppressant drugs, including cyclosporine and FK506, may also be effective for this purpose, but there is some evidence that these agents may actually promote development of allergic disease in children after solid organ transplantation.

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Pamela A. Guerrerio, MD, PhD
Elizabeth C. Matsui, MD
Baltimore, MD

Probiotics Have a Different Immunomodulatory Potential In Vitro Versus Ex Vivo on Oral Administration in Children With Food Allergy

PURPOSE OF THE STUDY. Previous studies have suggested that administration of probiotics in vitro can stimulate regulatory and T helper type 1 (Th1) immune responses. The authors studied both in vitro immunologic effects of probiotics and the ex vivo immunologic effects after oral administration of probiotics in children with food allergy, a Th2-mediated disease.

STUDY POPULATION. Thirteen food-allergic children aged 0.5 to 2.8 years were enrolled from the Department of Pediatric Dermatology and Allergology at Wilhelmina Children’s Hospital (University Medical Center, Utrecht, Netherlands).

METHODS. Probiotics (n = 7) or placebo (n = 6) were orally administered during 3 months. At baseline and after 1 and 3 months, peripheral blood mononuclear cells were stimulated with crude peanut extract, anti-CD3, or anti-CD40 and interleukin 4 (IL-4) in the presence (in vitro response) or absence (ex vivo response) of probiotics. The proliferation and production of interferon γ, IL-5, IL-13, IL-10, tumor necrosis factor α (TNF-α), IL-6, and immunoglobulin E (IgE) were analyzed. Sensitization to peanut, cow’s milk, and hen’s egg was determined before and after treatment.

RESULTS. The in vitro addition of probiotics to peripheral blood mononuclear cell cultures resulted in enhanced proliferation and production of interferon γ, IL-10, and TNF-α. After oral treatment, proliferation in the presence of probiotics increased, whereas in vitro IgE production decreased in the probiotics group compared with baseline. The ex vivo production of IL-10, TNF-α, and IL-6 tended to decrease. Th1 and Th2 cytokines were not altered. Sensitization remained unchanged.

CONCLUSIONS. Probiotics enhanced the production of Th1 and regulatory cytokines in vitro. Oral administration of probiotics resulted in a slightly decreased ex vivo production of IL-10, TNF-α, and IL-6, which indicates that probiotics have a different potential to modulate the immune response in vitro versus ex vivo.

REVIEWER COMMENTS. There is great interest in the potential for probiotics to divert the immune systems from the Th2 (allergic) profile. Although many studies have investigated the effects of probiotics in vitro, few have examined the effects in atopic children. This study, with a limited number of patients, demonstrates that results obtained in vitro may not reflect the effects of probiotics when they are ingested and exposed to the intestinal mucosa, thus suggesting that additional in vivo studies are necessary to better understand the mechanism of action and optimize the therapeutic potential of probiotics in atopic children.

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Julie Wang, MD
New York, NY
Immunodeficiency

PRIMARY IMMUNODEFICIENCY

STAT3 Mutations in the Hyper-IgE Syndrome

PURPOSE OF THE STUDY. To identify the genetic defect underlying the hyper-immunoglobulin E (IgE) (Job) syndrome.

STUDY POPULATION. Patients with hyper-IgE syndrome were ranked by a clinical scoring system. Fifty patients over the age of 16 years who had the highest scores (most features of the disease) were selected. Forty-eight family members also underwent genetic analysis.

METHODS. The authors used a combination of microarray screening of gene expression and analysis of cytokine production in vitro from lymphocytes subjected to various stimuli.

RESULTS. Lymphocytes from patients were found to have diminished response to the cytokine interleukin 6. The authors systematically analyzed the intracellular signaling molecules involved in the response to interleukin 6 and found that patients carried a mutation in 1 of the 2 copies of the gene encoding signal transducer and activator of transcription 3 (STAT3). They confirmed the biological importance of the mutations by showing that the STAT3 protein did not function normally within the cell.

CONCLUSIONS. STAT3 mutations are the genetic basis of the hyper-IgE syndrome.

REVIEWER COMMENTS. The first clinical description of hyper-IgE syndrome as a distinct entity was published in 1966. It was given the eponym “Job syndrome” as a biblical allusion because of the many severe skin abscesses that afflict patients with the condition. This report is the culmination of >40 years of investigation by many groups around the world to find the molecular basis of this disease. A similar report was published by another group around the same time (Minegishi Y, Saito M, Tsuchiya S, et al. Nature. 2007;448[7157]:1058–1062). We are reminded again of the power of modern molecular biological methods and the tremendous insights we gain when such diseases are finally understood at their “source.”

Population Prevalence of Diagnosed Primary Immunodeficiency Diseases in the United States

PURPOSE OF THE STUDY. To measure the prevalence of primary immunodeficiency diseases (PIDs) in the United States.

STUDY POPULATION. A random sample of 10 005 American households (26 657 people) was included in the study.

METHODS. Households were selected by random-digit dialing stratified according to time zone. Calls were placed by trained interviewers with computer assistance. Eighty percent of the households contacted completed the interview. Respondents were asked, “Has anyone in your household ever been diagnosed with a primary immunodeficiency disease such as common variable immunodeficiency, IgA [immunoglobulin A] deficiency, IgG subclass deficiency, or any other immunodeficiency? (This is not acquired immunodeficiency—AIDS).” If they replied “yes,” they were further questioned with details of the diagnosis and limited demographic information about the affected individual(s).

RESULTS. Twenty-three individuals in 18 households were identified as having a specific PID (including common variable immunodeficiency, IgA deficiency, IgG subclass deficiency, X-linked agammaglobulinemia, severe combined immunodeficiency, and chronic granulomatous disease). The calculated prevalence of diagnosed immunodeficiency was 1 in 2000 children, 1 in 1200 people of all ages, and 1 in 600 households. The 95% confidence limits for the estimate for all individuals were between 1 in 824 and 1 in 1956. Several of the identified individuals with primary immunodeficiency were not receiving therapy that is standard of care for their diagnoses (γ-globulin replacement).

CONCLUSIONS. Quoting the authors, “The current study suggests that these conditions are sufficiently common that primary care physicians are likely to see patients with underlying primary immunodeficiency disorders in their practice and should test for these disorders in patients with recurring, unusual or serious infections. In the absence of routine screening, physician awareness of the relative frequency of these disorders is critical to early diagnosis and treatment.”

REVIEWER COMMENTS. This is an extremely important message for all primary care physicians. These patients are in your practices now. The authors also pointed out that several studies have shown that many cases of PID are diagnosed late or are “mild” enough that they are never diagnosed and that patients suffer excess morbidity and mortality as a result. Some severe cases may be missed because children die before they are diagnosed. Thus, the true prevalence of PID is likely to be higher than
Recognition, Clinical Diagnosis and Management of Patients With Primary Antibody Deficiencies: A Systematic Review

PURPOSE OF THE STUDY. To create an evidence-based literature review of clinical diagnosis and management of primary antibody deficiency.

METHODS. Computer literature searches were conducted for randomized clinical trials in medical literature databases including the US National Library of Medicine (Medline), the Excerpta Medica database (EMBASE), the Cochrane Library, the Database of Abstracts of Reviews of Effects (DARE) of the Centre for Reviews and Dissemination (University of York), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) up to June 2006. Reports were rated on the basis of relevance and quality or type of evidence. Disease entities included were X-linked agammaglobulinemia, common variable immunodeficiency, hyper-immunoglobulin M (IgM) syndromes, IgG subclass deficiency with and without IgA deficiency, and specific antibody deficiency. Reports that involved only a limited number of patients were not included.

RESULTS. Individuals who present with recurrent respiratory infections of all types, especially with excessive frequency and severity, should be screened for antibody deficiency. In children, common associations included growth delay and failure to thrive, recurrent fevers without a source, and poor school attendance or performance. Chronic diarrhea was found in 40% to 60% of the patients at all ages. The median delay in diagnosis was 1 year but ranged to >10 years. Delayed diagnosis led to increased risk of bronchiectasis, pulmonary hypertension, and cor pulmonale. Randomized trials of the efficacy of γ-globulin replacement versus placebo do not currently exist. Many observational studies have confirmed the benefit of IgG therapy for reducing infectious morbidity. Higher IgG doses are associated with reduced incidence and severity of infections.

CONCLUSIONS. Delayed diagnosis was common as a result of lack of recognition of presenting symptoms and signs. Delay was less frequent when patients were referred to specialists. Delayed diagnosis led to delayed therapy (IgG) and a higher rate of infections and morbidity. Several areas for additional research were identified, including studies of efficacy and dose of IgG and adjunct therapies (antibiotics), microbiologic study of pathogens, identification of prognostic markers, and effective monitoring of disease (eg, lung function, other organs, cancer). Collaboration and pooling of data among centers nationally and internationally would likely lead to better data.

REVIEWER COMMENTS. This study again points out the human cost of delayed or undiagnosed immunodeficiency and the difficulties in accumulating high-quality data on therapy and outcomes. Several initiatives are taking shape in the United States and abroad to collaborate to answer many of the remaining questions pointed out in this study.

HUMAN IMMUNODEFICIENCY VIRUS

Functional Patterns of HIV-1-Specific CD4 T-Cell Responses in Children Are Influenced by the Extent of Virus Suppression and Exposure

PURPOSE OF THE STUDY. HIV-specific CD4+ T cells seem to play a critical role in antiretroviral immunity and particularly in maintaining cytotoxic T-cell responses. The objective of this study was to evaluate the function of HIV-specific T cells in antiviral treated, HIV-infected children.

STUDY POPULATION. The researchers evaluated 23 HIV-infected children who were treated with antiretroviral therapy for a mean of 7 years.

METHODS. Flow-cytometric analysis was used to measure the ability of HIV-specific T cells to secrete interleukin 2 (IL-2) and interferon γ (IFN-γ) after stimulation of patient cells with p55 gag protein.

RESULTS. Three patterns of intracellular cytokine generation were identified: in 10 subjects, antigen-specific cytokine production was characterized by IL-2 production, 8 subjects’ CD4+ T cells expressed IL-2 and IFN-γ, and 5 subjects’ T cells expressed IFN-γ alone. These 3 groups were then analyzed for factors that might explain the different patterns. The patterns correlated with viral load at the time of functional analysis and over the previous 2 years. The group with dominant IFN-γ responses had high viremia levels, a pattern similar to that observed in patients with uncontrolled viral replication. Patients with combined IL-2 and IFN-γ production had relatively lower viral loads but had experienced viral “blips” over the 2 years before analysis. This pattern was similar to
adults who were long-term nonprogressors or those whose conditions continued to progress despite antiretroviral therapy. The subjects with a dominant IL-2 response had very low levels of viremia and had not experienced viral “blips” over the previous 2 years. This pattern was similar to that generally observed in individuals who have cleared the infecting agent. It is important to note that this pattern has not been observed in HIV-infected adults.

CONCLUSIONS. Children with HIV have a higher frequency of HIV-specific CD4+ T cells compared with adults, and their recovery of an IL-2-secreting T-cell pattern indicates a greater capacity for immune restoration in children than adults.

REVIEWER COMMENTS. This elegant study provides a biological rationale for the clinical observation that young children started on antiretroviral therapy have the capacity for remarkable reconstitution of immune functions relative to those reported in adults and older children who have been infected for prolonged periods before antiretroviral therapy. Perhaps it is unfair to compare these results with findings in adults that included patients who were infected for many years before their initiation of therapy. A more appropriate comparative adult group would be those treated within 6 months of their diagnosis. Most importantly, this study demonstrates that children are “different” and that treatment early in infection allows excellent immune reconstitution if viral replication is completely controlled.

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Joseph A. Church, MD
Los Angeles, CA

Identification of Host Proteins Required for HIV Infection Through a Functional Genomic Screen

PURPOSE OF THE STUDY. The HIV genome encodes only 15 proteins and, therefore, must use multiple host-cell collaborators for successful replication and transmission. Required host-derived proteins include CD4 as the primary virus receptor and chemokine receptors as coreceptors. This study identified multiple other host proteins required for HIV activity.

METHODS. Human cells known to be susceptible to HIV were exposed in vitro to HIV. Using small interfering RNAs able to inhibit each known gene in the human genome 1 at a time, the investigators tested whether HIV could establish an infection and copy itself. HIV dependence on >21 000 human genes was examined.

RESULTS. More than 250 human genes were identified to be required for efficient HIV replication. Termed “HIV-dependency factors,” the products of these genes are known to participate in a broad array of cellular functions and implicate unsuspected pathways in the virus life cycle.

CONCLUSIONS. The extraordinary dependence of HIV on human host proteins for efficient transmission and replication provides many new potential targets for antiretroviral therapy.

REVIEWER COMMENTS. An example of targeting host proteins is the use of chemokine receptor 5 (CCR5) inhibitors. Many people with CCR5 deficiency are very resistant to HIV infection yet have limited if any clinical consequences. Maraviroc CCR5 inhibitor is approved for treatment for HIV infection. This study identified many more such potential targets.

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Joseph A. Church, MD
Los Angeles, CA

Proteinuria in Children Infected With the Human Immunodeficiency Virus

PURPOSE OF THE STUDY. Proteinuria is a common feature of HIV infection and a potential complication of therapy in adult patients. This study was performed to determine the prevalence of proteinuria in a group of children infected with HIV and to assess this process over time and the impact of antiretroviral therapy on it.

STUDY POPULATION. HIV-infected children (N = 286) were studied from 1998 through 2006.

METHODS. Proteinuria was determined by random urine protein/creatinine ratios, with “normal” defined as <0.2 and “nephrotic” defined as >1.0.

RESULTS. A total of 94 (33%) of the children had proteinuria at baseline. Of these, 32 had urine protein range ratios of ≥1.0. Clinically, the mortality rate was higher in those patients with proteinuria. It is important to note that 55 of the 94 patients with baseline proteinuria showed a good response to antiretroviral therapy, as indicated by a decrease in HIV viral load and a substantial reduction in the number of subjects who had proteinuria.

CONCLUSIONS. Control of HIV viremia with antiretroviral therapy reduces progression of HIV-associated proteinuria and improves the survival rate of infected children.

REVIEWER COMMENTS. Proteinuria is a common feature of HIV infection in children. Two features of this patient popu-
lation may affect the generalizability of the study findings: 85% of the patients were African American or African Caribbean, and the number of individuals with complicating hepatitis B or C was not indicated. Renal disease is more prevalent in HIV-infected black people than white people, particularly with respect to HIV-associated nephropathy. Chronic viral hepatitis may also cause secondary renal disease, likely secondary to an immunocomplex-associated inflammatory process. Regardless of these caveats, the authors’ conclusion is very much warranted: “surveillance of quantitative proteinuria with imaging and chemical indicators of renal dysfunction is very much warranted” for children with HIV infection.

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Joseph A. Church, MD
Los Angeles, CA

Semen-Derived Amyloid Fibrils Drastically Enhance HIV Infection

Seminal Plasma Reduces the Effectiveness of Topical Polyanionic Microbicides

PURPOSE OF THE STUDIES. Heterosexual intercourse is the major route of HIV transmission throughout the world. A variety of factors have been identified that are associated with increased transmission, including virus load, lack of circumcision, and the presence of sexually transmitted diseases. One approach to the reduction of male-to-female transmission has been the use of microbicides, and a major effort has been put forth to identify a safe and effective topical microbicide. The purpose of the Münch et al study was to identify factors in semen that might enhance HIV transmission, and the purpose of the Patel et al study was to examine why one of the most promising microbicides tested has failed thus far to reduce transmission in a large controlled trial.

STUDY POPULATION. Normal human seminal plasma was studied.

METHODS AND RESULTS. In the Münch et al study, investigators screened a complex peptide/protein library derived from human seminal fluid. The authors looked for novel inhibitors and enhancers of HIV infection. They identified fragments of prostatic acidic phosphatase that dramatically enhanced HIV infection. Functional and structural analysis showed that these peptides formed amyloid fibrils that captured HIV particles and strongly enhanced the number of productively infected cells in vitro by promoting virion-cell attachment. The authors termed this product “semen-derived enhancer of virus infection” (SEVI). Rats transgenically expressing human CD4 and chemokine receptor 5 (CCR5) are susceptible to HIV infection. In this model, SEVI significantly enhanced the infectivity of HIV in vivo. In the Patel et al study, seminal plasma was shown to dramatically reduce the activity of polyanionic microbicides to reduce infectivity of herpes simplex virus type 2. Further study demonstrated that fibronectin 1 and lactoferrin were the specific factors in seminal plasma that were responsible for this process. In a murine model, this interference in vitro translated to a loss of protection in vivo.

CONCLUSIONS. Components of seminal plasma increase HIV infectivity and reduce the effectiveness of topical polyanionic microbicides.

REVIEWER COMMENTS. That host factors are involved in HIV replication and transmission is not surprising. However, that amyloid fibrils associated with seminal plasma dramatically increase HIV infectivity was not expected. An increased understanding of the mechanism of this enhancement might assist in overcoming the obstacles noted by Patel et al. An extraordinary effort was put forth to identify a safe and effective microbicide that would prevent transmission of HIV. In vitro and in vivo models indicated that the compound, PRO 2000, would dramatically reduce HIV transmission in vivo. The failure of this approach and the finding that seminal plasma directly interferes with this function dramatically illustrate the need to evaluate seminal plasma as a potential interfering agent in the search for effective microbicides.


Joseph A. Church, MD
Los Angeles, CA
Infectious Disease and Vaccination

Duration of Humoral Immunity to Common Viral and Vaccine Antigens

**PURPOSE OF THE STUDY.** To better define the duration of humoral immunity and the role played by memory B cells.

**STUDY POPULATION.** There were 45 human subjects followed for up to 26 years. These participants were recruited from the Oregon National Primate Research Center. The only inclusion criteria was that subjects had at least 3 serum samples banked for at least 3 years before the study began. The average age at the start and end of the study was 37 and 52 years, respectively.

**METHODS.** Blood samples were drawn at least annually, and serum was banked. Antibody titers were measured to vaccinia, measles, mumps, rubella, varicella-zoster, Epstein-Barr, tetanus, and diphtheria. Each subject gave an average of 14 serum samples over an average of 15.2 years. Also, the investigators measured antigen-specific memory B cells by means of limiting-dilution analysis and compared memory B-cell frequencies to their corresponding serum antibody levels. The majority of subjects had vaccination to smallpox in childhood and had recovered from the other viral diseases such as measles and rubella.

**RESULTS.** The antibody responses to viral antigens were very stable, with estimated half-lives ranging from 50 years for varicella-zoster to >200 years for measles and mumps. Against tetanus and diphtheria, the antibody responses waned more rapidly with half-lives of 11 and 19 years, respectively. The investigators also found that B-cell memory was long-lived, but there was no significant correlation between peripheral memory B-cell numbers and antibody levels for 5 of the 8 antigens.

**CONCLUSIONS.** Serologic memory for multiple antigens is maintained for remarkably sustained periods of time. Also, memory B-cell numbers did not correlate with antibody titers, which suggests that peripheral memory B-cells and antibody-secreting plasma cells may represent independently regulated cell populations and may play different roles in the maintenance of immunity.

**REVIEWER COMMENTS.** At the end of the study, the average age of the participants was 52 years. Most had received vaccination to smallpox, but most had also contracted natural measles, mumps, or rubella during childhood. This study population, therefore, does not represent our current population of children with complex schedules of vaccinations. Furthermore, we cannot conclude from this study that vaccination-induced immunity is necessarily as long-lived as natural infection-induced immunity. Nonetheless, this report does give fascinating insight into the “adult” side of immunity to many of the childhood diseases against which we vaccinate. This study also sheds light on possible mechanisms for sustained humoral immunity, which it seems may not entirely depend on regulation by memory B cells.


Brian A. Smart, MD, FAAP
Glen Ellyn, IL

The Neglected Role of Antibody in Protection Against Bacteremia Caused by Nontyphoidal Strains of Salmonella in African Children

**PURPOSE OF THE STUDY.** To investigate whether specific antibody protects against nontyphoidal *Salmonella* (NTS) bacteremia.

**POPULATION STUDIED AND METHODS.** Admissions for NTS bacteremia during 1 year were reviewed (*N* = 352). Sera from 65 healthy Malawian children (median age, 24 months; range, 3–107 months) was used for in vitro NTS-killing assays. Purified immunoglobulin G (IgG) from patient sera was used to delineate the role of antibody versus complement. Immunoglobulin and complement deposition on bacteria was also assessed by flow cytometry. Complement dependency was tested by heat inactivation and by using C9-deficient serum.

**RESULTS.** Overall, 82% of the children with NTS bacteremia were <36 months old, but there was a nonuniform distribution with fewer-than-expected cases in children <4 months old (actual: 9.7% vs 16.7%), suggesting a role for passive humoral immunity. From healthy donors, 9 of 25 children <16 months of age had serum with normal in vitro killing, whereas 40 of 40 children >16 months of age did so. NTS killing in vitro was complement and membrane attack complex dependent. Effective killing corresponded to a specific IgG or IgM *Salmonella* titer of 1.5 U and was associated with the deposition of complement (C3 and C9) measured by flow cytometry. Resistance to killing by alternative complement activation was mediated by long-chain lipopolysaccharide and the rck gene product.

**CONCLUSIONS.** *Salmonella*-specific antibody that overcomes the complement resistance of NTS develops by 2 years of life in Malawian children and is mediated by specific IgG or IgM antibody.
NTS is the most common cause of bacteremia in Malawi and much of tropical Africa and is associated with high rates of mortality even with appropriate culture facilities and access to antibiotics. The finding that specific antibody is protective against this invasive, facultative intracellular pathogen supports the importance of vaccine development for this pathogen.

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