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, 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 Relevant to Pediatric Allergy and Immunology” supplement to *Pediatrics*, Visiting Professor Program, Pediatric Asthma Speaker’s Kit, 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), and a number of public education materials. The Section is also active in contributing to educational programs and resources such as *AAP News*, educational brochures, clinical reports, practical pediatrics courses, and many other endeavors.

To support training and to promote research in pediatric allergy and immunology, the Section awards travel grants to residents and training fellows to participate in and to present cases at the AAP NCE and provides outstanding abstract awards for training fellows and junior faculty members 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.

The reviews contained in the 2009 synopsis were written by Fellows of the AAP 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 pediatricians. 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; Theresa A. Bingemann, MD, Rochester, NY; Bradley E. Chipps, MD, Sacramento, CA; Joseph A. Church, MD, Los Angeles, CA; Karla L. Davis, MD, Landstuhl, Germany; John E. Duplantier, MD, Indianapolis, IN; 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; Jennifer Kim, MD, Chicago, IL; Mary V. Lasley, MD, Seattle, WA; Susan Laubach, MD, Washington, DC; Harvey L. Leo, MD, Ann Arbor, MI; Joann H. Lin, MD, McKinney, TX; Todd A. Mahr, MD, La Crosse, WI; Elizabeth C. Matsui, MD, MHS, 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, Leominster, MA; Christopher Randolph, MD, Waterbury, CT; Melinda M. Rathkopf, MD, Anchorage, AK; Wayne G. Shreffler, MD, PhD, New York, NY; Scott H. Sicherer, MD, FAAP, New York, NY; Elinor Simons, MD, MSc, Toronto, Ontario, Canada; Justin M. Skripak, MD, New York, NY; Brian A. Smart, MD, Glen Ellyn, IL; Jonathan M. Spigel, MD, PhD, Philadelphia, PA; Michael S. Tankersley, MD, San Antonio, TX; David E. Tunkel, MD, Baltimore, MD; Julie Wang, MD, New York, NY; Kirk H. Waibel, MD, Fort Sam Houston, TX; and Robert A. Wood, MD, Baltimore, MD.

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A Synopsis of the Synopses

This synopsis supplement reports advances and key observations that will affect the care of children with allergic and immunologic diseases now and in the near future. Reviewers for the synopsis supplement selected many articles that have clinical “pearls” and provide insights that are applicable for daily practice. For example, although there have been studies that support the “hygiene hypothesis,” that reduced infection has led to increased atopic disease, 2 studies reported this year did not show that antibiotic use per se is related to increased atopic outcomes. Curiously, 1 large study showed an association of atopy with use of acetaminophen, but additional prospective studies are needed. Also reported is a study that showed that obesity may increase the risk of atopic disease, providing further fuel to address the obesity epidemic. The efficacy of atopy prevention with probiotics continues to remain uncertain, with studies on both sides. Adding to data that do not support prolonged elimination of dietary allergens (eg, beyond 6 months) as a means for atopy prevention, a study that showed worse atopic dermatitis outcomes when milk protein introduction was delayed is reported. Another observation against prolonged food allergen avoidance as a prevention strategy is from a study that showed that peanut allergy is more common in Jewish children surveyed in the United Kingdom, where introduction of peanut is typically delayed, compared with Israel, where it is ingested more typically in the first year of life. However, randomized trials are still needed to determine the impact of timing of allergen ingestion on atopy outcomes. Regarding treatment of food allergy, a randomized, controlled trial of milk oral immunotherapy showed that treated subjects were able to significantly increase the amount of milk they could ingest. Although this is exciting and promising, additional studies are needed to characterize the safety and efficacy of the approach and also to determine whether the treatment induces a permanent cure or only an increased threshold during treatment. Additional observations regarding food allergy include reports of the utility of serum immunoglobulin E tests for diagnosing peanut, tree nut, and soy allergy. Several studies selected by our reviewers characterized eosinophilic esophagitis, which seems to be a persistent illness that should be considered in young children with atopy and gastrointestinal symptoms such as reflux and failure to thrive and in older children with reflux symptoms and dysphagia. Another gastrointestinal food-allergic disease being increasingly well characterized is food protein-induced enterocolitis syndrome, a disorder with severe vomiting and possible hypotension; symptoms begin ~2 hours after ingestion of the causal protein. Several articles on this topic have underscored the need for a high index of suspicion to avoid misdiagnosis, including appreciation that the illness is not associated with positive allergy tests for the trigger foods and that reactions mimic sepsis. Several studies have addressed the clinical management of atopic dermatitis, with emphasis on the etiologic role of bacteria, potential efficacy of measures to reduce skin infection such as “bleach baths,” and preemptive therapies rather than reactionary treatment. Numerous insights about asthma have also been reported. For example, 2 studies specifically documented improved asthma when exposure to environmental tobacco smoke and to pollution is reduced. The interrelationship of viral infections and risks of asthma/allergy has been explored in epidemiological and laboratory studies; for example, in a murine study, there was increased susceptibility to allergen sensitization with acute influenza A infection. Several studies explored approaches to using antiinflammatory medications for asthma, intermittently, regularly, or presymptomatically (eg, in response to viral infection). Although the results are preliminary, the observations from these studies provide interesting insights about relative risks/benefits of these approaches. Several studies evaluated the safety and efficacy of noninjection routes of allergen immunotherapy, by using oral or sublingual administration, with promising results. In the field of primary immunodeficiency, dissection of the molecular basis of these myriad disorders continues with identification of infection outcomes for those with myeloid differentiation protein 88 (MyD88) deficiency. In addition, a study showed promising long-term outcomes for gene therapy treatment of adenosine deaminase deficiency. Immunologic studies are identifying new potential means of reducing HIV transmission and replication, and several medical therapies have shown promise for controlling HIV infection.

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 the window toward understanding therapies on the horizon. For additional information about our Section, please visit www.aap.org/sections/allergy.

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Editor, Best Articles Relevant to Pediatric Allergy and Immunology

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Allergy

**PREDICTION, PREVENTION, AND THE "HYGIENE HYPOTHESIS"**

**Age at First Introduction of Cow Milk Products and Other Food Products in Relation to Infant Atopic Manifestations in the First 2 Years of Life: The KOALA Birth Cohort Study**

Snijders BE, Thijs C, van Ree R, van den Brandt PA. *Pediatrics*. 2008;122(1). Available at: www.pediatrics.org/cgi/content/full/122/2/e115

**PURPOSE OF THE STUDY.** To evaluate any associations between the introduction of cow’s milk products/other solid food products and infant atopic manifestations in the second year of life.

**STUDY POPULATION.** Mother-infant pairs previously enrolled in the ongoing prospective KOALA Birth Cohort Study to study the cause of allergic disease. A total of 2834 pregnant women were recruited at 34 weeks of gestation. Data from 2558 infants in the Netherlands were analyzed.

**METHODS.** Data on introduction of cow’s milk products and other food products, eczema, recurrent wheeze, allergies, and confounders were collected with repeated questionnaires at 34 weeks of gestation and 3, 7, 12, and 24 months after delivery. Allergen-specific immunoglobulin E was assessed from serum obtained from children at age 2 years. Analyses were performed through multivariate logistic regression. Reverse causation was addressed by performing risk-period-specific analyses that excluded infants with early symptoms of eczema or wheeze.

**RESULTS.** More delay (e.g., ≥7 months of age) in introduction of cow’s milk products was associated with a higher risk for eczema. In addition, delayed introduction of other food products was associated with an increased risk for atopy development at the age of 2 years. Exclusion of infants with early symptoms of eczema and recurrent wheeze (to avoid reverse causation) did not essentially change the results.

**CONCLUSIONS.** Delaying the introduction of cow’s milk products or other food products may not be favorable for preventing the development of atopy.

**REVIEWERS COMMENTS.** In giving advice to “allergic families,” we used to think that it was a good idea to keep children clean, away from pets, and to delay the introduction of “highly allergenic” foods such as cow’s milk. Were we wrong on all counts? There are many confounders when evaluating the relationship between early introduction of food products to infants and later development of atopy. The authors of this article used several statistical approaches to account for the main confounders, including breastfeeding, family history, and, importantly, reverse causation. Although it is difficult to absolutely exclude reverse causation, this authors suggested that delayed introduction of milk was associated with increased eczema. Because of studies such as this one, the focus has shifted away from the delayed introduction of cow’s milk protein and other food products as a means to decrease the risk of developing atopy. These findings provide a rationale for conducting interventional studies to determine whether early introduction of milk and other foods will actually help to prevent food allergies.

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**Antibiotic Use in the First Year of Life and Risk of Atopic Disease in Early Childhood**


**PURPOSE OF THE STUDY.** To investigate an association with antibiotic use in the first year of life and subsequent development of atopic disease in the first 5 years of life.

**STUDY POPULATION.** A prospective birth cohort of 198 children considered to be at high atopic risk was recruited prenatally and monitored for 5 years. Risk was based on ≥1 parent with a doctor’s diagnosis of asthma, hay fever, or eczema.

**METHODS.** Parents kept a daily diary of their child’s symptoms, including history of respiratory illnesses, and antibiotic use. The study physician evaluated children at regular intervals for the presence of eczema, and annual interviews took place, during which parents reported a diagnosis of asthma or wheezing. At 5 years of age, all children underwent skin-prick testing and gave serum samples for measurement of total immunoglobulin E. To determine the effect of antibiotic use on future atopic disease, a logistic regression model was used with propensity score adjustment, with adjustments for a calculated antibiotic predictor score, number of doctor visits, gender, child care, and pets.

**RESULTS.** Fifty-four percent of the children (107 of 198 children) received ≥1 course of antibiotics in the first year of life. Acute respiratory illness, and in particular lower respiratory illness, was the most common reason for use of antibiotics. Children who received antibiotics for wheezing lower respiratory illness between 7 and 12 months were more likely to be diagnosed with asthma (odds ratio [OR]: 3.1 [95% confidence interval (CI): 1.2–7.3]; P < .05). Asthma in general was associated with antibiotic use (unadjusted OR: 2.3 [95% CI: 1.2–
METHODS. A birth cohort study that collected reported antibiotic exposure before 3 months and before 15 months, along with outcomes (wheeze, asthma, eczema, rash, and inhaler use) at 15 months (N = 1011) and 4 years (N = 986). Questionnaires were administered by study nurses at recruitment and 3, 15, 24, 36, and 48 months of age, in home visits at 3 and 15 months and subsequently by telephone. Outcome measures were collected by using identical questions at 15, 24, 36, and 48 months, covering the period since birth or the previous visit. Analyses were limited to outcomes at 15 months (covering the recall period from birth to 15 months) and at 4 years (covering the recall period from 3 to 4 years). Asthma was defined as greater than 1 positive skin-prick test result at 15 months of age with a panel of common inhalant and food antigens.

RESULTS. Antibiotic exposure before 3 months was significantly associated with asthma developing between birth and 15 months (odds ratio [OR]: 2.32 [95% confidence interval [CI]: 1.5–3.7]; P = .0004); however, with adjustment for chest infections (univariate analysis), this association was reduced (OR: 1.6 [95% CI: 0.96–2.60]) and only trended toward statistical significance (P = .07). Multivariate analysis (with adjustment for gender, ethnicity, family history, parity, otitis media, and antibiotic use between 15 months and 4 years) further decreased this association (OR: 1.3 [95% CI: 0.8–2.2]; P = .4). Similarly, although the association of antibiotics with atopy initially trended toward statistical significance (OR: 1.44 [95% CI: 0.96–2.14]; P = .08), the association was reduced after adjustment for chest infections (OR: 1.36 [95% CI: 0.91–2.05]; P = .14). There was no effect of antibiotic exposure before 15 months on asthma developing after 15 months and remaining present between 3 and 4 years (OR: 1.4 [95% CI: 0.9–2.1]; P = .20). Antibiotic exposure before 3 months was not significantly associated with eczema and rash developing between 0 and 15 months, but exposure before 15 months was significantly associated with both eczema (OR: 1.8 [95% CI: 1.1–3.1]; P = .02) and rash (OR: 1.6 [95% CI: 1.02–2.53]; P = .04) developing after 15 months and remaining present at 4 years; however, these associations also lost statistical significance with both univariate and multivariate analyses.

CONCLUSIONS. There is a statistically significant association between antibiotic exposure in infancy and the subsequent presence of asthma and eczema; however, these associations lose statistical significance with adjustment in univariate and multivariate analyses. The effect of antibiotics on respiratory disease may be a result of confounding by chest infections at an early age when asthma may be indistinguishable from infection.

REVIEWERS COMMENTS. Increases in both asthma prevalence and use of antibiotics in recent years have led some to postulate connections between the 2. Retrospective studies in general have shown strong associations between early antibiotic use and the symptoms of asthma, although these associations have been weaker in prospective studies. Reverse causation as an explanation has been suggested by some (ie, people with asthma may tend to have more respiratory infections that require treatment with antibiotics). This study was limited by a...
lack of data regarding the reason for early antibiotic use, but it suggests that much of the effect of antibiotics on respiratory disease is a result of the confounding effects of early chest infection. More prospective studies are needed to better illuminate this complex association.

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Association Between Obesity and Atopy in Chinese Schoolchildren
Leung TF, Kong APS, Chan HIS, et al. *Int Arch Allergy Immunol.* 2009;149(2):133–140

PURPOSE OF THE STUDY. To investigate the association between asthma traits, atopy, and obesity-related markers in Chinese adolescents.

STUDY POPULATION. Chinese children (*N* = 486) who were randomly selected from a Hong Kong obesity study of adolescents had their allergy features assessed.

METHODS. Anthropometric measurements were made, with BMI greater than local age- and gender-specific 85th percentile defining overweight and BMI greater than 95th percentile defining obesity. Fasting blood samples were collected to measure levels of allergen-specific immunoglobulin E (to dust mite, cat, and cockroach), lipids, and inflammatory biomarkers.

RESULTS. The median age was 15.0 years (interquartile range: 14.0–16.0 years), and the median BMI was 19.3 kg/m² (interquartile range: 17.5–21.7 kg/m²). There were 62 overweight children (12.8%) and 36 obese children (7.4%). There were 239 atopic subjects (49.2%). Neither overweight nor obesity status was associated with asthma, allergic rhinitis, or eczema (*P* > .25). Atopy was also not associated with age-adjusted BMI, waist circumference, serum lipid profiles, or fasting glucose levels. Atopy and presence of allergen-specific immunoglobulin E did not differ between overweight or obese children and those with normal BMI (*P* > .25).

Subgroup analysis suggested that cockroach sensitization was more common among boys who were obese or overweight (*P* = .045). The white blood cell (WBC) count was significantly higher among atopic versus nonatopic children (mean: 6.5 × 10⁹ vs 6.2 × 10⁹ cells per L; *P* = .006). Logistic regression revealed higher WBC count to be a risk factor for atopy (odds ratio: 18.97; *P* = .004).

CONCLUSIONS. Obesity is not associated with asthma or atopy. A high WBC count is an important risk factor for atopy in boys and girls. Gender does not exert any consistent effect on the association between obesity and allergy sensitization in children.

Association of Obesity With IgE Levels and Allergy Symptoms in Children and Adolescents: Results From the National Health and Nutrition Examination Survey 2005–2006

PURPOSE OF THE STUDY. To study the association of obesity with total and allergen-specific immunoglobulin E (IgE) levels and allergy symptoms in children and adolescents.


METHODS. Eligible persons who completed both the household interview and medical examination components of the National Health and Nutrition Examination Survey and had height and weight measured were included in the study. Total serum IgE and allergen-specific IgE tests were performed depending on age. Atopy was defined as a positive response (≥0.35 kU/L) to ≥1 of the allergens tested. BMI was calculated for all study participants, and detailed questions regarding physical activity, household smoking, maternal smoking during pregnancy, and birth weight were asked.

RESULTS. Total serum IgE levels were higher among overweight and obese children versus normal-weight children, unrelated to smoking exposure, birth weight, or physical activity. The odds ratio for atopy was increased for the obese children, compared with normal-weight children. Most of the children with atopy were sensitized to foods, and there was no association seen between obesity and reported allergy symptoms and hay fever.

REVIEWER COMMENTS. In developed countries, childhood asthma and obesity have been increasing in prevalence, and there is increased interest in determining whether there is an association between the 2. Both involve inflammatory processes, but often the findings are as inconclusive as determining whether the chicken or the egg came first. In this cross-sectional study, the authors found no strong correlation between atopy and obesity. This suggests that other factors, including genetic and environmental effects, are separately affecting atopic and obesity features, especially by the time a child has reached adolescence. A prospective study of birth cohorts may further define whether there is a significant relationship between weight gain, development of atopic features, and changes in obesity- and atopy-related laboratory values.

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There was a strong relationship between C-reactive protein levels and total IgE levels.

CONCLUSIONS. Overweight status in children is associated with allergic predisposition, especially to foods. Because childhood obesity continues to be an enormous health care concern facing US children, this increased risk of allergy is yet another motivating factor to combat childhood obesity.

REVIEWERS COMMENTS. The authors of this study attempted to correlate childhood obesity with increased atopy, particularly to foods. However, the definition of atopy relied on an elevated serum-specific IgE level, which may not be clinically relevant, especially for food allergy without clinical history. The study authors recognized that BMI is not the best measure of obesity because of larger bone structure and muscle mass in some children, which further confounds the classification of overweight and obese children. Studies also showed that underweight children had increased risk of atopic disease, but this was not addressed in this study. Any effort to reduce or to prevent childhood obesity is beneficial but, in terms of atopic diseases, maybe we should take the "3 bears" approach: not too skinny, not too fat; normal weight is perfect.

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Association Between Paracetamol Use in Infancy and Childhood, and Risk of Asthma, Rhinoconjunctivitis, and Eczema in Children Aged 6–7 Years: Analysis From Phase Three of the ISAAC Programme

PURPOSE OF THE STUDY. The authors evaluated the associations between exposure to paracetamol (acetaminophen) in infancy and childhood and development of asthma and other atopic conditions in early school-aged children.

STUDY POPULATION. The study included 205,487 children 6 to 7 years of age from 73 centers in 31 countries.

METHODS. Parents or guardians completed written questionnaires regarding the presence of asthma, rhinoconjunctivitis, and eczema symptoms; child and family demographic information; and exposure to environmental risk factors including medications, breastfeeding, diet, home exposures, and traffic pollution. Acetaminophen administration for fever in the child’s first year of life and the frequency of acetaminophen use in the previous 12 months (none; medium, once per year or more; or high, once per month or more) were determined.

RESULTS. Acetaminophen use for fever in the first year of life was associated with symptoms of asthma (odds ratio [OR]: 1.46 [95% confidence interval [CI]: 1.36–1.56]), rhinoconjunctivitis (OR: 1.48 [95% CI: 1.38–1.60]), and eczema (OR: 1.35 [95% CI: 1.26–1.45]) for children 6 to 7 years of age and was associated with severe asthma symptoms and with rhinoconjunctivitis and eczema after exclusion of children with wheeze. The overall population attributable risk of asthma was 21% to 40%. The association between asthma and current acetaminophen use was dose dependent (medium frequency OR: 1.61 [95% CI: 1.46–1.77]; high frequency OR: 3.23 [95% CI: 2.91–3.60]); dose-response relationships were also seen for rhinoconjunctivitis and eczema.

CONCLUSIONS. Acetaminophen use in infancy and childhood was associated with the development of asthma, rhinoconjunctivitis, and eczema in 6- to 7-year-old children, and the associations seemed to be dose-responsive for childhood acetaminophen exposure.

REVIEWER COMMENTS. This large, multinational, retrospective study demonstrated an association between previous and current acetaminophen use and childhood atopic conditions that persisted across populations with different lifestyles, medical access and practices, and types of febrile childhood illnesses. Prospective studies of acetaminophen use during pregnancy and a randomized, controlled trial that compared acetaminophen with another antipyretic medication also suggested associations between acetaminophen and childhood asthma, although an association between decreased aspirin use and asthma development has also been hypothesized. Before these findings can be interpreted as causal, additional prospective observational or randomized studies should be performed and should include information on covariates such as parental atopy and asthma, types of febrile illnesses, and use of other antipyretic agents.

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Allergic Disease and Atopic Sensitization in Children in Relation to Measles Vaccination and Measles Infection

PURPOSE OF THE STUDY. To determine the role of measles vaccination and infection in the outcome of allergic disease and atopic sensitization.
STUDY POPULATION. A total of 14,893 children 5 to 13 years of age were included from the cross-sectional, multicenter, Prevention of Allergy—Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) study, conducted in 5 European countries.

METHODS. Four groups of children were compared, those in farming communities, those attending Steiner schools (which are known for avoidance of immunizations), and nonfarming and non-Steiner reference groups. By using parental questionnaires based on previously validated questionnaires (including the International Study of Asthma and Allergies in Children), 14,893 children (69% response rate) were evaluated for environmental exposures, history of vaccinations and infections, lifestyle factors, and symptoms and diagnoses of allergic diseases. Atopic sensitization was defined as ≥1 allergen-specific immunoglobulin E level of ≥0.35 kU/L against inhalant allergens and/or foods. A sample of children with complete information on measles vaccination and infection was invited to undergo an additional blood test, and 4,049 children (83% response rate) did so, with parental consent.

RESULTS. In reviewing the entire group of children, atopic sensitization was inversely related to measles infection and vaccination. After exclusion of children who confirmed symptoms of wheezing and/or eczema in the first year of life, an inverse relationship was noted between measles infection but not vaccination and “any allergic symptom” or “any diagnosis of allergy by a physician.”

CONCLUSIONS. The authors concluded that measles infection may be protective against allergic conditions in children.

REVIEWER COMMENTS. The literature is inconsistent on the relationship between measles infection and allergic disease or atopic sensitization. The predominant confounder in these studies is determining and controlling for whether the exposure precedes the disease, which is a problem in this study as well. The strengths of the study are its size and international design, with a high prevalence of measles infection. However, there was a low prevalence of allergic disease and sensitization in the reference group. The authors also cannot exclude other vaccinations included in the measles-mumps-rubella vaccine or other aspects of the anthroposophic lifestyle that may affect the observed relationship. Additional prospective cohort studies are needed to establish causality.

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Relevance of the Hygiene Hypothesis to Early vs. Late Onset Allergic Rhinitis

PURPOSE OF THE STUDY. To compare the effects of siblings, infections, and rural environment on the development of allergic rhinitis before and after 7 years of age.

STUDY POPULATION. The population-based cohort of participants in the Tasmanian Longitudinal Health Study (TAHS) was studied. Initial data were collected on 8,583 children 7 years of age, comprising 99% of the schoolchildren in Tasmania born in 1961. The most recent follow-up evaluation occurred in 2004 and captured 5,729 of the original participants at the age of 44 years, with the balance either lost to follow-up monitoring or deceased.

METHODS. Subjects were categorized according to outcome, as those with early-onset allergic rhinitis (developed before the age of 7 years), those with late-onset allergic rhinitis (developed after the age of 7 years), and a reference group of those who did not report allergic rhinitis. The exposures considered were siblings, infections, tonsillectomy, and farm residence during childhood. Potential confounders considered were gender, maternal and paternal atopy, mother’s age at participant’s birth, paternal socioeconomic status in 1968, and personal socioeconomic status in 2004. Univariate associations were evaluated by using $\chi^2$ tests. Multinomial logistic regression was used to examine independent effects of different exposures on outcome with adjustment for confounders. The main analysis included 3,429 subjects.

RESULTS. Subjects with sibling exposure before the age of 2 had less early-onset allergic rhinitis than did those with no siblings (<1-year sibling exposure, odds ratio [OR]: 0.6 [95% confidence interval [CI]: 0.3–1.0]; 1- to 3-year sibling exposure, OR: 0.6 [95% CI: 0.4–0.9]; >3-year sibling exposure, OR: 0.4 [95% CI: 0.3–0.8]). This effect was dose dependent, with a P value of .0001 for trend. It was stronger than the effect of sibling exposure before 6 months or before 4 years. The trend for the effect of sibling exposure before the age of 2 was apparent (P = .001), although weaker, in late-onset allergic rhinitis. Early- but not later-onset allergic rhinitis decreased with viral infections during childhood (OR: 0.7 [95% CI: 0.5–0.9]). Tonsillectomy before the age of 7 increased the rate of early- but not later-onset allergic rhinitis (OR: 1.7 [95% CI: 1.2–2.5]).

CONCLUSIONS. Exposures related to the hygiene hypothesis are more strongly related to early- than late-onset allergic rhinitis. The immunologic mechanisms for these risk factors are poorly understood. Additional research should focus on early-onset allergic rhinitis when ex-
Probiotic Supplementation in the First 6 Months of Life in at Risk Asian Infants: Effects on Eczema and Atopic Sensitization at the Age of 1 Year


PURPOSE OF THE STUDY. To determine the effect of probiotic supplementation from birth to 6 months of age on eczema and allergic sensitization at 1 year of age in Asian infants at risk of allergic disease.

STUDY POPULATION. A total of 253 infants with a family history of allergic disease, defined as having a first-degree relative with doctor-diagnosed asthma, allergic rhinitis, or eczema, and positive skin-prick test result to dust mite, were voluntarily recruited prenatally at the clinics or eczema, and positive skin-prick test result to dust mite, were voluntarily recruited prenatally at the clinics.

METHODS. The subjects were randomly assigned to receive ≥60 mL/day of commercially available cow’s milk-based formula either with or without probiotic supplementation from birth to the age of 6 months. The probiotics used were Bifidobacterium longum (10^7 colony-forming units per g) and Lactobacillus rhamnosus (2 × 10^8 colony-forming units per g). The primary outcome was eczema (pruritic rash with chronic relapsing course), and the secondary outcome was allergen sensitization. Questionnaires and pediatrician evaluations were performed at 1, 3, 6, and 12 months. The scoring atopic dermatitis index was used to objectively define the severity of atopic dermatitis. Skin-prick tests (to soy, milk, egg yolk, egg white, and 2 locally prevalent dust mites) were performed at the 12-month visit. The 2 outcomes were compared by using x^2 tests, and logistic regression was used to calculate the odds ratio and to adjust for potential confounders (gender, birth order, prenatal smoking exposure, and feeding history).

RESULTS. The incidence of eczema in the probiotic group (22%) was similar to that in the placebo group (25%) (odds ratio: 0.8 [95% confidence interval: 0.4–1.5]). Severity among those with eczema according to the scoring atopic dermatitis index was not significantly different (P = .17). The rate of sensitization at 1 year showed no difference between the 2 groups (24% [probiotic group] vs 19% [placebo]).

CONCLUSIONS. The results of this study do not support the role of early-life probiotic supplementation as a modality for primary eczema prevention.

Impact of Maternal Atopy and Probiotic Supplementation During Pregnancy on Infant Sensitization: A Double-Blind Placebo-Controlled Study


PURPOSE OF THE STUDY. To explore factors in infant sensitization and the effect of probiotics.

STUDY POPULATION. The researchers evaluated 171 mother-infant pairs from an ongoing, placebo-controlled, double-blind study with nutrition modulation through dietary counseling and probiotic supplementation.
METHODS. Mothers with no chronic or metabolic disease before or during early pregnancy had dietary counseling and were randomly assigned to receive either probiotics (Lactobacillus rhamnosus strain GG and Bifidobacterium lactis Bb12) or placebo from the first trimester of pregnancy to the end of exclusive breastfeeding. Atopic sensitization of the infants was assessed by skin-prick test to cow’s milk, egg white, wheat, rice, gladin, cod, soya bean, birch, 6 grasses, cat, dog, Dermatophagoides pteronyssinus (dust mite), latex, potato, carrot, and banana at the ages of 6 and 12 months. The mothers were skin tested for these antigens as well as peanut, hazelnut, alder, and mugwort in their third trimester of pregnancy. Infants were examined at 1, 6, and 12 months of age. Breast milk samples were collected immediately after birth and 1 month after delivery. Concentrations of transforming growth factor β2 (TGF-β2) and soluble CD14 were measured in breast milk by using commercial sandwich enzyme-linked immunosorbent assays. The concentrations of interferon γ, tumor necrosis factor α, interleukin (IL)-10, IL-6, IL-4, and IL-2 were measured via flow cytometry. Infant sensitization assessed by skin-prick test at the age of 12 months was the primary variable. The effects of probiotic intervention, allergy status of the mother, and duration of total and exclusive breastfeeding on infant sensitization were analyzed by using the χ² test. The t test for independent samples was used to compare the probiotic and placebo groups.

RESULTS. At the age of 12 months, 30% of the infants showed ≥1 positive reactions on the skin-prick test. Allergic disease and positive skin-prick test results in the mother were likely to be associated with increased risk of sensitization in the child. The total duration of breastfeeding affected the risk of sensitization in the infant according to the allergy status of the mother; the risk of sensitization increased for infants with allergic mothers breastfeeding for >6 months or exclusively breastfeeding for >2.5 months (odds ratio: 4.8; P = .005). Probiotic supplementation had a protective effect against sensitization in infants with mothers with sensitization. The concentration of TGF-β2 tended to be higher in the colostrum of the mothers in the probiotic group, compared with those in the placebo group (probiotic/placebo ratio: 1.5; P = .02). A low level of TGF-β2 in the colostrum seemed to be associated with a positive skin-prick test result in the infant. Probiotic supplementation had a protective effect against sensitization in a subgroup of infants with maternal sensitization: 26% of the infants in the probiotic group versus 50% in the placebo group had positive skin-prick test results. Atopic eczema was diagnosed at the age of 12 months in 9.7% of the infants in the probiotic group and in 17.6% of the infants in the placebo group.

CONCLUSIONS. Maternal skin-prick test reactivity accompanied by allergic disease may increase infant vulnerability to sensitization. Breastfeeding by atopic mothers increases the likelihood of sensitization in infants. Probiotics provide protection from sensitization in infants at high risk.

Some reviewers comments: The authors of this article raise interesting questions about the impact of breast milk in the prevention of atopic disease. They noted a protective benefit of probiotic supplementation in their study population and theorized that the possible mechanism for this protective effect is through an increase in anti-inflammatory TGF-β2 in breast milk. The authors noted possible limitations of probiotics, including appropriate selections of anti-inflammatory probiotic strains and risk of disease in the infant. This is a fascinating area for future study.

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Cord Blood Allergen-Specific IgE Is Associated With Reduced IFN-γ Production by Cord Blood Cells: The Protection Against Allergy–Study in Rural Environments (PASTURE) Study

PURPOSE OF THE STUDY. To investigate the relationship between allergen-specific cord blood (CB) immunoglobulin E (IgE) levels, parental allergy sensitization, CB cytokine production, and environmental influences.

STUDY POPULATION. This study included families recruited for the multicenter Protection Against Allergy–Study in Rural Environments (PASTURE) study, an ongoing longitudinal birth cohort study designed to evaluate risk factors and preventative factors for atopic disease. Pregnant women in their third trimester were recruited for participation from Finland, Germany, France, Switzerland, and Austria.

METHODS. CB samples were collected from umbilical cord veins, and parental blood samples were collected by peripheral vein puncture; the levels of allergen-specific IgE against 20 common inhalant and food allergens were measured by using the Allergy Screen (Mediwiss Analytic, Moers, Germany) test panel for atopy. The Allergy Screen result was compared with the skin-prick test result and showed a concordance of 92%. Serum IgA levels were determined by immunoturbidimetry. CB samples were stimulated by using astandardized protocol
ALLERGENS AND ENVIRONMENTAL EXPOSURES

Early Exposure and Sensitization to Cat and Dog: Different Effects on Asthma Risk After Wheezing in Infancy


PURPOSE OF THE STUDY. Birth cohort studies have suggested that early exposure to furred pets protects from later asthma and allergy. The aim of this study was to evaluate the association between exposure or sensitization to cat or dog in infancy and later asthma and allergy assessed at the median ages of 4.0, 7.2, and 12.3 years.

STUDY POPULATION. Children 1 to 23 months of age who had wheezing and respiratory distress that required hospital care during an acute respiratory tract infection were enrolled.

METHODS. Exposure to cat and dog in infancy was assessed by interviewing the parents. The child was considered to be sensitized if the allergen-specific immunoglobulin E level to cat or dog was ≥0.35 kU/L or if there was a positive skin-test response.

RESULTS. When the 20 children with persistent childhood asthma (doctor-diagnosed asthma at all 3 control visits) were compared with the other 61 children, early exposure to dog (odds ratio [OR]: 0.14; P = .034) decreased the asthma risk, and early sensitization to cat (OR: 5.92; P = .008) and dog (OR: 9.33; P = .001) increased the asthma risk. There was less cat- and dog-keeping in atopic families, and the effect of sensitization was, but the effect of exposure was not, robust to adjustments in multivariate analyses.

CONCLUSIONS. This study demonstrates that, in long-term follow-up evaluation after early wheezing, early sensitization to cat and dog increases the risk of later asthma but early exposure to cat or dog has no such effect. Dog-keeping was less frequent in atopic families, which may explain why the protective effect of early exposure to dog was lost in multivariate analyses.

REVIEWERS’ COMMENTS. Studies have shown that early high-dose exposure to allergens may be protective for the development of allergy, and children who do not develop early allergic sensitization to environmental allergens are at lower risk for having persistent wheezing symptoms. This study’s results are consistent with those of previous studies; although early sensitization to cat and dog increases the risk for later asthma in children at high risk, early high-dose exposure to furred animals does not seem to be a risk factor. It should be noted that

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atopic families tended to have pets less frequently, which might have introduced confounding effects.

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Can the Use of HEPA Cleaners in Homes of Asthmatic Children and Adolescents Sensitized to Cat and Dog Allergens Decrease Bronchial Hyperresponsiveness and Allergen Contents in Solid Dust?

PURPOSE OF THE STUDY. Because pet allergies are associated with asthma, the authors investigated whether high-efficiency particulate-arresting (HEPA) filtration had any effect on reducing indoor allergens and bronchial hyperreactivity in children with asthma who were sensitized to cat and dog.

STUDY POPULATION. A total of 30 children with asthma (age: 6–17 years) who were sensitized and exposed to cat and/or dog allergen(s) at home completed the study. The children did not have dust mite or mold sensitivities, and those being treated for asthma stayed on treatment throughout this time.

METHODS. This was a randomized, controlled trial in which the children were assigned to 1 of 2 groups. For 12 months, 1 group was exposed to HEPA air cleaners that were placed in the living room and bedroom, and the other group was exposed to paper sham filters. Filters were on for >50% of the time. Pulmonary function testing and cold-air challenges were performed at baseline, 6 months, and 12 months into the study. Serum eosinophil cationic protein, specific immunoglobulin E to several aeroallergens, current medications, and clinical symptoms (nighttime awakenings, physical exercise symptoms, breathing limitations, and nasal stuffiness) were assessed. The amounts of cat (Fel d 1) and dog (Can f 1) allergens in the filters and bulk dust samples were also collected.

RESULTS. Forced expiratory volume in 1 second at baseline lung function improved in the entire study population (median: 90% at initial visit, 98% at 6 months, and 95% at 12 months; \( P < .001 \)). However, there was no significant change in eosinophil cationic protein, use of medication, or quality of life for the 2 groups. Although after 12 months there seemed to be a trend for a decrease in change in forced expiratory volume in 1 second after cold-air challenge in the active group (8.1%–5.4%) versus the sham group (4.3%–8.2%), the difference was not statistically significant (\( P = .336 \)). Active filters retained higher amounts of cat and dog allergens in their main filter devices, compared with sham filters.

CONCLUSIONS. Although HEPA air cleaners were able to retain airborne pet allergens, they had no significant effect on bronchial hyperreactivity.

REVIEWER COMMENTS. High-efficiency air filtration is often recommended to patients with asthma with known allergenic sensitivities, to reduce exposure to indoor pet allergens (which are \( \approx 5 \mu m \) in size). HEPA filtration can filter out particles as small as 0.3 \( \mu m \) with up to 99.97% efficiency. This study did not find a significant effect of HEPA filtration on bronchial hyperreactivity after 1 year of use, but there seemed to be a trend toward improvement in bronchial hyperreactivity. Although this study revealed a very limited role for HEPA use in asthma therapy, future studies should evaluate whether HEPA filtration may help prevent or delay the development of asthma in younger children with atopy who are at increased risk of developing asthma.

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Higher Immunoglobulin E Antibody Levels to Recombinant Fel D 1 in Cat-Allergic Children With Asthma Compared With Rhinoconjunctivitis

PURPOSE OF THE STUDY. To measure immunoglobulin E (IgE) and IgG4 antibodies to an engineered recombinant major cat allergen, rFel d 1, among sera from cat-allergic children and adults.

STUDY POPULATION. One hundred forty cat-allergic children and adults with rhinoconjunctivitis and/or asthma were selected; all had positive skin-prick test results to cat dander extract (CDE). Seventy-five healthy, age-matched, CDE-skin-test–negative children and adults were selected as control subjects.

METHODS. Sera from the 140 patients were tested for IgE and IgG4 antibodies to CDE and rFel d 1 by ImmunoCAP (Phadia, AB Uppsala, Sweden) and for IgE to rFel d 1 by enzyme-linked immunosorbent assay.

RESULTS. Ninety-eight percent of patients (all but 1) and none of the control subjects had evidence of specific IgE to rFel d 1. Specific IgE results to rFel d 1 and CDE correlated strongly (\( r = 0.85; \ P < .001 \)) among the 140 patients; however, results to rFel d 1 were, on average, 30% higher (\( P < .0001 \)). IgE responses to rFel d 1 among children with asthma were higher (median: 19.4 kU/L), compared with children with rhinoconjunctivitis only
(median: 6.6 kU/L; \( P < .05 \)) and adults with asthma (median: 3.0 kU/L; \( P < .01 \)). There was a threefold increased risk of asthma for one half of the children with the highest IgE levels (odds ratio: 3.23 [95% confidence interval: 1.19–8.79]) by the enzyme-linked immunosorbent assay. Children with asthma also displayed significantly higher IgG4 levels than did adults with asthma.

CONCLUSIONS. Recombinant major cat allergen (rFel d 1) seems to be at least equally sensitive for in vitro diagnosis of cat allergy, compared with the current extract-based test. Elevated specific IgE antibody levels to rFel d 1 are suggested to be a risk factor for asthma in cat-allergic children.

REVIEWERS COMMENTS. In vitro diagnosis of allergic sensitization is currently confirmed by using allergen extracts derived from natural source materials. The authors previously described creation of this recombinant major cat allergen, rFel d 1. Investigation with such purified recombinant proteins is a current area of intense interest within the field of allergy and immunology, because these engineered proteins may offer improved diagnostic specificity and theoretically may offer superior therapy for type 1 hypersensitivity. Previous research showed that allergen-specific IgE levels are predictive for the likelihood of allergic disease including asthma; however, some allergen-avoidance studies failed to show significant evidence of improvement or protection. This study gives further support to cat allergy causing asthma.

TOBACCO AND AIR POLLUTION

Atopic Diseases, Allergic Sensitization, and Exposure to Traffic-Related Air Pollution in Children

PURPOSE OF THE STUDY. To assess the relationship between exposure to traffic-related air pollutants and allergic disease outcomes in a prospective birth cohort during the first 6 years of life.

METHODS. A birth cohort of 3061 children in the Munich, Germany, metropolitan area were followed with serial questionnaires of their parents inquiring about asthma, hay fever, and eczema. Specific immunoglobulin E against common allergens was determined at the age of 6 years. Air pollution measurements were made for particulate matter ≤2.5 μm in diameter and nitrogen dioxide. Distances between the children’s street address and the nearest main road were noted. Outcomes of atopic disease and allergic sensitization were compared with the children’s exposure to the pollutants.

RESULTS. Positive associations were found between the distance to the nearest main road and asthma, hay fever, eczema, and sensitization, with the highest odds ratios (ORs) for children living <50 m from busy streets. For particulate matter ≤2.5 μm in diameter, statistically significant effects were found for asthma (OR: 1.56 [95% confidence interval [CI]: 1.03–2.37]), hay fever (OR: 1.59 [95% CI: 1.11–2.27]), and allergic sensitization to pollen (OR: 1.40 [95% CI: 1.20–1.64]). Nitrogen dioxide exposure was associated with eczema, whereas no association was found for allergic sensitization.

CONCLUSIONS. The results provide strong evidence for the adverse effects of traffic-related air pollutants on atopic diseases and allergic sensitization.

REVIEWER COMMENTS. Several previous studies suggested an association between exposure to air pollution and the development of atopic sensitization and disease. This study supports that connection, even adding a “dose-response” element in which the closer you live to a busy street, the more likely you are to develop allergic disease.

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 Changes in Environmental Tobacco Smoke Exposure and Asthma Morbidity Among Urban School Children

PURPOSE OF THE STUDY. Using data from a large randomized trial of supervised asthma therapy in urban elementary schools, the authors of this study sought to document the relationship between changes in environmental tobacco smoke (ETS) exposure and childhood asthma morbidity.

STUDY POPULATION. There were 290 children with physician-diagnosed persistent asthma that required daily controller medication who were enrolled in 1 of 36 participating schools.

METHODS. By using data from a randomized, clinical trial of supervised asthma therapy versus usual care, asthma morbidity and ETS exposure data were collected from caregivers via telephone interviews at baseline and at a 1-year follow-up time. No smoking cessation counseling
or ETS exposure education was provided to caregivers; however, children were given 20 minutes of asthma education, with a discussion on avoidance of asthma triggers including ETS.

RESULTS. At baseline, 28% of the caregivers reported ETS exposure in the home, and 19% reported exposure outside the primary household only. At the follow-up time, caregivers were asked whether ETS exposure had increased, decreased, or stayed the same, with results as follows: 74% reported no change, 17% reported decreased exposure, and 9% reported increased exposure. Among children whose ETS exposure decreased, there were fewer hospitalizations ($P = .034$) and emergency department visits ($P < .001$) reported in the 12 months before the second interview, compared with the 12 months before the first interview. These children were also less likely to have an episode of poor asthma control, compared with the children with no change or increased exposure (odds ratio: 0.45 [95% confidence interval: 0.23–0.88]).

CONCLUSIONS. This study demonstrated associations between ETS exposure reduction and fewer episodes of poor asthma control and fewer respiratory-related emergency department visits and hospitalizations.

REVIEWER COMMENTS. Approximately 60% of US children 3 to 11 years of age are exposed to ETS. This study demonstrated that reduction in ETS exposure improved asthma outcomes. Limitations of this study are that it was questionnaire-based, relying on caregivers’ report and that it was based on recall over the prior 12 months. It is promising that a benefit was seen even without specific counseling on ETS exposure and tobacco cessation. With more-targeted education and counseling, a greater benefit may be seen. It is important for pediatricians to play an active role in inquiring about ETS exposure and offering parents guidance on smoking cessation; this is especially important for children with asthma.

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Less Air Pollution Leads to Rapid Reduction of Airway Inflammation and Improved Airway Function in Asthmatic Children

PURPOSE OF THE STUDY. To investigate whether relocating children with asthma from an environment of high pollution to one of low pollution has an effect on short-term airway inflammation.

STUDY POPULATION. This was a case study of 37 children, ≥7 years of age, with untreated, mild, persistent asthma who were recruited from an urban asthma clinic in Italy and followed at a rural school camp for 1 week. The children came from homes that had implemented dust mite precautions, and they stayed in a local hotel at the camp.

METHODS. Environmental measurements were collected from permanent or mobile air quality–monitoring stations (recording concentrations of benzene, particulate matter of ≤10 μm in diameter, ozone, nitrogen dioxide, and carbon monoxide), portable volumetric allergen samplers (recording levels of 23 pollen species), and local meteorological sources. Clinical measurements were collected on day 0 before relocating and on day 7 in the rural environment. Data collected included nasal eosinophils, fractional exhaled nitric oxide ($\text{FeNO}$), peak expiratory flow (PEF), and urinary leukotriene E$_4$ (LTE$_4$) levels.

RESULTS. Temperature and atmospheric pressure were significantly lower ($P < .0001$ and $P < .003$, respectively) in the rural environment, whereas humidity and wind speed were similar. All pollutants were significantly lower in the rural environment, with the greatest difference seen in benzene (20-fold) and nitrogen dioxide (15-fold) concentrations ($P < .0001$). Only the Fagaceae pollen species, to which no child demonstrated sensitivity, was significantly higher in the rural environment ($P < .01$). The children had positive skin-prick test results to dust mite (100%), Gramineae (43%), Oleaceae (30%), Urticaceae (19%), and Cupressaceae and Betulaceae (3%). There was an average fourfold decrease in nasal eosinophils ($P < .002$), a decrease in mean FE$_{NO}$ ($P < .028$), and an increase in mean PEF. Urinary LTE$_4$ changes were variable and not consistent among participants.

CONCLUSIONS. Removing children with allergic asthma from a highly polluted environment can rapidly reverse airway inflammation and improve airway function. Decreases in upper and lower airway inflammatory biomarkers (nasal eosinophils and FE$_{NO}$, respectively) and an increase in PEF could not be attributed to altered exposure to aeroallergens. Changes in urinary LTE$_4$ levels were not seen; they may be slower to respond or may depend on other factors.

REVIEWER COMMENTS. Many studies have demonstrated the negative effect of pollutants on asthma outcomes. Here, the authors attempted to mimic a real-life situation and showed that pollutant effects may be reversible in children. This study supports the theory that the increase in asthma seen in industrialized countries may be the result of crowded, polluted, urban environments. The rapidity of responses in these children has implications for clean air policies. An important next step would be to...
Milk OIT is effective in the treatment of cow’s milk allergy, with anticipated and acceptable adverse effects noted.

REVIEWERS COMMENTS. Oral and sublingual administration of allergen-specific immunotherapy has become increasingly important in the field of food allergies. These therapies have the potential not only to protect patients from serious reactions (clinical desensitization) but also possibly to allow for development of tolerance to the food allergen. This study demonstrated an increased threshold for reactions to milk in children treated with OIT, indicating clinical desensitization to the allergen. Of the reactions noted, most were not serious and did not require any treatment, which illustrates the relative safety of OIT. However, dosing protocols and length of therapy need to be further investigated (including long-term tolerance assessments), to provide improved efficacy with the lowest adverse effects.

Early Consumption of Peanuts in Infancy Is Associated With a Low Prevalence of Peanut Allergy

PURPOSE OF THE STUDY. To determine the prevalence of peanut allergy (PA) among Israeli and United Kingdom Jewish children and to evaluate the relationship of PA to peanut consumption by infants and mothers.

STUDY POPULATION. The study included Jewish children between the ages of 4 and 19 years who attended targeted primary and high schools. Eligible Jewish schools in greater London, United Kingdom, and Israeli schools in the Mehoz Merkaz region of Tel Aviv were selected because they were thought to represent comparable residential environments. The mothers of Jewish infants 4 to 24 months of age in general practitioner clinics in the United Kingdom and Tipat Halav clinics in Israel were also surveyed about the timing of ingestion of peanut.

METHODS. Two validated questionnaires were used. The Food Allergy Questionnaire was completed by high school pupils and by parents on behalf of primary school pupils; it asked about allergies to cow’s milk, hen’s egg, sesame, peanut, tree nuts, asthma, hay fever, and eczema and parental occupation. The Food Frequency Questionnaire, a validated consumption questionnaire given to mothers in the waiting room, made a detailed determination of peanut, sesame, and other solid-food consumption during the child’s first year and by the...
mother during pregnancy and lactation. All children with a questionnaire-based diagnosis of PA were invited for allergy testing; PA was confirmed if skin-prick test results, specific immunoglobulin E (IgE) measurements, or both were greater than the 95% positive predictive values or if children had a positive oral peanut-challenge result.

RESULTS. The Food Allergy Questionnaires were distributed to 10,786 children, and 81.8% were returned. Mothers returned 176 Food Frequency Questionnaires; none declined participation. The prevalence of PA in the United Kingdom was 1.85% and that in Israel was 0.17% (P < .001). After adjustment for atopy, the relative risk for PA in the United Kingdom was 5.8 (95% confidence interval: 2.87–11.8) for all children and 9.8 (95% confidence interval: 3.1–30.5) for primary school children. In terms of dietary assessments, the Kaplan-Meier plots for the age of introduction of solid foods were similar in the 2 countries; the introduction of egg, soybean, wheat, vegetables, fruits, and tree nuts was similar. However, with the introduction of peanut there was a significant difference between the 2 countries; by 9 months of age, 69% of Israelis were eating peanut, compared with only 10% of United Kingdom infants. The median monthly consumption of peanut in Israeli infants 8 to 14 months of age was 7.1 g of peanut protein and that in United Kingdom infants was 0 g (P < .001). Similar contents of major peanut allergens were demonstrated in products from the 2 countries, as well as similar levels of IgE binding between the products.

CONCLUSIONS. The prevalence of PA is 10-fold higher in Jewish children in the United Kingdom, compared with that seen in Jewish children in Israel. The differences cannot be explained by differences in age, gender, ancestry, atopy, or socioeconomic class. The most obvious difference in the diet of infants in the 2 populations occurs in the introduction of peanut. Israeli infants are introduced to peanut during early weaning and continue to eat peanut more frequently and in higher amounts than United Kingdom infants, who avoid peanut. It has been proposed that different methods of preparing peanut could be responsible for the different rates of PA in different countries, but commonly consumed peanut-containing foods in both countries are derived from roasted peanut butter, and equivalent amounts of total protein, major peanut allergen, and IgE binding were demonstrated among these foods.

REVIEWERS COMMENTS. This study demonstrated a strong inverse association between peanut consumption in infancy and the prevalence of PA in childhood. It is compelling that the early introduction of frequent and high doses of peanut protein in infants may lead to oral tolerance. Although there is inherent selection bias and recall bias with questionnaires in general, the authors of this study attempted to reduce both of these factors. Until recently, dietary avoidance of peanut during pregnancy, breastfeeding, and early childhood was recommended in the United States. This article prompts us to question our practices and recommendations in terms of introduction of peanut into our children’s diet and how it may affect their propensity to develop PA. An ongoing study, Learning Early About Peanut Allergy (LEAP), which is being conducted by the authors of this article, should provide much-needed evidence for guidelines on the introduction of peanut into the diet of infants and children.

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Dietary Advice, Dietary Adherence and the Acquisition of Tolerance in Egg-Allergic Children: A 5-yr Follow-up

PURPOSE OF THE STUDY. To assess sources of dietary advice, adherence to advice, factors that influence adherence, and impact of dietary adherence on acquisition of tolerance among egg-allergic children.

STUDY POPULATION. One hundred sixty-seven children diagnosed with immunoglobulin E–mediated egg allergy and followed by a tertiary pediatric allergy center in Australia.

METHODS. In 2006, a questionnaire was mailed to parents of egg-allergic children who were seen in the clinic in 2003. The questionnaire included demographic data, initial and subsequent reaction history, and information on self-injectable epinephrine prescriptions. Reaction severity was categorized as grade 1 (localized erythema/urticaria), 2 (generalized erythema/urticaria, angioedema, and/or gastrointestinal symptoms), or 3 (generalized urticaria and stridor, wheeze, or cardiovascular compromise). The questionnaire also assessed the type and source of dietary advice given, dietary adherence, characteristics that affect adherence, and acquisition of tolerance to egg. Adherence to dietary advice was defined as following given advice “all of the time.” Oral tolerance to egg was based on the results of an oral food challenge (OFC).

RESULTS. The mean age of the study population was 6.6 years (mean follow-up period: 5.5 years). Coexisting atopic disorders were prevalent, with 83% of children having other food allergies and 56% having asthma. Only 21% reported having a prescription for self-injectable epinephrine, 47% reported accidental exposures, and 39% reported subsequent clinical reactions to
Effect of Maternal Egg Consumption on Breast Milk Ovalbumin Concentration


PURPOSE OF THE STUDY. To assess human milk ovalbumin concentrations after daily maternal ingestion of 1 cooked egg for a 3-week period.

STUDY POPULATION. There were 32 mothers of singleton, breastfed, egg-sensitive infants with moderate-to-severe eczema. Egg sensitivity was identified by a positive skin-prick test result. Eczema was evaluated by using a standardized scoring system.

METHODS. Families had an initial home visit by an experienced dietitian, which involved collection of demographic and dietary information. All women and children were asked to follow an egg-free diet from day 1 through the duration of the trial. Adherence to the egg-free diet was assessed via detailed dietary intake records for both mothers and children on days 1 to 3, 10 to 12, and 21 to 23. Mothers were randomly allocated to receive identical-appearing egg-free muffins or muffins containing 1 (55 g) whole egg. Each mother was given a 3-week supply of frozen muffins corresponding to her randomization group and consumed 1 muffin per day on days 3 through 23. Atopic dermatitis assessments were performed for each child at the commencement and completion of the trial. The mothers completed the Infant’s Dermatitis Quality of Life Index 3 times during the trial. On days 3, 12, and 23, the mothers manually expressed 5 mL of breast milk into sterile containers before and 2, 4, and 6 hours after eating the test muffin. Breast milk samples were stored in the home freezer and collected on day 24. The breast milk samples were queried for ovalbumin concentration by using a sandwich enzyme-linked immunosorbent assay method. Breast milk ovalbumin concentrations (nanograms per milliliter) were plotted against time, and the resulting curve was used to determine peak ovalbumin concentrations and total ovalbumin excretions (nanograms per milliliter per hour). Independent-sample t tests, Mann-Whitney U tests, and Pearson’s χ² tests were used to investigate differences between the diet groups.

RESULTS. Women in the egg group had higher ovalbumin concentrations in breast milk than did the control group at all time points. Within each dietary group, the frequency of ovalbumin detection, peak ovalbumin concentration, and total ovalbumin excretion did not differ at days 3, 12, and 23. Ovalbumin was not detected in the breast milk of 25% of the women in the egg group. Infant eczema symptom scores were significantly reduced with time for both groups.

CONCLUSIONS. Human milk ovalbumin is related to maternal dietary egg intake. Comparable detection of ovalbumin across time suggests that ovalbumin does not accumulate in human milk. One quarter of the women had no ovalbumin detected in their breast milk on any of the study days, which suggests that some women either do not excrete ovalbumin in their breast milk when challenged with 1 egg or have delayed excretion beyond 6 hours. Maternal dietary avoidance of well-cooked egg may not be necessary for all breastfed infants with egg sensitivity and eczema.
For breastfed infants with food allergy, strict avoidance of the offending food proteins for both mother and child is frequently recommended. Total dietary avoidance of egg is difficult for patients to achieve. Additional study is needed to substantiate or to refute the preliminary observation that regular maternal ingestion of a small quantity of well-cooked egg did not markedly exacerbate eczema symptoms in egg-sensitive breastfed infants.

PERSPECTIVE COMMENTS. Previous attempts have been made to establish wheat IgE levels that would predict clinical reactivity and prognosis. This study, in attempting to do that, included the largest population of wheat-allergic patients that has yet been described. Patients were included on the basis of a retrospective chart review and, because the inclusion criteria did not require an oral food challenge, it is possible that at the time of initial enrollment some of the patients were no longer allergic to wheat. Tolerance was appropriately determined by food challenge; however, not all patients were challenged. This might have been because a patient had a convincing reaction after an unintentional exposure to wheat, but the authors did not make that clear. In addition, some patients had ingestion reactions while trying wheat at home, which, as the authors acknowledged, raises the possibility that wheat allergy was overdiagnosed. Another limitation is that the population (in which 90% of the children included had other food allergies) might not be representative of the general population. The authors found that peak wheat-specific IgE levels were helpful in determining prognosis. However, in clinical practice, it is difficult to determine whether the peak wheat-specific IgE level for an individual patient has been reached. Because some patients with higher specific IgE levels do tolerate wheat, the authors acknowledge that wheat IgE is less helpful in predicting clinical reactivity and prognosis, compared with other foods.

The Natural History of Wheat Allergy

PURPOSE OF THE STUDY. Wheat allergy is among the most common of food allergies, affecting ~0.4% of children, but little is known about its natural history. The purpose of this study was to determine at what age wheat allergy is outgrown and to identify clinical and laboratory predictors of tolerance development.

STUDY POPULATION. Participants were children from the Johns Hopkins pediatric allergy clinic who had a history of symptomatic reaction (presumed immunoglobulin E [IgE]-mediated) to wheat and a positive wheat-specific IgE test result. Inclusion criteria were met by 103 children.

METHODS. The study was a retrospective, medical record review. Resolution of allergy was determined by the results of food-challenge testing. Kaplan-Meier survival curves were generated to depict resolution of wheat allergy.

RESULTS. The median initial wheat-specific IgE level was 24 kU/L, and the median peak wheat-specific IgE level was 73 kU/L. Rates of resolution of wheat allergy were 29% by the age of 4 years, 56% by the age of 8 years, 65% by the age of 12 years, and 70% by the age of 14 years. Higher wheat-specific IgE levels were associated with worse outcomes. A total of 63 of 103 participants underwent a food challenge during the study period. The peak wheat-specific IgE level recorded was a useful predictor of persistent allergy, although many children with even the highest levels of wheat IgE outgrew wheat allergy.

CONCLUSIONS. The median age of resolution of wheat allergy was 6.5 years in this population. However, 35% of the patients remained allergic into their teenage years.

High Levels of IgG4 Antibodies to Foods During Infancy Are Associated With Tolerance to Corresponding Foods Later in Life

PURPOSE OF THE STUDY. To examine the serum and salivary antibody responses to food-elimination diets and to identify immunologic parameters related to oral tolerance.

STUDY POPULATION. Prospective study of 89 children <2 years of age with eczema.

METHODS. Children with eczema were examined at 3 time points, that is, at enrollment, after a 6-week treatment period, and at 4.5 years of age. Treatment included topical emollients and/or steroids for all children and a 6-week egg- and/or milk-elimination diet for 60 of the 89 children in the cohort of children who were diagnosed with an allergy to 1 or both foods. Laboratory data
The Use of Serum-Specific IgE Measurements for the Diagnosis of Peanut, Tree Nut, and Seed Allergy


PURPOSE OF THE STUDY. The authors of this study sought to determine the usefulness of peanut-, tree nut-, and seed-specific immunoglobulin E (IgE) measurements for the diagnosis of symptomatic allergies and to learn more about the relationships among these foods.

STUDY POPULATION. Children and adults (N = 324) referred to a private allergy practice and to an academic center allergy clinic for evaluation of suspected IgE-mediated peanut, tree nut, or seed (sesame seed, mustard seed, poppy seed, rapeseed, and cottonseed) hypersensitivity were enrolled in the study. Patients ranged in age from 2.4 months to 40.2 years (median: 6.1 years). The male/female ratio was 198:126. Atopic dermatitis occurred at some point in life in 57% and asthma in 58%. Many had or “outgrew” other food allergies.

METHODS. Patients answered a questionnaire about their perceived food allergies. Allergen-specific diagnoses were based on questionnaire, medical history, and, when relevant, skin-prick test results and serum-specific IgE levels. Sera were analyzed for specific IgE to peanuts, tree nuts, and seeds by ImmunoCAP (Phadia AB, Uppsala, Sweden).

RESULTS. Seventy-two percent of the patients had convincing histories of peanut allergy. Of these, 86% had sensitization to ≥1 tree nut, with 34% having clinical allergy. The majority of study patients had never ingested tree nuts, which made it difficult to determine the true prevalence of these nut allergies. Tree nut clinical allergy occurred with a frequency ranging from 16.4% for walnuts to 1.5% for Brazil nut. Seventeen percent of the patients reported reactions to sesame seed. The ranges of increased serum-specific IgE levels for each food varied widely among patients with positive histories. The relationship between diagnoses and allergen-specific IgE levels was estimated through logistic regression, with curves illustrating the likelihood of receiving a positive clinical diagnosis in relation to the specific IgE concentration. Positive predictive values (95%) were established for peanut and walnut (13 and 18.5 kUA/L, respectively) but with sensitivities of just 60% and 17%, respectively. High correlations were found between IgE results for walnut and pecan and between those for cashew and pistachio.

CONCLUSIONS. Quantification of food-specific IgE is a valuable tool that can aid in the diagnosis of symptomatic food allergy and might decrease the need for double-blind, placebo-controlled, food challenges.
In Vitro and In Vivo Cross-reactivity Studies of Legume Allergy in a Mediterranean Population


PURPOSE OF THE STUDY. Legume allergy, mainly to lentils and chickpeas, is the fifth most common cause of food allergy in Spanish children. Serological cross-reactivity among legumes is frequent, but its clinical relevance is controversial. The aim of this study was to investigate the cross-reactivity among lentils, chickpeas, peas, white beans, and peanuts and its clinical relevance in pediatric patients.

STUDY POPULATION. Fifty-four children with clinical allergy to legumes were included.

METHODS. Cross-reactivity was evaluated with enzyme-linked immunosorbent assay inhibition experiments and oral food challenges to legumes. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis immunoblots were conducted with raw and boiled legume extracts.

RESULTS. Enzyme-linked immunosorbent assay inhibition experiments demonstrated >80% inhibition with lentil, chickpea, and pea extracts. Immunoblots performed with raw legume extracts (lentil, chickpea, and pea) and individual sera revealed that >50% of the sera identified an allergen of ~50 kDa in all 3 legume extracts. In all 3 boiled extracts, an intense band at ~50 kDa was visualized by using a serum pool. The oral legume challenges demonstrated that 37 children (69%) were allergic to ≥2 legumes (median: 3 legumes). The most frequent associations were allergy to lentils and chickpeas (57%), allergy to lentils and peas (54%), and allergy to lentils, chickpeas, and peas (43%).

CONCLUSIONS. In vitro inhibition experiments demonstrated a high degree of cross-reactivity among lentils, chickpeas, and peas. Food challenges confirmed that clinical allergy to all 3 legumes is frequent in this cohort of Spanish children.

REVIEWER COMMENTS. Although legumes are not major allergens in the United States and some European countries, they are a common cause of food allergies in Mediterranean countries. The authors demonstrated that, in their group of Spanish children, there was a high degree of in vitro and in vivo cross-reactivity among legumes, which is in contrast to North American children, in whom clinical reactivity to >1 legume is considered to be infrequent (eg, children with peanut allergy typically tolerate most legumes). These contrasting results highlight the fact that genetic and dietary influences (among other factors) can have significant influences on food allergy. Additional studies are needed to elucidate the contribution of dietary habits and genetics to food allergy.

Epidemiology of Atopic Patch Tests With Food and Inhalant Allergens in an Unselected Population of Children


PURPOSE OF THE STUDY. The atopy patch test (APT) has been used as a diagnostic tool for patients with suspected food or inhalant allergy. The authors of this study assessed the prevalence of positive APT results with food or inhalant allergens in an unselected population of schoolchildren. The authors also evaluated the link between positive APT reactions and skin-prick tests (SPTs) for food and inhalant allergens, circulating eosinophils, and histamine skin reactivity.

STUDY POPULATION. The study included an unselected population of 380 children 9 or 13 years of age living in Rome, Italy.

METHODS. APTs were carried out with food (native or standardized) and inhalant allergens. All children also underwent SPTs with 5 common inhalant and 4 food allergens.

RESULTS. The prevalence of positive APT reactions for foods in unselected children ranged between 4% and 11% for hen’s egg, tomato, and wheat flour and was similar for the 2 age groups studied. The prevalence of
positive APT reactions for milk was significantly lower in children of age 13 than in children of age 9 (P = .013). No concordance emerged between positive APT and SPT results for foods. Conversely, APT and SPT results for inhalant allergens yielded statistically significant concordance (P < .001).

CONCLUSIONS. The APT produces positive reactions for food or inhalant allergens in a significant number of subjects in the general population of schoolchildren. Inhalant allergens probably induce a positive APT reaction through an immunoglobulin E–linked process, whereas food allergens probably do not.

REVIEWER COMMENTS. The APT has been investigated as a new diagnostic tool for patients with food or inhalant allergies when non–immunoglobulin E–mediated reactions are considered, such as in identifying triggers for atopic dermatitis, allergic eosinophilic esophagitis, and food protein–induced enterocolitis syndrome. However, studies have demonstrated conflicting results for the utility of this test. Here, the authors investigated the prevalence of positive results of APT in an unselected population of schoolchildren and found that APTs produced positive reactions for foods in 4% to 11% of cases and for inhalant allergens in 4% to 30%, depending on the allergen used. This is important information to consider when investigating the APT as a potential diagnostic tool.

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14 Years of Eosinophilic Esophagitis: Clinical Features and Prognosis

PURPOSE OF THE STUDY. To define the presenting symptoms of eosinophilic esophagitis (EE) and describe the clinical course of treated and untreated patients with EE.

STUDY POPULATION. Patients referred to the Children’s Hospital of Philadelphia over a 14-year period who were diagnosed with EE.

METHODS. Retrospective and prospective chart review of patients diagnosed with EE and followed for ≥1 year.

RESULTS. A total of 330 children were identified, of whom 68% were <6 years of age at the time of diagnosis; the majority were male. Children who presented at a younger age had symptoms of failure to thrive, feeding difficulties, gastroesophageal reflux disease, and vomiting, whereas older children presented with abdominal pain, dysphagia, and food impaction. When foods exacerbated EE (up to 17% for milk), 7 foods (milk, egg, wheat, soy, corn, beef, and chicken) accounted for two thirds of the cases. During the follow-up period, <5% had complete resolution of their EE, but those who did achieve resolution had fewer foods (2.4 foods) identified at initial testing. Untreated patients who returned years after their initial diagnosis had continued progression of disease.

CONCLUSIONS. Avoidance of causative foods and medical treatment can significantly improve EE symptoms; however, the chances of long-term resolution of EE are disappointing, with <5% of patients achieving complete resolution.

REVIEWER COMMENTS. As the experience builds at tertiary referral centers, more is understood regarding EE. One should think EE when presented with the triad of male gender, atopy, and gastrointestinal symptoms. One impressive aspect of this cohort was that >2500 biopsies were performed for 330 patients. Allergy skin–prick testing and patch testing with subsequent food avoidance are important, but continued surveillance of local tissue changes and not relying strictly on reported clinical symptoms is equally important.

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Predictors of Response to Proton Pump Inhibitor Therapy Among Children With Significant Esophageal Eosinophilia

PURPOSE OF THE STUDY. To determine predictors of the histologic response to proton pump inhibitor (PPI) therapy among children with significant esophageal eosinophilia (SEE), defined as ≥15 eosinophils per high-powered field (hpf) on esophageal mucosal biopsy (EMB).

STUDY POPULATION. Patients between the ages of 1 and 18 years who underwent esophagogastroduodenoscopy between 1999 and 2006 were eligible for the study. Indications for esophagogastroduodenoscopy included regurgitation, vomiting, heartburn, abdominal pain, dysphagia, and sensation of food impaction. Patients with SEE were eligible for this investigation if they were treated with a PPI (omeprazole, esomeprazole, or lansoprazole) and underwent repeat esophagogastroduodenoscopy to assess the response to the PPI. Patients were excluded if they were receiving corticosteroid, dietary elimination, or montelukast therapy for any indication.

METHODS. Response to PPI therapy among children with SEE treated with a PPI who underwent repeat EMB was
Food Protein-Induced Enterocolitis Syndrome: 16-Year Experience

Mehr S, Kakakios A, Frith K, Kemp AS. Pediatrics. 2009;123(3). Available at: www.pediatrics.org/cgi/content/full/123/3/e459

PURPOSE OF THE STUDY. To investigate possible patterns in demographic features, causative foods, clinical features, treatments at presentation, and outcomes in children diagnosed with food protein-induced enterocolitis syndrome (FPIES).


METHODS. Diagnosis was made by pediatric allergists after referral to the allergy clinic (74%) or from the emergency department (ED) (26%), using previously published criteria. Cases were identified by codes signifying allergic and dietetic gastroenteritis and colitis or by searching for key words in letters written by allergists.

RESULTS. Thirty-two children fulfilled all criteria, and 3 presented with 1 typical episode and no other causal explanation. Sixty-six episodes were recorded, with a mean presenting age of 5.5 months and a median of 2.2 episodes before diagnosis (range: 1–4 episodes). Most children reacted to 1 food, and 6 children reacted to 2 foods. Causative foods included rice (n = 14), soy (n = 12), cow’s milk (n = 7), oat (n = 2), sweet potato (n = 2), banana (n = 1), fish (n = 1), chicken (n = 1), and lamb (n = 1). The mean time from ingestion to reaction was 1.8 hours. Symptoms included vomiting (100%), lethargy (85%), pallor (67%), and diarrhea (24%). Information regarding evaluation of 64 episodes included admission from the ED (25 of 39 visits), abdominal imaging (34%), septic evaluation (28%), and surgical consultation (22%). A decreased body temperature of <36°C was noted in 6 (24%) of 25 episodes. Thrombocytosis not accounted for by hemoconcentration was noted in 15 (63%) of 24 blood counts performed. Only 2 of 19 initial cases presenting to the ED were correctly diagnosed. Other initial diagnoses included food allergy (26%), viral infection/sepsis (21%), gastroenteritis (21%), resolved intussusception (11%), or no diagnosis (11%). Treatments at presentation included intravenous fluid resuscitation (n = 19), antibiotics (n = 8), oxygen (n = 6), air or barium enema (n = 4), parenteral epinephrine treatment (n = 2), and laparotomy (n = 1). Tolerance was demonstrated by 3 years of age in 5 of 6 undergoing soy challenges and 4 of 5 undergoing rice challenges.

CONCLUSIONS. Delayed diagnosis and misdiagnosis is common in FPIES, leading to incorrect and/or invasive treatment. Thrombocytosis, in addition to previously recognized leukocytosis, may be a laboratory clue upon initial presentation. Diarrhea and body temperature of <36°C were associated with more-severe episodes. Foods commonly considered hypoallergenic (ie, rice) may cause FPIES. The prognosis of developing tolerance by age 3 years is favorable.

REVIEWER COMMENTS. Currently, FPIES is a clinical diagnosis. The authors attempted to identify subjective criteria that may be used to diagnose FPIES; however, thrombocytosis and decreased body temperature are factors that will continue to lead to other common diagnoses, such as sepsis or gastroenteritis. The authors argue that, although cases increased in incidence during the 16 year period, 43 (mean age: 8.5 years; male: 67%) met inclusion criteria. After PPI therapy, 17 patients (40%) were responders. There were no significant differences in demographic features, presenting symptoms, endoscopic findings, or histologic findings between responders and nonresponders. Among patients with 15 to 20 eosinophils per hpf on EMB, 50% were responders; among patients with >20 eosinophils per hpf on EMB, 29% were responders. Seven (41%) of 17 patients with abnormal pH monitoring and 5 (45%) of 11 patients with normal monitoring were responders.

CONCLUSIONS. Forty percent of patients with SEE demonstrated histologic response to PPI therapy. None of the clinical characteristics evaluated predicted response, and response was not dependent on pH study results. The role of PPI therapy in treating SEE warrants further prospective investigation.

REVIEWER COMMENTS. Esophageal eosinophilia has become an increasing clinical concern in the pediatric population. These investigators set out to determine predictors of histologic response to PPI therapy among children with SEE. They correctly identified significant limitations in their retrospective study. For example, the treatment and evaluation of these patients were not standardized at their institution. In addition, not all patients were treated with PPI, doses were not uniform, and not all patients treated with PPI underwent repeat endoscopy. A selection bias cannot be excluded with this study design. Prospective controlled investigations examining the role of PPI, as well as other therapies (eg, enteral corticosteroid therapy), in patients with SEE are definitely needed.
years, the number of episodes before diagnosis remained the same, indicating continued misdiagnosis. This, along with the inappropriate and sometimes risky treatments used in error, points out the need for greater awareness of the symptom pattern and triggers, especially rice, milk, and soy.

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Prospective Follow-up Oral Food Challenge in Food Protein-Induced Enterocolitis Syndrome

PURPOSE OF THE STUDY. To determine tolerance rates to cow’s milk and soy for infants affected by food protein-induced enterocolitis syndrome (FPIES).

STUDY POPULATION. Twenty-three patients (7 female and 16 male) with infantile FPIES were prospectively followed.

METHODS. Infants with a diagnosis of FPIES were diagnosed by positive oral food challenges for milk or soy formula at 36 days of age (SD: 14 days; range: 13–58 days). These infants were prospectively followed until >2 years of age. They underwent ≥2 follow-up oral challenges. The first follow-up oral challenges were performed at 6 months of age, and patients were randomly allocated to either milk (N = 11) or soy (N = 12). Second and third follow-up oral challenges were performed at 2-month intervals, in a crossed and switched-over manner. The challenge consisted of a single open oral feeding of 0.03 to 0.05 mg of cow’s milk protein or soy protein per kg of body weight.

RESULTS. Seventy-two oral food challenges with cow’s milk or soy were performed in 23 patients with FPIES. There were 27 positive challenges (37.5%). For all positive challenges, projectile vomiting and lethargy were noted at ~1 to 4.5 hours. Symptoms less commonly seen were cyanosis in 6 challenges (22.2%) and hypotension in 3 challenges (11.1%). No false-negative challenges were seen among the 45 negative challenges. Tolerance rates for milk at 6, 8, and 10 months of age were 27.3%, 41.7%, and 63.6%, respectively. Tolerance rates for soy at 6, 8, and 10 months of age were 75.0%, 90.9%, and 91.7%, respectively. Mean ages for outgrowing reactivity to cow’s milk and soy among the 23 patients were 12.0 months (SD: 4.4 months; range: 6–20 months) and 7.8 months (SD: 2.1 months; range: 6–14 months), respectively. Solid-food FPIES was observed in 2 of the patients (rice, beef, and egg in 1 child >11 months of age and fish and shellfish in 1 child >12 months of age). These 2 children became tolerant to these foods after 2 years of age.

CONCLUSIONS. The study reveals that infants with FPIES lose intolerance to soy protein at an earlier age, compared with cow’s milk. The authors suggest that soy oral challenge should be performed at 6 to 8 months of age and that milk oral challenge should be conducted when the child is >1 year of age. Challenge should be conducted under close medical supervision. The authors also found that a smaller than previously published challenge dose (0.03 to 0.05 mg of cow’s milk or soy protein per kg of body weight) was adequate in inducing symptoms.

REVIEWER COMMENTS. Performing oral challenges in infants affected by FPIES is not a light undertaking, as evidenced by the number of children who had a positive oral challenge, cyanosis, and hypotension. This article gives insight to clinicians regarding when and how to perform oral challenges for infants affected by milk and/or soy protein-induced enterocolitis syndrome.

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Rice: A Common and Severe Cause of Food Protein-Induced Enterocolitis Syndrome
Mehr SS, Kakakios AM, Kemp AS. Arch Dis Child. 2009;94(3):220–223

PURPOSE OF THE STUDY. To examine the characteristics of children presenting with food protein-induced enterocolitis syndrome (FPIES) attributable to rice and to determine whether there were any differences from those presenting with cow’s milk and/or soy FPIES.

STUDY POPULATION. Retrospective study of 31 children presenting with FPIES (14 with rice and 17 with milk/soy) to the Children’s Hospital at Westmead, Australia, during a 16-year period (1992–2007).

METHODS. Possible cases of FPIES were identified from the hospital medical record database and from electronically stored departmental letters written by allergists/immunologists. Previously published criteria were used for the diagnosis of FPIES, and cases were differentiated into typical and atypical presentations. The Mann-Whitney U test or Student’s t test was used for comparisons between nonparametric and parametric continuous variables. P < .05 was considered significant.

RESULTS. There were 14 children with 26 episodes of rice FPIES, compared with 17 children with 30 episodes of cow’s milk (n = 10) and soy (n = 7) FPIES. Children with rice FPIES were more likely to have FPIES caused by another food (36%) than were children with FPIES caused by cow’s milk/soy (0%). Rice triggered more severe reactions, resulting in higher rates of intravenous
fluid resuscitation (42% vs 17%), compared with reactions caused by cow’s milk/soy.

CONCLUSIONS. This study emphasizes the emerging importance of rice, a food commonly thought to be “hypoallergenic,” as a significant trigger of FPIES. Episodes triggered by rice caused more severe reactions requiring intravenous fluid resuscitation than did episodes caused by cow’s milk or soy.

REVIEWERS COMMENTS. Clinicians who take care of infants should be aware that rice can cause FPIES and such reactions may be more severe than those caused by cow’s milk and/or soy. The clinical presentation can mimic sepsis or an intraabdominal surgical emergency. It is important to consider the diagnosis of rice FPIES, particularly when evaluating children 3 to 6 months of age presenting with vomiting and/or diarrhea ~2 hours after ingesting the suspect food. Infants with rice FPIES tend to have multiple episodes, to have more severe reactions, and to require admissions to the hospital before the final diagnosis is correctly made.

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Impact of Peanut Allergy on Quality of Life, Stress and Anxiety in the Family
King RM, Knibb RC, Hourihane JOB. Allergy. 2009; 64(3):461–468

PURPOSE OF THE STUDY. To determine the impact of peanut allergy (PA) on quality of life (QoL) and reported anxiety of children with PA, their parents, and their older siblings.

STUDY POPULATION. Participants included 46 families of children with clinical PA (history of acute allergic symptoms with positive skin-prick test results or specific immunoglobulin E). Inclusion required a non–food-allergic/intolerant older sibling ≥15 years of age and parents.

METHODS. Families completed QoL, anxiety, and perceived stress scales. In addition, parents and siblings completed QoL proxy questionnaires.

RESULTS. Mothers rated significantly poorer QoL (psychological and physical) and scored significantly higher on anxiety and stress than did fathers. Children with PA scored significantly lower for QoL (physical health-related, school, and general) and experienced significantly greater separation anxiety than did their siblings. Mothers reported statistically significantly greater impact on QoL of the children with PA, compared with the children themselves, their fathers, or their siblings.

CONCLUSIONS. Mothers reported significantly poorer QoL and suffer more anxiety and stress than fathers. Mothers may overestimate the impact of PA on QoL of children with PA. Children with PA have lower QoL and higher separation anxiety than their older siblings.

REVIEWER COMMENTS. This work indicates not only that there is an impact of PA on QoL of the family as a unit but also that there are differences in impact on QoL and anxiety between family members. The differences in psychological impact could be related to the different roles played by each member of a family. Mothers may be more involved in meal preparation, care coordination, and health care for the child with PA. It may be helpful for health care providers to encourage shared responsibility when possible and to attempt to include many family members in food allergy–management education. Providing written educational material, encouraging participation in support groups, working on positive coping strategies, and potentially recommending appropriate psychological support may all be helpful interventions to help families cope as a unit.

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Evaluation of a Group Intervention for Children With Food Allergy and Their Parents

PURPOSE OF THE STUDY. To assess whether a group intervention designed for children with food allergy and their parents could improve parent-perceived competence and decrease parent-perceived burden in coping with food allergy.

STUDY POPULATION. Food-allergic, English-speaking children 5 to 7 years of age, without developmental disabilities, and their parents were recruited if they visited an allergist through the Children’s Hospital Boston in the year before the study.

METHODS. After consent was obtained, questionnaires were completed by the parents before the workshop, immediately after the workshop, and 4 to 8 weeks after the workshop. Parents completed the Family Coping with Food Allergy Questionnaire, which assesses perceived competence, and the Food Allergy Quality of Life-Parental Burden Questionnaire, which assesses the perceived burden in having a child with food allergy. Parents and children completed evaluations of the workshop as well. The workshop was 3.5 hours in length, with parent groups run by a pediatric psychologist and a pediatric allergist or pediatric nurse practitioner. There were presentations regarding various topics related to

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food allergy, followed by a group discussion. Child life specialists led the groups for children, which were aimed at providing a safe environment for children to express their feelings regarding food allergies and increasing confidence in management skills.

RESULTS. Sixty-one children and their parents were included in the study sample. Seventy-eight percent of participants showed improvement in competence scores from before the workshop to after the workshop ($P < .001$), and 74% showed improvement from before the workshop to the follow-up evaluation ($P < .001$). In addition, 63% of participants demonstrated a significant decrease in parent-perceived burden from before the workshop to the follow-up evaluation ($P = .002$).

CONCLUSIONS. This study provides preliminary support for the effectiveness of a half-day workshop in reducing parent-perceived burden and increasing parent-perceived competence in coping with children with food allergies.

REVIEWER COMMENTS. This study is a good start in identifying factors that can improve the quality of life of our families with food allergies. We need larger studies with more-diverse patient populations and control groups to identify which factors are most helpful and to determine whether the findings are clinically significant.

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Use of Multiple Doses of Epinephrine in Food-Induced Anaphylaxis in Children

PURPOSE OF THE STUDY. Data from mixed or adult populations indicate that 16% to 35% of anaphylactic reactions from various causes require >1 dose of epinephrine. This study sought to determine the prevalence and risk factors for administration of repeated doses of epinephrine in food-induced anaphylaxis in children.

STUDY POPULATION. Questionnaires ($N = 542$) were distributed to parents or caregivers of consecutive patients up to 18 years of age presenting for initial or follow-up evaluation for food allergy. The study was conducted at a hospital-based, pediatric allergy clinic and a private practice-based, pediatric, food-allergy, referral clinic at Mount Sinai Hospital (New York, NY).

METHODS. An anonymous 2-page questionnaire regarding details of as many as 2 anaphylactic reactions was administered. Data collected from the past 2 reactions requiring epinephrine included suspect food, onset of symptoms, and timing of treatment with single or multiple doses of epinephrine. The Mann-Whitney rank-sum test was used to compare medians and the $t$ test to compare means.

RESULTS. Overall, 413 questionnaires were included in the analysis. A total of 78 children reported 95 reactions for which epinephrine was administered. Of the 95 reactions, 77 (81%) required a single dose, 12 (13%) required 2 doses, and 6 (6%) required 3 doses of epinephrine. Peanut, tree nut, and cow’s milk were responsible for >75% of the reactions requiring epinephrine. Children receiving >1 dose of epinephrine more often had asthma ($P = .27$), compared with those receiving 1 dose. The amount of food allergen ingested and the delay in administering the initial epinephrine dose were not risk factors for receiving multiple doses of epinephrine. Of the second doses of epinephrine, 94% were administered by a health care professional.

CONCLUSIONS. Nineteen percent of food-induced anaphylactic reactions in this referral population required >1 dose of epinephrine. Additional studies are required to identify risk factors for severe anaphylaxis and to aid in establishing guidelines for prescribing multiple doses of epinephrine autoinjectors for children with food allergies.

REVIEWERS COMMENTS. The retrospective design and selected referral-based population with multiple food allergies are limitations to this study. These results, however, contribute to a body of evidence that suggests 2 doses of epinephrine may be required for our at-risk food-allergic patients. It is hoped that with additional studies we will improve our ability to identify those food-allergic patients most at risk for severe anaphylaxis.

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Epinephrine Auto-injectors: First-Aid Treatment Still Out of Reach for Many at Risk of Anaphylaxis in the Community

PURPOSE OF THE STUDY. Epinephrine is a life-saving medication for the treatment of anaphylaxis, and epinephrine auto-injectors (EpiPen [Dey, Napa, CA] or Twinject [Sciele Pharma, Inc., Atlanta, GA]) are universally recommended as essential first-aid treatment for anaphylaxis. A survey conducted in 2003 at the World Allergy Organization (WAO) raised concerns regarding lack of universal availability and affordability of epinephrine auto-injectors in many countries. This study was conducted at the WAO meeting as a follow-up study to determine whether availability and affordability of epinephrine auto-injectors had improved worldwide between 2003 and 2007.
STUDY POPULATION. Participants included allergy and immunology specialists in the 2007 WAO House of Delegates.

METHODS. The same survey that was designed for use in 2003, with 2 additional questions, was self-administered at the 2007 WAO meeting. Responses were tabulated by country.

RESULTS. Completed surveys were received from \( \geq 1 \) representative of all 44 countries with voting delegates (100% response rate). Auto-injectors containing 0.3 mg of epinephrine were available in 59.1% of countries, up from 56.4% in 2003, and auto-injectors containing 0.15 mg of epinephrine were available in 59.1% of countries, up from 43.6% in 2003. In no country were doses appropriate for infants available, in either 2003 or 2007. The unsubsidized median cost of 1 auto-injector was US $97.87 (range: $65.50–$168.66), up from $30 to $110 in 2003.

CONCLUSIONS. Since 2003, the global availability of auto-injectors containing 0.3 mg of epinephrine has improved slightly and the availability of those containing 0.15 mg of epinephrine has improved even more. Auto-injector costs have increased since 2003. The lack of availability and affordability of epinephrine auto-injectors remains a concern in many countries. Availability is especially limited in Asia, Africa, the Middle East, and Latin America.

REVIEWERS COMMENTS. It would be nice to follow this survey with other assessments of epinephrine availability (eg, polling more physicians and polling pharmacies), because the WAO physician population is not likely representative of the population at large. Although the accuracy of survey responses regarding availability or lack of availability was verified by contacting manufacturers, verification regarding accuracy of cost was not done. It is important to point out that the cost figures do not reflect what patients ultimately pay, because these figures do not factor in government subsidies or reductions from private health insurance. Importantly, this study finds that in no country was an appropriate infant dose available; this is obviously a problem for infants at risk for anaphylaxis. The authors also point out that, in more than one half of the countries in which epinephrine is available, it is not standard practice to recommend that people at risk for anaphylaxis carry 2 doses of epinephrine at all times. This is a potential concern, because up to 35% of anaphylaxis episodes occurring in the community are treated with \( \geq 2 \) doses. Furthermore, because this study points out that global availability is relatively limited, physicians should encourage at-risk patients to travel with auto-injectors.

## ATOPIC DERMATITIS AND ALLERGIC SKIN DISEASE

### Association of Staphylococcal Superantigen-Specific Immunoglobulin E With Mild and Moderate Atopic Dermatitis


**PURPOSE OF THE STUDY.** To examine the frequency of allergic sensitization to staphylococcal superantigens in young children with mild-to-moderate atopic dermatitis (AD).

**METHODS.** AD severity was assessed with objective scoring of AD. Levels of serum immunoglobulin E to staphylococcal enterotoxin A (SEA), SEB, SEC, SED, and toxic shock syndrome toxin 1 were measured with ImmunoCAP tests (ImmunoCAP, Phadia AB, Uppsala, Sweden). Comparisons between mild AD and moderate AD were performed by using logistic regression.

**RESULTS.** The prevalence of allergic sensitization to staphylococcal superantigens in patients with mild and moderate AD was 38% and 63%, respectively. Allergic sensitization to staphylococcal superantigens, particularly SEA and SED, was found to be associated with moderate AD, compared with mild AD.

**CONCLUSIONS.** These results suggest that allergenic sensitization to staphylococcal superantigens is common even in young children with mild-to-moderate AD, and such sensitization may contribute to the disease severity of these patients.

**REVIEWER COMMENTS.** Approximately 90% of patients with AD are colonized with *Staphylococcus aureus*, which may contribute to the worsening of skin inflammation in these patients. *S aureus* worsens AD by secreting superantigens (eg, SEA, SEB, SEC, and toxic shock syndrome toxin 1) and structural molecules within the cell wall that induce skin inflammation. An association between allergic sensitization to specific staphylococcal superantigens and AD has been recognized for some time now. Furthermore, superantigens have been demonstrated to induce corticosteroid resistance of T cells in vitro. This could contribute to difficulty in the management of AD, because topical corticosteroids are the most common medications used for treatment of AD. Recognition of this association in patients with AD, even those with mild-to-moderate disease, may lead to better overall control of skin symptoms following the use of a combination of antiinflammatory drug treatment and appropriate antibiotic therapy.
Methicillin-Resistant Staphylococcus aureus Colonization in Children With Atopic Dermatitis


PURPOSE OF THE STUDY. To determine the prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in children with atopic dermatitis (AD).

STUDY POPULATION. Observational cross-sectional study of 54 children seen in the dermatology clinic at the Children’s Hospital of Philadelphia in October and November 2004.

METHODS. Eczema severity was determined with the Eczema Area and Severity Index. Culture swabs (BBL CultureSwab [Becton, Dickinson, Sparks, MD]) were used. All cultures were plated for up to 5 days for the growth of S aureus, and methicillin-sensitivity tests were performed on positive S aureus cultures. Patients’ families provided information on medical histories, medication use, and other identifying risk factors for health care–associated MRSA, by completing a detailed, self-administered questionnaire.

RESULTS. Eighty percent of the patients (43 of 54 patients) were colonized with S aureus, and 16% (7 of 54 patients) were colonized with MRSA. MRSA was associated with previous hospitalization, with an odds ratio of 26.2 (95% confidence interval: 2.1–316.0), and the combination use of calcineurin inhibitors and topical corticosteroids. Other risk factors for MRSA (health care worker in household, oral antibiotic therapy, previous skin infections, and history of previous MRSA) were not identified. Eczema severity, defined by Eczema Area and Severity Index score, was not a risk factor for MRSA.

CONCLUSIONS. AD patients have a high rate of S aureus colonization and MRSA (16%) colonization, compared with the general public (1%–3%).

REVIEWER COMMENTS. The prevalence of MRSA was low in the study of patients with AD, which suggests that standard S aureus antibiotics can be used for first-line therapy. The possibility of local variation of MRSA colonization is important to consider before using oral cephalosporin treatment. Eczema severity might be a risk factor for MRSA, because the use of combination therapy or previous hospitalization as a marker for severe disease is associated with MRSA colonization.

Treatment of Staphylococcus aureus Colonization in Atopic Dermatitis Decreases Disease Severity

Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Pediatrics. 2009;123(5). Available at: www.pediatrics.org/cgi/content/full/123/5/e808

PURPOSE OF THE STUDY. To determine the rate of methicillin-resistant Staphylococcus aureus (MRSA) colonization in children with moderate-to-severe atopic dermatitis (AD) and to investigate the use of bleach baths and intranasal mupirocin treatment in management.

STUDY POPULATION. Patients (N = 31) 6 months to 17 years of age with moderate-to-severe AD and signs of bacterial skin infection were recruited from a dermatology clinic in Children’s Memorial Hospital (Chicago, IL).

METHODS. This was a randomized, investigator-blinded, placebo-controlled study. All patients were initially treated with cephalosporin for 14 days and were then assigned randomly to receive intranasal mupirocin ointment (versus petrolatum placebo) twice daily for 5 days per month and to use one half cup of bleach (versus placebo water) in 40 gallons of bathwater for soaking for 5 to 10 minutes twice weekly. Treatment was undertaken for 3 months. The primary outcome measure was the Eczema Area and Severity Index score.

RESULTS. S aureus was cultured from 81% of the nares and 87% of lesional skin samples, and the prevalence of MRSA was 4% of nasal cultures and 7.4% of skin cultures. Treated subjects, compared with control subjects, showed significantly greater mean reductions from baseline in Eczema Area and Severity Index scores at the 1-month and 3-month visits (P = .004). The improvement was attributable to score changes for body areas that had been submerged in the dilute bleach baths (score change at 3 months: treated: −4.9; placebo: −0.9; P = .0005).

CONCLUSIONS. The authors concluded that chronic use of dilute bleach baths with intermittent intranasal application of mupirocin ointment decreased the clinical severity of AD in patients with clinical signs of secondary bacterial infections and that these patients did not have increased susceptibility to MRSA.

REVIEWER COMMENTS. Noting the significant role of S aureus in the etiology of AD (as reviewed above), the use of bleach baths has been recommended for many years; however, study of the approach has been lacking. Clinicians must recognize that the approach here was targeted to a specific population (moderate-to-severe AD with superinfection) and more than just bleach baths were used (initial cephalaxin treatment and also mupirocin and emollient/antiinflammatory drug therapies). While we await additional studies on the efficacy and safety (including promotion of resistance) of the studied ap-
IL-21R Is Essential for Epicutaneous Sensitization and Allergic Skin Inflammation in Humans and Mice

PURPOSE OF THE STUDY. To examine the role of interleukin 21 (IL-21) in the pathogenesis of atopic dermatitis (AD).

STUDY POPULATION. Nine subjects with acute AD lesions and 5 healthy control subjects.

METHODS. Samples were obtained for skin biopsy and immunohistochemical analysis of IL-21 and IL-21 receptor (IL-21R) levels. A murine model for epicutaneous sensitization and dermatitis induced by repetitive application of antigen (ovalbumin) or hapten (oxazolone) after mechanical injury (tape stripping) was then used to examine the role of the IL-21 pathway in dendritic cell activation and migration and T cell stimulation.

RESULTS. The expression of IL-21 and IL-21R was elevated in acute AD lesions, compared with the normal skin of healthy control subjects. IL-21 was most strongly expressed in mononuclear cells in the dermis, whereas IL-21R was most strongly expressed by keratinocytes. Two wild-type mouse strains develop allergic epicutaneous sensitization after antigen or hapten application to skin that has been damaged by tape stripping. IL-21R-deficient mice, which lack expression of the receptor, are deficient in both the development of local inflammation and the associated T-helper 2-skewed systemic immune response. IL-21R-deficient dendritic cell populations are normal in their capacity to induce naive T cell activation; however, they are abnormal in their ability to upregulate chemokine receptor 7 and to migrate appropriately to draining lymph nodes after minor skin trauma.

CONCLUSIONS. IL-21 and IL-21R expression is elevated in acute AD lesions, and IL-21R is required in a model of epicutaneous allergic sensitization that resembles human AD.

REVIEWER COMMENTS. The etiology of AD is unknown, although recent studies underscored a role for skin barrier defects that might enhance allergic sensitization. The discovery in this report of the importance of IL-21 for epicutaneous sensitization, along with the observed elevation of IL-21/IL-21R in human AD lesions, suggests that this pathway may be a key player in the vicious cycle of barrier defect, sensitization, inflammation, and worsening barrier defect. IL-21 is also known in other models to induce T-helper 17 cells and to suppress immunoglobulin E, neither of which was reported in this study and which may not accord so well with our current understanding of AD. Nevertheless, this early report may be a first step toward identifying a new target for intervention and treatment.

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 determine the efficacy and safety of 3 times per week maintenance use of tacrolimus in the prevention of atopic dermatitis (AD) exacerbations.

STUDY POPULATION. Multicenter, randomized, double-blind, placebo-controlled study of 383 patients over the age of 2 years with moderate-to-severe AD.

METHODS. The study consisted of stabilization and maintenance phases. During stabilization, subjects received tacrolimus ointment (0.03% [2–16 years] or 0.1% [≥16 years]) or corticosteroid (alclometasone dipropionate, 0.05% ointment [2–16 years], or triamcinolone acetonide, 0.1% ointment [≥16 years]) twice daily for 4 days at AD flare sites, followed by a 2-week, open-label phase. Subjects demonstrating a response to tacrolimus were then asked to participate in the maintenance portion of the study. The maintenance phase was a randomized, double-blind, vehicle-controlled, 40-week study in which topical application was performed once daily, 3 times per week, at previous eczema flare sites.

RESULTS. Subjects receiving tacrolimus experienced more symptom-free days (177 vs 134 days; \( P = .003 \)). Time to relapse was longer in patients treated with tacrolimus versus vehicle (169 vs 43 days; \( P = .037 \)). Patients receiving tacrolimus seemed less likely to experience relapse (62% vs 66% with ≥1 relapse during treatment; \( P = .55 \)) and had fewer relapses during the treatment period (maximum of 3 relapses in 5.6% of the tacrolimus group versus 3–6 relapses in 16.9% of the vehicle group). The severity of relapses was milder in the treatment group, with only 29% in the tacrolimus group having moderate relapse, compared with 51% in the vehicle group. During the open-label trial, 83% of pa-
patients in both the tacrolimus and vehicle groups responded to tacrolimus treatment of relapse. With regard to safety, patients treated during the stabilization phase with tacrolimus versus topical steroid were more likely to have cutaneous site reactions (18% vs 9%; \( P = .015 \)) during the first 4 days of treatment; this was not seen during the rest of the treatment course.

CONCLUSIONS. Tacrolimus maintenance therapy increased the number of symptom-free days and the time to relapse, compared with vehicle alone.

REVIEWERS COMMENTS. AD is a disease characterized by intermittent flares and symptom-free periods. Maintenance, intermittent, topical corticosteroid dosing regimens have been successful in preventing relapse. The use of maintenance steroid-sparing therapies is desirable. This study indicates that maintenance therapy may prevent relapse occurrence and decrease the severity of disease and provides an interesting treatment option for patients with AD with frequent relapses. Also, in light of recent Food and Drug Administration warnings concerning topical calcineurin inhibitors, it is valuable to know that dosing could be reduced to 3 times weekly for maintenance. Overall, this well-designed study provides convincing support for maintenance therapy of AD with topical nonsteroidal calcineurin inhibitors. Similar results were seen in 3 other studies using 2 or 3 times per week dosing schedules for topical steroids and topical calcineurin inhibitors. These studies indicate that maintenance therapy is superior to as-needed use of topical medications for patients with moderate-to-severe AD.

Three Times Weekly Tacrolimus Ointment Reduces Relapse in Stabilized Atopic Dermatitis: A New Paradigm for Use


PURPOSE OF THE STUDY. To evaluate the safety and efficacy of intermittent topical tacrolimus as maintenance therapy in patients with moderate-to-severe atopic dermatitis.

STUDY POPULATION. Subjects 2 to 15 years of age with moderate-to-severe atopic dermatitis.

METHODS. Subjects underwent stabilization with either 0.05% aclometasone ointment or 0.03% tacrolimus in a double-blind fashion for 4 days, followed by twice-daily, open-label, 0.03% tacrolimus treatment for all subjects. Subjects who became “clear” or “almost clear” entered phase II (maintenance phase) and underwent double-blind, random assignment to either 0.03% tacrolimus or vehicle applied once daily, 3 times per week, for up to 40 weeks. Emollients were permitted, but corticosteroid use was prohibited; open-label tacrolimus use was permitted to treat relapses.

RESULTS. A total of 206 patients were randomly assigned, and 50 subjects completed the study. There were no significant differences between groups at baseline. Aclometasone-treated patients showed more improvement in the acute phase than did tacrolimus-treated patients, and there were no differences in application-site adverse events between groups. During maintenance, tacrolimus-treated patients had a significantly greater number of disease-free treatment days, compared with vehicle-treated patients (mean: 174 vs 107 days; \( P = .0008 \)), and a longer time to first relapse (median: 116 vs 31 days; \( P < .04 \)).

CONCLUSIONS. Long-term intermittent application of 0.03% tacrolimus to clinically normal-appearing but previously affected skin was significantly more effective than vehicle at maintaining disease stabilization in patients with moderate-to-severe atopic dermatitis. The safety profile of intermittently applied tacrolimus was similar to that of vehicle.

REVIEWERS COMMENTS. Atopic dermatitis is a chronic relapsing disease. Prevention of relapse is aimed at skin hydration and avoidance of triggers. Adverse effects of topical steroids limit their long-term use and, although there are concerns that calcineurin inhibitors may carry an increased risk of malignancy, long-term data on the safety of topical calcineurin inhibitors contradict this notion. This study shows promise that intermittent application of 0.03% tacrolimus offers a novel, steroid-sparing approach to maintaining stabilization of atopic dermatitis that seems both safe and efficacious.

MAS063DP Is Effective Monotherapy for Mild to Moderate Atopic Dermatitis in Infants and Children: A Multicenter, Randomized, Vehicle-Controlled Study


PURPOSE OF THE STUDY. To examine the safety and efficacy of MAS063DP (Atopiclair [Graceway Pharmaceuticals, Bristol, TN]), a topical nonsteroidal antiinflammatory agent, in the management of mild-to-moderate atopic dermatitis in infants and children.
STUDY POPULATION. Infants and children (N = 142) between the ages of 6 months and 9 years with mild-to-moderate atopic dermatitis affecting ≥5% of body surface area and scores of ≥40 of 100 on a visual analog scale (VAS) for pruritus.

METHODS. Subjects were randomly assigned to apply MAS063DP or vehicle cream 3 times per day to affected areas, as well as those prone to flares, after a washout period. Assessments were made at baseline and days 3, 8, 15, 22, 29, and 43. The primary end point was the subject’s Investigator’s Global Assessment (IGA) score on day 22 (0 indicates clear skin and 5 indicates severe disease activity). Treatment success was defined as an IGA score of 0 or 1. Secondary end points included IGA scores at other time points, subject/caregiver assessment of pruritus as evaluated with the VAS and an ordinal scale of 0 to 3, onset and duration of itch relief, Eczema Area and Severity Index, subject/caregiver assessment of global response, and need for rescue medication during a flare.

RESULTS. For the primary end point of IGA score at day 22, there was a highly significant difference between the 2 groups (analysis of covariance, P < .0001) in favor of the treatment group. In intention-to-treat analysis, 53 (77%) of 69 subjects achieved treatment success, compared with none in the vehicle group. The mean treatment difference was −1.636 (95% confidence interval: −1.928 to −1.344) in favor of MAS063DP. The secondary end point of IGA scores at other time points demonstrated treatment success for 39.1% of the MAS063DP-treated subjects by day 8, 71% by day 15, and 78.2% by day 29. Treatment success in the vehicle-treated group did not exceed 7.1%. The difference was significant at all time points (Fisher’s exact test, P < .0001). Other secondary end points that demonstrated significant benefit in the treatment group versus the vehicle group included the VAS score, Eczema Area and Severity Index score, subject/caregiver assessment of global response from baseline, onset of itch relief and duration of action, and need for rescue medication (8.7% in the treatment group and 28.6% in the vehicle group). No serious adverse events were related to MAS063DP, although stinging (8.3%), burning (6.9%), and fever (6.9%) were common adverse events (the latter 2 occurring more frequently in the vehicle group). Rates of treatment discontinuation because of adverse events were 9.9% in the MAS063DP group and 16% in the vehicle group.

CONCLUSIONS. MAS063DP is safe and effective in the treatment of mild-to-moderate atopic dermatitis in infants and children.

REVIEWS COMMENTS. Concerns about adverse effects of topical corticosteroids and calcineurin inhibitors elicit understandable parental apprehension. The results of this study show promise for an alternative therapy for mild-to-moderate atopic dermatitis in infants and children. Although this study did not monitor for the theoretical risk of systemic toxicity after prolonged use, no systemic adverse events have been reported in post-marketing surveillance.

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Adenoидectomy Outcomes in Pediatric Rhinosinusitis: A Meta-analysis

PURPOSE OF THE STUDY. The objective of this study was to evaluate the available medical literature for evidence that adenoïdectomy is an effective procedure for treating children with medically refractory rhinosinusitis.

STUDY POPULATION. Articles were obtained by using database searches and manual searches. These articles studied children, ≤18 years of age, who underwent adenoïdectomy alone for management of medically refractory rhinosinusitis. The mean of the mean age of patients for each included series was 5.8 years, with a range of means of 4.4 to 6.9 years.

METHODS. A meta-analysis was performed of the available literature on adenoïdectomy as treatment for sinusitis in this population, using searches of Medline, Embase, and Cochrane databases as well as manual searches of reference lists. Studies were selected for meta-analysis by meeting the following criteria: (1) the study evaluated the efficacy of adenoïdectomy as the only surgical intervention for sinusitis; (2) the study was published in the English language; and (3) the study had a sample size of ≥5. Statistical analysis was performed with random-effects modeling, with the outcome measure being caregiver report or perceived presence or absence of symptomatic improvement.

RESULTS. Of the 78 articles identified through the database search and several others through manual search of references published between 1952 and 2007, 8 met inclusion criteria and 8 were statistically analyzed. These included 5 cohort studies and 4 case series. There were no randomized, controlled trials. The mean sample size was 46 (range: 10–121). All studies reported an improvement in symptoms or outcomes in ≥50% of patients. The statistical model accounting for interstudy variance estimated that 69.3% (95% confidence interval: 56.8%–81.7%; P < .001) of patients experienced symptomatic improvement with adenoïdectomy. When the 3 articles submitted by a single author were excluded, the improvement after adenoïdectomy was ≥83%.

CONCLUSIONS. The authors concluded that, although the literature is sparse and of only moderate-to-good quality, there is substantial support for the efficacy of adenoïdectomy for treatment of children with medically refractory sinus disease. In addition, they suggested that these results, combined with the simplicity of adenoïdectomy, compared with other surgical procedures, support the use of adenoïdectomy before other surgical procedures in this population.

REVIEWERS COMMENTS. Adenoïdectomy has long been used as a treatment for sinusitis in children who do not respond to observation or medical therapy. This systematic literature review supports such use of adenoïdectomy. Although a large majority of children experience improvement after adenoïdectomy, it is clear that this procedure is not curative for many and may be ineffective for some.

The need for prospective study of the various medical and surgical treatments for pediatric sinusitis remains, with uniform entry criteria, well-defined outcomes, and randomization between treatment modalities and appropriate controls.

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Effect of Adenoïdectomy on Respiratory Function: A Randomised Prospective Study

PURPOSE OF THE STUDY. Previous studies reported that the risk of childhood asthma is increased more than threefold in children with recurrent otitis media who have undergone adenoïdectomy. The purpose of this study was to provide information on young children who were monitored to 3 years, to assess the effect of adenoïdectomy on lung function and the development of atopy.

STUDY POPULATION. Of the 217 children recruited, 166 children completed the follow-up trial. These children were 12 to 48 months of age, had recurrent or persistent otitis media treated with adenoïdectomy and tympanostomy or tympanostomy alone, and were monitored to 3 years after random assignment.

METHODS. The study included young children with recurrent otitis media (≥3 episodes in 6 months or ≥5 episodes in 12 months). All children underwent tympanostomy tube placement and were randomly assigned to undergo adenoïdectomy as well. At the end of the 3-year follow-up period, impulse oscillometry (as a measure of exercise-induced bronchoconstriction), exhaled nitric oxide measurement (as a measure of bronchial inflammation), and skin-prick testing (as a measure of atopy) were performed for these children.

RESULTS. There was no significant difference in baseline lung function, exercise-induced bronchoconstriction, exhaled nitric oxide concentration, or the development of positive skin-prick test results between children who underwent adenoïdectomy and those who did not.
During the first, second, and third years of the follow-up period, no significant differences in the mean number of otitis media episodes were observed between the 2 groups.

CONCLUSIONS. Adenoidectomy does not increase the risk of childhood asthma or the development of allergy. Recurrent respiratory tract infections during early childhood seem to be connected to the risk of bronchial hyperreactivity. The authors also suggest that adenoidectomy is not warranted as first-line treatment for the prevention of otitis media in children <4 years of age, especially those who do not have adenoidal hyperplasia or chronic adenoid infection.

REVIEWER COMMENTS. Adenoidectomy is one of the most common surgical procedures performed for children. It is reassuring to know that it does not promote the development of asthma or atopy. However, for children who do not have adenoidal hyperplasia or chronic adenoidal infection, adenoidectomy does not reduce the number of subsequent ear infections and may be unnecessary.

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Immunopathology of Chronic Rhinosinusitis in Young Children

PURPOSE OF THE STUDY. To use immunohistopathological methods to define further the lymphocytic inflammation in pediatric chronic rhinosinusitis (CRS).

STUDY POPULATION. Nineteen children (median age: 3.0 years) with CRS corroborated by axial computed tomographic scans of the sinuses were included. Archival maxillary sinus mucosal tissue samples from 5 adults were used for comparison.

METHODS. Maxillary sinus biopsies were performed, and immunostaining was performed on tissue samples for the following: CD3, CD4, CD8, CD68, CD20, κ, λ, and CD56. Myeloperoxidase stain was used to identify neutrophils.

RESULTS. The epithelium contained significantly increased numbers of CD8+, myeloperoxidase-positive, and CD68+ cells in the pediatric CRS group, compared with the adult control subjects. There were trends toward higher numbers of CD3+ and CD4+ cells. There were insufficient epithelial tissue samples to perform staining for CD20, κ, λ, and CD56. Submucosa from pediatric CRS subjects contained significantly higher numbers of CD20+, κ+, λ+, myeloperoxidase-positive, and CD68+ cells, with a trend toward a higher number of CD4+ cells.

CONCLUSIONS. In contrast to adult subjects with CRS, for whom the inflammatory response is predominantly eosinophilic, the inflammatory response of pediatric subjects with CRS is characterized by a mixed lymphocyte population, macrophages, and neutrophils. These observations suggest 2 possibilities, that is, a different pathogenic mechanism in children with CRS or progression of the inflammatory response with protracted disease.

REVIEWER COMMENTS. This study provides basic insight into CRS in children. Additional studies need to be performed to determine whether the identified inflammatory response persists or progresses to the characteristic inflammatory response seen in adults.

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Asthma

PATHOPHYSIOLOGY

Wheezy Rhinovirus Illnesses in Early Life Predict Asthma Development in High-Risk Children


PURPOSE OF THE STUDY. Childhood asthma often preceded by episodes of viral wheezing. Whether specific viral infections confer more risk for future development of asthma is incompletely understood. Associations between the timing and cause of early viral infections and the subsequent risk of childhood asthma were assessed in a cohort of children at high risk.

STUDY POPULATION. A total of 259 children were monitored prospectively from birth to 6 years of age in the Childhood Origins of Asthma (COAST) study. To qualify for the COAST study, ≥1 parent was required to have respiratory allergies (defined as ≥1 positive aeroallergen skin tests) and/or a history of physician-diagnosed asthma.

METHODS. The etiology and timing of specific viral wheezing respiratory illnesses during early childhood were assessed by using nasal lavage, culture, and multiplex reverse transcriptase-polymerase chain reaction assays. The relationships of these virus-specific wheezing illnesses and other risk factors to the development of asthma were analyzed.

RESULTS. A specific viral etiology was identified in 90% of wheezing illnesses. Wheezing with respiratory syncytial virus (RSV) (odds ratio [OR]: 2.6), rhinovirus (RV) (OR: 9.8), or both RV and RSV (OR: 10) from birth to age 3 years was associated with increased asthma risk at age 6 years. In year 1, both RV wheezing (OR: 2.8) and aeroallergen sensitization (OR: 3.6) independently increased asthma risk at age 6 years. By age 3 years, wheezing with RV (OR: 25.6) was more strongly associated with asthma at age 6 years than was aeroallergen sensitization (OR: 3.4). Nearly 90% of children with wheezing with RV at age 3 subsequently developed asthma, regardless of the presence or absence of aeroallergen sensitization.

CONCLUSIONS. In children at high genetic risk, early childhood wheezing in the outpatient setting caused by RV infection is a strong risk factor for the development of asthma at age 6 years.

REVIEWER COMMENTS. We have been familiar with the previous studies focused on associations of early RSV infections and the subsequent risk for asthma. Persistent wheezing associated with early-onset RV infection seems to be a better indicator of asthma risk than RSV infection. It will be interesting to follow the COAST study results as they monitor these children throughout childhood and beyond. A still-unanswered question is: do early viral infections cause asthma or just unmask predisposed asthma?

Evidence of a Causal Role of Winter Virus Infection During Infancy in Early Childhood Asthma


PURPOSE OF THE STUDY. In the first year of life, ~20% of children have ≥1 episode of respiratory illness with wheezing. Other studies have shown that certain respiratory viruses confer an increased risk of developing later childhood asthma. Whether these common respiratory viruses cause asthma or are a marker of individuals predisposed to developing asthma is unknown. The timing of birth in relation to the winter virus peak and whether this alters the risk of developing early childhood asthma are investigated in this study.

STUDY POPULATION. A population-based, birth cohort study of 95,310 children who were born between 1995 and 2000 and followed through 2005, who were continuously enrolled in the Tennessee Medicaid program from birth through early childhood, representing 25% of the annual births in Tennessee, was performed.

METHODS. The criteria for defining asthma variables and classification represent a minor flaw, because they were not defined a priori and were based on adult data. However, the authors used well-designed methods to make certain that the main outcome variables were defined in the best way the data allowed. Infant birth in relation to the winter virus peak was defined for each infant as the infant’s age in days from birth to the first winter virus peak. The annual winter virus peak was defined as the first day of the week with the highest number of bronchiolitis hospitalizations for that winter season.

RESULTS. During the 5 winter virus seasons, the risk of developing asthma tracked with the timing of infant birth in relation to the winter virus peak among the 95,310 children studied from birth through early childhood. Infant birth ~4 months before the winter virus peak carried the highest risk, with a 29% increase in the odds of developing asthma, compared with birth 12 months before the peak (odds ratio: 1.29). Infant age at the winter virus peak was comparable to or greater than other known risk factors for asthma, such as maternal smoking or maternal asthma. Over the 5 study seasons,
the increase in the incidence of bronchiolitis during infancy paralleled the subsequent increase in the cumulative incidence of current high-risk asthma defined between 4 and 5.5 years of age and offset by 5 years from the birth season in the same cohort of children.

CONCLUSIONS. This study demonstrates that the timing of birth in relation to the winter virus season confers a differential and definable risk of developing early asthma, establishing winter virus seasonality as a causal factor in asthma development. The authors have demonstrated that increasing rates of infant bronchiolitis in the past 10 years parallel the 5-year–offset increases in asthma at 5 years of age among these children.

REVIEWER COMMENTS. Timing of birth in relation to the winter virus peak independently predicts asthma development, with the highest risk estimated to be birth at 121 days before the winter virus peak of any given year. This age confers a 29% increased risk of developing childhood asthma. These findings, taken with findings from the Childhood Origins of Asthma study (reviewed above), are exciting and will fuel the debate about interventions for avoiding viral infections in infancy (are they a creditable target?). There is controversy in this area, because children who attend day care centers and who are more exposed to recurrent respiratory infections have been shown to have less asthma later in life. Possibly some subgroups at greater risk of developing asthma, such as infants who are young at the beginning of the virus season and those with an atopic background, may benefit most from preventive and therapeutic interventions.

Acute, But Not Resolved, Influenza A Infection Enhances Susceptibility to House Dust Mite-Induced Allergic Disease


PURPOSE OF THE STUDY. To examine the consequences of exposure to a low dose of the common aeroallergen house dust mite (HDM) during the course of an influenza A infection.

METHODS. The response to allergen exposure was evaluated at 3 distinct time points, relative to influenza infection. To evaluate responses to allergen exposure during the acute phase of infection, mice were inoculated intranasally with influenza type A virus and then exposed to a low dose of HDM daily for 10 days during the peak of acute inflammation. The second experiment investigated whether HDM-associated changes in the inflammatory response were transient or long-lasting. The mice were inoculated with influenza A and challenged with HDM as described previously, but the animals were allowed to rest for a period of ≥30 days, after which they were reexposed to HDM for 3 consecutive days. In the final experiment, mice were exposed to HDM after resolution of the influenza infection.

RESULTS. In mice inoculated with influenza A, there was a preferential increase in the activation of CD8+ T cells over CD4+ T cells and an increase in antigen-presenting cells, particularly plasmacytoid dendritic cells, as expected after a viral infection. Exposure to a low dose of HDM during the acute phase of influenza infection led to significantly increased numbers of mononuclear cells and eosinophils in the lung. Flow cytometry revealed a robust increase in the number of CD4+ T cells, specifically T-helper 2 (Th2) cells, and this increase in Th2 cells was much stronger in the influenza-infected HDM group, compared with the HDM-alone group. Exposure to HDM during the acute phase of influenza infection also resulted in significantly elevated levels of HDM-specific immunoglobulin G1 (IgG1) and IgG2a. Mice exposed to HDM allergen during the acute infection also demonstrated enhanced lung dysfunction and significantly greater goblet cell metaplasia and mucus production, compared with mice treated with HDM allergen alone. Mice that were rechallenged with HDM (experiment 2) showed responses similar to those listed above. Finally, mice with a first exposure to HDM that occurred after resolution of the influenza infection had an attenuated HDM-associated inflammatory response.

CONCLUSIONS. The study shows that the Th1 immune environment created during the acute phase of influenza infection leads to enhanced, rather than attenuated, allergic sensitization and inflammation in response to aeroallergen exposure and that these effects are long-lasting. In contrast, allergen exposure that occurs after resolution of the influenza infection does not result in an enhanced inflammatory response.

REVIEWERS COMMENTS. There has been great interest in finding ways to divert the immune system away from a Th2 allergic profile. Previous studies suggested that viral infection may afford protection against allergic disease by promoting Th1 responses. This study clearly shows that, despite the Th1 state induced by influenza A infection, the immune system is driven to a robust response to concomitant allergen exposure. Whether influenza or other viruses play a similar role in humans remains to be seen.
Alveolar Macrophage Phagocytosis Is Impaired in Children With Poorly Controlled Asthma

PURPOSE OF THE STUDY. Because alveolar macrophages (AMs) are important in innate immunity, evidence was sought that AM phagocytosis might be impaired in poorly controlled asthma.

STUDY POPULATION. Children 5 to 17 years of age underwent bronchoscopy with bronchoalveolar lavage for clinical indications ranging from poor asthma control despite maximal inhaled corticosteroid (ICS) doses to suspected aspiration, suspected atypical infection, or confirmation of habitual cough or vocal cord dysfunction. A control group consisted of healthy, nonsmoking adults. Poorly controlled asthma was defined by ≥12% forced expiratory volume in 1 second reversibility with bronchodilator and daily asthma symptoms requiring bronchodilator use on ≥5 of 7 days. Severe disease was defined by baseline forced expiratory volume in 1 second <80% of predicted and asthma-related hospitalization within the past year. Pediatric subjects had received ≥8 weeks of ICS treatment.

METHODS. Bronchoalveolar lavage fluid AMs were isolated from 12 children with moderately severe asthma, 16 children with severe asthma, 10 children without asthma treated with ICS for chronic cough, and 10 healthy adults. AMs were stimulated with lipopolysaccharide and exposed to fluorescein isothiocyanate-conjugated inactivated Staphylococcus aureus. Phagocytosis was quantified by using a phagocytic index (PI) calculated from the percentage of phagocytic cells multiplied by the relative fluorescence units (RFU) of S. aureus per cell. Apoptosis was determined from the percentage of cells positive for poly(adenosine diphosphate-ribose) polymerase.

RESULTS. Phagocytosis, as measured by unstimulated PI, was decreased in children with asthma (healthy control: 9330 ± 3992 RFU; chronic cough: 9042 ± 5976 RFU; moderate asthma: 4361 ± 2536 RFU; severe asthma: 3153 ± 1886 RFU; P < .001). PI was unchanged in all groups with lipopolysaccharide stimulation. Children with severe asthma also had increased apoptosis in both unstimulated and stimulated states (P < .001), which correlated with PI. The degree of corticosteroid treatment did not correlate with PI.

CONCLUSIONS. AM function is compromised in children with poorly controlled asthma, as characterized by decreased phagocytosis and increased apoptosis, and might account for the aberrant response to respiratory infection commonly seen in this population.

REVIEWERS COMMENTS. The most-severe impairment in phagocytosis occurred in the children with the most-severe asthma. In practice, clinicians treating children experiencing exacerbations of already severe asthma are usually left with the question: is it all asthma, or is there lower respiratory infection to monitor and/or to treat? Although this study used a bacterial microbial stimulus, it is well known that innate AM activation is also important for clearance of respiratory viruses. Various studies suggested that the respiratory burst of AMs might be impaired in patients with asthma, resulting in decreased microbe killing. Additional study regarding the dynamic relationships between the respiratory burst and phagocytosis in the population with asthma is needed.
had significantly shorter ICU length of stay, duration of continuously nebulized albuterol therapy, and duration of supplemental oxygen therapy and were significantly less likely to require intravenous β2-AR agonist therapy, compared with those with the Arg/Arg or Arg/Gly genotype. Genetic polymorphisms at position 27 were not associated with response to β2-AR agonist therapy or with the other clinical outcomes measured.

CONCLUSIONS. In this group of children with severe asthma exacerbations, those with the Gly/Gly genotype at position 16 of the β2-AR had more-rapid responses to β2-AR agonist therapy and shorter ICU lengths of stay.

REVIEWERS COMMENTS. This article provides further evidence of the complexity of asthma genetics. The relationship between β2-AR genotypes and responses to β2-AR agonists is controversial, with different studies coming to opposing conclusions. Responses may depend largely on how the β2-AR agonist is dosed (short-term, single-dose treatment versus long-term, repeated dosing). This study was limited by the small study size. However, the study presents another step toward linking asthma genotypes with asthma phenotypes. This should allow the use of pharmacogenetics to treat specific patient populations in an evidence-based manner, an exciting future!

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Chromosome 17q21 Gene Variants Are Associated With Asthma and Exacerbations But Not Atopy in Early Childhood

PURPOSE OF THE STUDY. To determine the association between the 17q12–q21 locus and various clinical characteristics of asthma and atopic sensitization during childhood.

STUDY POPULATION. The Copenhagen Prospective Study on Asthma in Childhood (COPSAC) included a birth cohort of 411 children born to mothers with a history of asthma. Three hundred seventy-six of these children were enrolled at age 1 month and seen at ages 1 month, 4 years but not 6 years. Parents recorded daily symptoms. End points included investigator-diagnosed asthma or atopic disease and objective measurements of lung function and atopic sensitization, at various follow-up points.

RESULTS. Homozygosity for the T allele at SNP rs7216389 was associated with experiencing wheezing (hazard ratio [HR]: 1.64 [95% confidence interval [CI]: 1.05–2.59]), asthma (HR: 1.88 [95% CI: 1.15–3.07]), and acute severe exacerbations (HR: 2.66 [95% CI: 1.58–4.48]). Significantly increased bronchial hyperresponsiveness was seen at ages 1 month and 4 years but not 6 years. However, increased risk of asthma exacerbations persisted through age 6 years (incidence ratio: 2.48 [95% CI: 1.42–4.32]). There was no increased risk for eczema, rhinitis, or atopic sensitization.

CONCLUSIONS. The rs7216389 SNP at the 17q12–q21 locus was associated with increased risk of asthma, asthma exacerbations, and bronchial hyperresponsiveness. However, it was not associated with any increased risk of atopic sensitization, eczema, or rhinitis.

REVIEWER COMMENTS. This particular polymorphism was shown previously to be associated with increased risk for developing asthma. The data from this study describe the clinical phenotype associated with this SNP in a population of infants and young children at increased risk for asthma. It seems to confer a specific risk for asthma without increased atopy. This study was performed with a selected population at high risk for asthma, and future research will need to determine whether these findings are replicable in the general population.

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Serum Vitamin D Levels and Markers of Severity of Childhood Asthma in Costa Rica

PURPOSE OF THE STUDY. To determine whether vitamin D levels are associated with asthma severity and allergy during childhood.

STUDY POPULATION. Six hundred sixteen Costa Rican children with asthma, 6 to 14 years of age, were included. Asthma was defined as physician-diagnosed asthma and ≥2 respiratory symptoms or asthma attacks in the past year.

METHODS. Study participants were identified on the basis of questionnaires sent to 113 Costa Rican schools. Participants answered additional questions and underwent pulmonary function testing, methacholine challenge testing, allergy skin-prick testing, serum total immunoglobulin E (IgE) and allergen-specific IgE measurements, peripheral blood eosinophil counts, and serum 25-hydroxyvitamin D3 measurements. Linear and logistic regression models were created to assess associations between factors.
RESULTS. Twenty-eight percent of participants had vitamin D levels of <30 ng/mL, which is the lower limit of the normal range. Each 1-log unit increase in vitamin D level was associated with decreased odds of any hospitalization in the past year (odds ratio [OR]: 0.05 [95% confidence interval [CI]: 0.004–0.71]), use of inhaled corticosteroids and/or leukotriene inhibitors in the past year (OR: 0.18 [95% CI: 0.05–0.67]), and increased airway hyperresponsiveness (OR: 0.15 [95% CI: 0.024–0.097]). In multivariate analysis, increasing serum levels of vitamin D were associated with lower total serum IgE levels, peripheral eosinophil counts, and dust mite–specific IgE levels.

CONCLUSIONS. Vitamin D deficiency is relatively frequent in Costa Rican children, and lower levels are associated with increased markers of allergy and asthma severity.

REVIEWER COMMENTS. Maternal vitamin D intake during pregnancy has been inversely associated with asthma symptoms in early childhood. However, no study has examined the relationship between measured vitamin D levels and markers of asthma severity in childhood. This study found an association between reduced vitamin D levels and markers of allergy severitv in a population of Costa Rican children with asthma. Additional study of this topic using an unsolicited birth cohort, a case-control approach, or a clinical trial of vitamin D supplementation would be a preferable next step. Also of note, although the authors used the current standard “normal” lower threshold to define vitamin D deficiency, there is substantial debate about what the appropriate lower limit should be.

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TH17 Cells Mediate Steroid-Resistant Airway Inflammation and Airway Hyperresponsiveness in Mice

PURPOSE OF THE STUDY. To investigate the function of T-helper 17 (TH17) cells in the context of antigen-induced airway inflammation.

METHODS. The authors examined the role of TH17 cells in asthma by using a mouse model in which severe combined immunodeficient (SCID) mice were challenged with ovalbumin. On day 0, ovalbumin-specific TH2 or TH17 cells were adoptively transferred into the SCID mice. The SCID mice were challenged with ovalbumin for 3 consecutive days after cell transfer. Mice were treated with dexamethasone or phosphate-buffered saline (control) before cell transfer on day 0 and before ovalbumin challenge on day 2. In a separate experiment, wild-type mice and interleukin 17 (IL-17) receptor-null mice underwent the same protocol.

RESULTS. Transfer of ovalbumin-specific TH2 or TH17 cells into the SCID mice, followed by ovalbumin challenge, resulted in specific cellular influx into the airways and airway hyperreactivity (AHR). TH2 cell reconstitution resulted in airway inflammation that consisted mostly of eosinophils and lymphocytes and was sensitive to dexamethasone. TH17 cell reconstitution resulted in a primarily neutrophilic airway response that was resistant to dexamethasone. Adoptive transfer of ovalbumin-specific TH2 or TH17 cells, followed by ovalbumin challenge, resulted in AHR in both cases, but the AHR was sensitive to dexamethasone in the mice reconstituted with TH2 cells and not in the mice reconstituted with TH17 cells. The inflammatory and cellular responses associated with TH17 cell transfer were mediated primarily by IL-17, because IL-17 receptor-knockout mice did not develop airway neutrophilia after adoptive transfer of ovalbumin-specific TH17 cells, followed by ovalbumin challenge.

CONCLUSIONS. Reconstitution of SCID mice with TH17 cells in a model of antigen-induced airway inflammation leads to airway neutrophilia and AHR. TH17 cell-mediated neutrophil influx into the airways and AHR are resistant to dexamethasone treatment.

REVIEWERS COMMENTS. Asthma is a significant cause of morbidity and death in the pediatric population, and steroid-resistant asthma is a particularly challenging asthma phenotype to manage. This study provides insight into a possible mechanism of steroid-resistant asthma, involving neutrophil recruitment into the lung tissues by TH17 cells in an IL-17–dependent pathway. Future research should be directed at determining whether the findings in this mouse model are applicable to humans and identifying patients with this asthma phenotype. If these findings prove applicable to humans, then TH17 cell- and IL-17–specific therapies may prove useful for patients with steroid-resistant asthma.

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DIAGNOSIS AND MANAGEMENT

Wheezing and Bronchial Hyper-responsiveness in Early Childhood as Predictors of Newly Diagnosed Asthma in Early Adulthood: A Longitudinal Birth-Cohort Study

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PURPOSE OF THE STUDY. To estimate the contributions of gender and early life factors to newly diagnosed and persistent asthma in young adults.

STUDY POPULATION. The study evaluated 849 enrollees of the Tucson Children’s Respiratory Study who had adult data at 22 years of age.

METHODS. The cohort was derived from all healthy infants born in Tucson, Arizona, between 1980 and 1984. Shortly after birth, the parents completed a questionnaire on demographic data and were instructed to see a collaborating pediatrician at the first sign of lower respiratory illness. Physician-diagnosed asthma or wheezing was assessed at 2, 3, 6, 8, 11, and 16 years of age. At 6 years of age, allergy skin-prick tests were performed for all participants, and cold air bronchial challenge was performed for participants with a history of lower respiratory illness. At 22 years of age, an in-depth evaluation was performed with questionnaires on asthma symptoms, asthma medication use, and smoking history. Allergy skin-prick tests and spirometry were performed for participants still living in the Tucson area.

RESULTS. Subjects with adult data at 22 years of age were more likely to have nonsmoking, nonminority parents with higher levels of education than were those without adult data. Of the 849 participants, 255 (30%) had asthma diagnosed at some time in their lives, 181 (22%) had active asthma, and 224 (26%) reported current smoking. Participants with inactive asthma had pre- and postbronchodilator spirometry results comparable to those of participants who never had asthma. Participants with newly diagnosed asthma had lower forced expiratory volume in 1 second/forced vital capacity ratios, which were not bronchodilator responsive. Factors associated with newly diagnosed asthma, chronic asthma, or shortness of breath with wheezing at 22 years of age included female gender, parental asthma, late-onset (>3 years of age) wheeze, persistent wheeze, *Alternaria* mold sensitivity at 6 years of age, cold air bronchial hyperresponsiveness, and reduced air flow rates at 6 years of age. Seventy percent of participants with current asthma and 63% with newly diagnosed asthma reported episodes of wheeze before 6 years of age. Male gender was a significant indicator of asthma remission by early adulthood. The combination of *Alternaria* sensitivity and cold air bronchial hyperresponsiveness at age 6 years and persistent wheeze at age 6 years were strong predictors of chronic asthma at age 22 years.

CONCLUSIONS. Children with transient early wheezing were at much less risk for chronic asthma that persisted through childhood or reappeared more intensely in early adult life, compared with children with persistent or late-onset wheezing. Women were twice as likely to have new asthma diagnosed between 16 and 22 years of age.

Predicting an Asthma Exacerbation in Children 2 to 5 Years of Age


PURPOSE OF THE STUDY. To identify symptoms and other factors that may be predictive of an asthma exacerbation in children 2 to 5 years of age.

STUDY POPULATION. Children 2 to 5 years of age who participated in a previous, double-blind, randomized, multicenter, parallel-group, placebo-controlled, 12-week study of 4 mg of montelukast for the treatment of persistent asthma.

METHODS. A posthoc analysis was performed with data collected on 689 patients. Caregivers provided twice-daily answers in a validated, asthma-specific, diary record of daytime symptoms (cough, wheeze, difficulty breathing, and activity limitation), nighttime cough symptoms, β₂-adrenergic receptor agonist use, and medical visits for worsening asthma. Scoring for daytime symptoms used a 6-point scale from 0 (no symptoms or limitations) through 5 (very severe symptoms or limitation) and scoring for nighttime cough used a 5-point scale from 0 (no nighttime cough) through 4 (coughed all night and disturbed the caregiver’s sleep). To identify predictors of an exacerbation (worsening symptoms that led to oral corticosteroid use, an unscheduled visit to a physician or emergency department, or hospitalization), information was analyzed by using general estimating equations with an exchangeable, within-subject, logarithmic odds ratio regression structure.

RESULTS. A total of 196 (28%) of the 689 patients enrolled had ≥1 asthma exacerbation during the study period, and 235 exacerbations occurred overall. Each of the...
diary symptoms and $\beta_2$-adrenergic receptor agonist use increased significantly, but at different rates, before an exacerbation. Only the combination of wheeze, daytime cough, and $\beta_2$-adrenergic receptor agonist use were predictive of an exacerbation. Overall, 149 (66.8%) of 223 exacerbations were predicted correctly 1 day before the exacerbation. The false-positive rate was 14.2%.

CONCLUSIONS. An imminent asthma exacerbation was predicted by a combination of increased cough, wheeze, and $\beta_2$-adrenergic receptor agonist use at night, although individual symptoms were not predictive.

REVIEWER COMMENTS. If earlier prediction of asthma exacerbations were possible, then earlier treatment and decreased severity and utilization of health care resources might result. This study provides some evidence that early prediction is possible. However, the study is limited by the lack of a standard definition for an asthma exacerbation in young children and the lack of access to some outcome measures, such as unscheduled visits and hospitalization exacerbation. The ability to predict exacerbations remains to be proved. Parental education is imperative in predicting exacerbations in young children.

Evaluation of Chronic Cough in Children

PURPOSE OF THE STUDY. To evaluate chronic cough in children in accordance with the 2006 American College of Chest Physicians (ACCP) guidelines.

STUDY POPULATION. The study included 108 children between 6 and 14 years of age who presented with a cough lasting $>$4 weeks.

METHODS. Using the algorithm suggested by the ACCP guidelines for chronic cough in children, a detailed history was obtained and a physical examination was completed. Patients were reevaluated at 2- to 4-week intervals. All patients underwent pulmonary function testing and chest radiography. Additional testing was performed as clinically indicated. Patients were classified into the following diagnostic categories: (1) asthma and asthma-like symptoms, (2) protracted bronchitis, (3) gastroesophageal reflux disease (GERD), (4) upper airway cough syndrome (UACS), (5) natural recovery, (6) bronchiectasis, (7) tuberculosis, and (8) Mycoplasma pneumoniae infection.

RESULTS. The most common causes of chronic cough in this age group were asthma plus asthma-like symptoms (25%), protracted bronchitis (23.4%), and UACS (formerly postnasal drip) (20.3%). GERD accounted for $<5\%$ of cases.

CONCLUSIONS. The authors concluded that ACCP guidelines for the management of chronic cough in children were effective. This study demonstrated the importance of the “watch, wait, and review” step. When therapy is initiated, the response to treatment should be evaluated at 2- to 4-week intervals, to prevent unnecessary evaluation of chronic cough. The causes of cough in children differ from the causes in adults. The evaluation of cough in children should include asthma, bronchitis, and UACS in the differential diagnosis. When treatment is initiated, a detailed investigation should be made for patients who do not respond to the treatment.

REVIEWERS COMMENTS. Chronic cough in children is a common problem, and the most common causes are slightly different from those in adults, for whom GERD is listed in the top 3 causes. This study, the authors concluded that GERD could be the result of cough and not just the cause. In this study, asthma and asthma-like symptoms were the most common cause. This may be attributable to the age of the participants. Previous studies in children included participants $<$2 years of age, for whom the diagnosis of asthma is more difficult. Observing and reevaluating children every 2 to 4 weeks when they present with chronic cough may decrease the need for extensive testing.

Severe Exacerbations in Children With Mild Asthma: Characterizing a Pediatric Phenotype

PURPOSE OF THE STUDY. To describe a population of children with mild baseline asthma who were admitted to the ICU with severe exacerbations.

STUDY POPULATION. A retrospective cohort study of 298 children with asthma (age: 2–18 years) who were admitted to the Connecticut Children’s Medical Center ICU with a severe asthma exacerbation between April 1997 and December 2006 was performed.

METHODS. Children were identified as having mild asthma if their disease was classified as intermittent or mild persistent according to current National Heart, Lung, and Blood Institute (NHLBI) guidelines; classifications of
baseline asthma status were updated to current terminology for patients who were prospectively identified before the recent revisions to the NHLBI guidelines. The validated Modified Pulmonary Index Score was used to assess illness severity. Data regarding demographic characteristics, severity of illness at presentation, types and durations of therapies received, and duration of hospitalization were collected retrospectively.

RESULTS. A total of 298 children with asthma were admitted to the ICU with severe exacerbations. Of those, 164 (55%) had previous mild intermittent or mild persistent asthma. These children, compared with children with moderate and severe persistent asthma, were noted to be younger (7.6 ± 3.9 vs 9.8 ± 4.6 years; \( P < .0001 \)) and less likely to have been admitted to the hospital for asthma previously (42% vs 77%; \( P < .0001 \)). In the mild asthma group, fewer Hispanic children (30% vs 47%; \( P = .003 \)) and more white children (42% vs 24%; \( P = .001 \)) were identified. Other demographic features were similar between the groups. No significant differences in the ICU length of stay, hospital length of stay, or therapies received existed between the 2 groups. Admission Modified Pulmonary Index Scores correlated closely with hospital length of stay. Thirteen children (8%) with mild asthma were intubated, which was fewer than those with moderate/severe persistent asthma (17%; \( P = .03 \)). The intubated children with mild asthma were younger (6.9 ± 4.7 vs 11.4 ± 4.1 years; \( P = .009 \)), less likely to be Hispanic, and less likely to have been previously intubated (\( P = .03 \)).

CONCLUSIONS. There was a significant subset of children with mild baseline asthma who developed severe exacerbations requiring ICU admission. These children were younger, were less likely to have a history of asthma-related admission, and had differences in race/ethnicity, compared with children with baseline moderate or severe asthmatic disease. These findings suggest that current classifications of pediatric asthma do not predict asthma phenotypes during acute exacerbations.

REVIEWERS COMMENTS. This study reveals a trend toward younger white, rather than Hispanic or black, children diagnosed with mild asthma (according to current NHLBI classification criteria) requiring ICU admission. In addition, almost 10% of children with mild asthma classification required intubation during hospitalization. This raises concerns regarding the poor predictive capacity of the current classification system in identifying children at risk for severe exacerbations.

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Modifiable Risk Factors for Suboptimal Control and Controller Medication Underuse Among Children With Asthma


PURPOSE OF THE STUDY. There were 2 objectives for the study. (1) to define the rates of suboptimal control and underuse of controller medication in children with asthma and (2) to characterize how parental behaviors relate to these patterns.

STUDY POPULATION. The study included 754 children 2 to 13 years of age with persistent asthma in a Medicaid plan and a large provider group.

METHODS. Telephone interviews were conducted with parents of participants to determine rates of suboptimal control and controller underuse. Suboptimal control was defined as ≥4 symptom days, ≥1 symptom night, or ≥4 albuterol use days in the previous 2 weeks. Controller underuse was defined as suboptimal control and parental report of < 6 days/week of inhaled steroid use.

RESULTS. There were 37% of children (280 of 754 children) with suboptimal control. This was more common in Hispanic children (51%) than in black (37%) or white (22%) children. Underuse of controller medication was documented for 133 children, 48% of those with suboptimal asthma control and 18% overall. Suboptimal control was related to modifiable factors, including low parental expectations for symptom control and concern about competing household responsibilities. Controller medication underuse was related to modifiable factors, including parental evaluation of asthma control in conflict with the National Heart, Lung, and Blood Institute guidelines and lack of a schedule for asthma medications.

CONCLUSIONS. The conclusion of the authors was that deficiencies in asthma control and controller medication use are associated with potentially modifiable parental beliefs, which seem to mediate racial/ethnic and socioeconomic disparities in suboptimal control and controller medication underuse.

REVIEWER COMMENTS. This study population included only insured children, and the findings may not be generalizable to uninsured populations. Another limitation is that the study depended on parental reports and 2-week recall of symptoms and medications. However, the implications from the findings are very important, that improvement in asthma control requires sensitivity in addressing parental beliefs and household concerns.

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Parenting Asthmatic Children: Identification of Parenting Challenges

PURPOSE OF THE STUDY. To identify the child behavior and asthma management tasks that parents report as being difficult to manage.

STUDY POPULATION. Cross-sectional cohort of 255 parents of children with asthma 2 to 10 years of age.

METHODS. Parents completed 5 online multidimensional questionnaires, that is, (1) Family Background Questionnaire, to assess family demographic features and socioeconomic status; (2) Strengths and Difficulties Questionnaire (SDQ), to identify children’s emotional and behavioral problems; (3) Parenting Scale, a 30-item questionnaire to measure dysfunctional discipline styles such as laxness, overreactivity, and verbosity; (4) Asthma Behavior Checklist (ABC), an instrument developed specifically for the study to assess 22 behaviors that parents with children with asthma often manage (eg. child refuses to take medication to school); and (5) Asthma Parent Tasks Checklist (APTC), an instrument designed for the current study to assess 17 asthma management tasks that parents often manage (eg. identifying child’s asthma triggers). Statistical analysis was performed by using 1-way analysis of variance.

RESULTS. On the basis of published cutoff values for SDQ-assessed total difficulties, parents rated their children as follows: 20.9% in the clinical range, 13.7% in the borderline range, and 65.5% in the normal range. Children with scores in the abnormal range on the SDQ had higher ABC extent scores than did children with scores in the normal range. Results for parenting and asthma behavior difficulties indicated low levels of dysfunctional parenting; however, a substantial minority (22.7%) of parents were rated in the clinical range. Parents whose total Parenting Scale scores placed them in the clinical range reported more asthma behavior difficulties, compared with those who scored in the nonclinical range.

CONCLUSIONS. An appropriate parenting intervention program needs to target behavior management skills, in addition to the application of these behavior management principles to asthma management. The ABC and APTC could be used in addition to parental asthma education to facilitate discussions with parents regarding the management of their child’s asthma and to allow health care professionals and parents to focus together on specific action plans. The ABC and APTC also could be used to evaluate the impact of implemented interventions.

REVIEWERS COMMENTS. Appropriate parenting interventions targeting basic behavior and asthma management skills and supplying tools for applying these behavior management principles are ideal. The authors recognize the concern of parents in entrusting their children’s schools and other caregivers, and research focused in this direction may provide increased confidence for parents and overall improvement in the quality of life for children with asthma.

Patterns of Asthma Control Perception in Adolescents: Associations With Psychosocial Functioning
Rhee H, Belyea MJ, Elward KS. J Asthma. 2008;45(7):600–606

PURPOSE OF THE STUDY. To identify and to describe the patterns of asthma control perception in relation to actual symptom reports in adolescents and to compare the group with accurate control perception with the group with inaccurate perception.

STUDY POPULATION. A group of 126 adolescents with asthma, 13 to 20 years of age, were interviewed prospectively.

METHODS. Patterns of control perception were constructed on the basis of participants’ ratings of their perceptions of asthma control and self-reported asthma symptoms by using latent class analysis. Analyses of variance and multinomial logistic regressions were computed for group comparisons.

RESULTS. Participants were classified into 4 groups according to the patterns of control perception. Accurate groups included those whose asthma was well controlled (62%) or poorly controlled (7%), and inaccurate groups included those with nighttime symptoms (25%) or daytime symptoms (6%). Minority participants (P < .001) and those with low socioeconomic status (P < .001) were more likely to be represented in the inaccurate group than were their counterparts. The well-controlled accurate group consistently reported higher levels of asthma-related knowledge (P = .02), more-positive attitudes toward asthma (P < .001), fewer barriers to self-management (P = .04), and higher quality of life (P < .001) than did the inaccurate group.

CONCLUSIONS. This study demonstrated that accuracy of asthma control perception could be classified into 4 categories on the basis of patterns of various asthma symptoms. Adolescents’ tendency toward underperception was evident. The inaccurate groups are at greater risk for psychosocial impairments. This study underscores the importance of an intervention that improves the accuracy of asthma control perception in adolescents while...
Effects of Improved Home Heating on Asthma in Community Dwelling Children: Randomised Controlled Trial

PURPOSE OF THE STUDY. To assess whether nonpolluting, more-effective home heating (heat pump, wood pellet burner, or flued gas) has a positive effect on the health of children with asthma.

STUDY POPULATION. A randomized, controlled trial of 409 children, 6 to 12 years of age, with doctor-diagnosed asthma was performed in the household setting in 5 areas in New Zealand.

METHODS. Nonpolluting, more-effective home heaters were randomly installed in the intervention houses. Outcome measurements were made during the winter months of 2005 (baseline) and were repeated after the intervention in the winter of 2006. The primary outcome was change in lung function (peak expiratory flow rate and forced expiratory volume in 1 second [FEV1]). The secondary outcomes were reported asthma symptoms, scores for lower respiratory tract symptoms from diaries, daily asthma drug use, health care utilization, and days of missed school. Indoor nitrogen dioxide levels were measured in the living room and 0.57°C (95% CI: 0.05–1.08°C; P = .001). In the child’s bedroom. Indoor nitrogen dioxide levels were significantly reduced in the intervention group, compared with the control group, in the living room (geometric mean: 8.5 vs 15.7 μg/m3; P < .001) and the child’s bedroom (7.3 vs 10.9 μg/m3; P < .001).

RESULTS. Of 409 households, 349 (85%) remained in the study and were randomly assigned, with 175 assigned to the intervention group and 174 to the control group. After the intervention, lung function tests showed nonsignificant improvement in daily FEV1 (difference in mean FEV1: 130.7 mL [95% confidence interval [CI]: −20.3 to 281.7 mL]; P = .09) and peak expiratory flow rate (difference in mean peak expiratory flow rate: 12.29 l/min [95% CI: −4.57 to 29.15 l/min]; P = .15). However, on the basis of parental reports and diaries, children in the intervention group had significant reductions in asthma symptoms and improved well-being, compared with the control group. They had fewer reports of poor health (adjusted odds ratio [OR]: 0.48 [95% CI: 0.31–0.74]; P < .001), less sleep disturbed by wheezing (OR: 0.55 [95% CI: 0.35–0.85]; P < .001), less dry cough at night (OR: 0.52 [95% CI: 0.32–0.83]; P = .01), and reduced scores for lower respiratory tract symptoms (OR: 0.77 [95% CI: 0.73–0.81]; P = .013). The intervention group also had 1.8 fewer days (95% CI: 0.11–3.13 days; P < .04) off school, 0.4 fewer visits (95% CI: 0.11–0.62 visits; P = .01) to a doctor for asthma, and 0.25 fewer visits (95% CI: 0.09–0.32 visits; P = .01) to a pharmacist for asthma than did the control group. Exposure to low temperatures was 50% less in the intervention group (95% CI: 0.49–1.93; P = .001). The mean temperature of the control households was lower than that of the intervention households by 1.10°C (95% CI: 0.54–1.67°C; P < .001) in the living room and 0.57°C (95% CI: 0.05–1.08°C; P = .001) in the child’s bedroom.

CONCLUSIONS. Installing nonpolluting, more-effective heating in the households of children with asthma did not significantly improve lung function but did significantly reduce symptoms of asthma, days off school, health care utilization, and exposure to nitrogen dioxide.

REVIEWERS COMMENTS. Asthma is aggravated by the outdoor and indoor environments. Indoor temperatures, damp, mold, and pollutants have been implicated as important factors. This study shows the impact of nonpolluting, home-heating systems on symptoms in children with asthma. In this randomized, controlled trial, significant improvements in frequency and severity of symptoms were noted and there were trends toward improved lung function. These trends toward improved health effects should increase public awareness of this intervention while additional studies are undertaken.
**Preliminary Findings**

Recent studies in the United States and Europe have shown that certain characteristics of atopy in the child and atopy and asthma in the parents were predictive of subsequent asthma, which led to the development of the Asthma Predictive Index. In the current study, cord blood immunoglobulin E levels, childhood eczema, and parental asthma history did not affect the negative associations of wheezing in the first few years with subsequent development of asthma. Wheezing at >4 years was associated with current asthma at age 6 to 7 years.

**Conclusions**

1. The Tucson study determined that certain characteristics of atopy in the child and atopy and asthma in the parents were predictive of subsequent asthma, which led to the development of the Asthma Predictive Index. In the current study, cord blood immunoglobulin E levels, childhood eczema, and parental asthma history did not affect the negative associations of wheezing in the first few years with subsequent development of asthma. Wheezing at >4 years was associated with current asthma at age 6 to 7 years.

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**Seasional Patterns in Health Care Use and Pharmaceutical Claims for Asthma Prescriptions for Preschool- and School-Aged Children**

Van Dole KB, Swern AS, Newcomb K, Nelsen L. *Ann Allergy Asthma Immunol.* 2009;102(3):198–204

**Purpose of the Study.** The goal of the study was to determine how seasonal patterns of asthma medication prescription claims relate to seasonal patterns of asthma-related health care use (outpatient visits, emergency department visits, and hospitalizations) for children.

**Study Population.** Data were collected for preschool-aged children (2–5 years of age) and school-aged children (6–12 years of age).

**Methods.** An ecological analysis of data from insurance claims records from 2002 through 2004 was conducted with a large US health care plan (United Healthcare) database. Patterns of health care use and estimates of prescription asthma controller and reliever use were determined. Controller medications were defined as inhaled corticosteroids, leukotriene receptor antagonists, and long-acting β2-adrenergic receptor agonists. Reliever medications were defined as short-acting β2-adrenergic receptor agonists only. Rates were constructed by week; deviations from annual mean rates were used to determine peaks in use.

**Results.** Rates of emergency department visits, outpatient visits, and hospitalizations were lowest during summer months; rates increased beginning in September, peaking in October or November. Asthma controller and reliever medication claims increased beginning in September, peaking in December.

**Conclusions.** The data suggest that children who reduce their asthma medications during the summer do not resume taking asthma medications until symptoms of asthma worsen. The summer hiatus and other factors may contribute to seasonal increases in health care use.
Management of Asthma Based on Exhaled Nitric Oxide in Addition to Guideline-Based Treatment for Inner-City Adolescents and Young Adults: A Randomised Controlled Trial


PURPOSE OF THE STUDY. To determine whether the use of exhaled nitric oxide (NO) measurements to modify asthma treatment regimens improves asthma control when used as an adjunct to management based on national asthma care guidelines.

STUDY POPULATION. A randomized, double-blind, parallel-group trial at 10 centers in the United States monitored a total of 546 inner-city subjects, 12 to 20 years of age, with poorly controlled asthma.

METHODS. Physician assessment was performed every 6 to 8 weeks for 46 weeks, during which patients were evaluated for asthma symptoms, pulmonary function, and exhaled NO, a marker of airway inflammation. At each visit, treatment was stepped up or down on the basis of theNational Asthma Education and Prevention Program (NAEPP) asthma care guidelines for the control group or the NAEPP guidelines plus measurements of fraction of exhaled NO (FeNO) for the NO group.

RESULTS. There was no difference between the control group and the NO group with respect to asthma symptoms, pulmonary function, or asthma exacerbations. By the end of the study, patients in the NO group were receiving higher doses of inhaled corticosteroids (difference in fluticasone doses: 119 μg; P = .001) than were those in the control group, with a greater number receiving long-acting β₂-adrenergic receptor agonists. Adverse events did not differ between the treatment groups.

CONCLUSIONS. The addition of FeNO as an indicator of asthma control resulted in higher doses of inhaled corticosteroids, without clinically important improvements in symptomatic asthma control.

REVIEWERS COMMENTS. Because asthma symptoms and exacerbations are linked to underlying airway inflammation, it seems that using measurements of biomarkers that are indicators of airway inflammation (FeNO) to direct asthma management would improve asthma control. However, this study showed that use of current NAEPP guidelines for asthma treatment alone provided good asthma control for inner-city adolescents and young adults. The addition of FeNO measurements resulted in higher doses of inhaled corticosteroids and long-acting β₂-adrenergic receptor agonists, without producing additional improvements in asthma symptoms, lung function, or need for health care.

MEDICAL THERAPIES

Episodic Use of an Inhaled Corticosteroid or Leukotriene Receptor Antagonist in Preschool Children With Moderate-To-Severe Intermittent Wheezing


PURPOSE OF THE STUDY. To examine the effectiveness of episodic use of an inhaled corticosteroid (ICS) or leukotriene receptor antagonist (LTRA) in preschool-aged children with moderate-to-severe intermittent wheezing associated with respiratory tract illness (RTI).

STUDY POPULATION. Children 12 to 59 months of age with ≥2 episodes of wheezing with RTI in the previous year and either 2 urgent care visits for wheezing, 2 wheezing...
episodes requiring oral steroid treatment (<6 courses), or 1 episode requiring urgent care and oral steroid treatment.

METHODS. The study design was a randomized, double-blind, placebo-controlled trial, with children assigned randomly to 1 of 3 treatment groups with instructions to treat for 7 days at the onset of each RTI-associated symptom set during a 12-month period: (1) budesonide suspension (1 mg twice daily) plus LTRA placebo, (2) montelukast (4 mg daily) plus ICS placebo, or (3) ICS placebo plus LTRA placebo. All groups received albuterol 4 times per day for the first 48 hours of illness plus as-needed dosing. Orally administered steroids were available if needed, but other asthma medications were prohibited. Symptom/treatment diaries were maintained, and clinic/telephone follow-up evaluations were conducted. The primary outcome was the proportion of episode-free days (EFDs). Secondary outcomes included severity of lower respiratory tract symptoms in the 14-day period after initiation of treatment, time to initiation and number of orally administered steroids, number of wheezing episodes, days missed from day care and work, caregiver quality of life, unscheduled visits because of acute wheezing, and linear growth.

RESULTS. Two hundred thirty-eight children were randomly assigned and were well matched with respect to baseline characteristics. Adherence to therapy was similar between the groups. EFDs did not differ among the 3 treatment groups (adjusted EFD mean: budesonide: 76%; montelukast: 73%; placebo: 74%). Relative to placebo, there were significant reductions in trouble breathing (budesonide: 37.5%; montelukast: 36.8%; \( P = .003 \)) and interference with activity (budesonide: 31.9%; \( P = .01 \); montelukast: 39.6%; \( P = .001 \)). Wheezing scores were reduced with montelukast (33.5%; \( P = .02 \)) but not with budesonide (24.6%; \( P = .09 \)). Overall, total symptom scores were reduced with montelukast (29.6%; \( P = .006 \)) and budesonide (24.6%; \( P = .02 \)). Among participants with positive asthma predictive index status, both budesonide and montelukast significantly reduced scores for trouble breathing (budesonide: 48.0%; \( P = .001 \); montelukast: 40.3%; \( P = .007 \)) and activity interference (budesonide: 43.6%; montelukast: 53.7%; \( P < .001 \)); only montelukast reduced wheezing (\( P = .049 \)). Similar findings were seen for children with previous oral steroid therapy use.

CONCLUSIONS. For preschool-aged children with moderate-to-severe intermittent wheezing, episodic use of either budesonide or montelukast early in RTIs did not increase the proportion of EFDs. However episodic use of an ICS or LTRA decreased symptom burden, particularly for those with risk factors for asthma or greater illness severity (use of oral corticosteroid therapy).

REVIEWERS COMMENTS. This study was conducted to address an important clinical question: is the episodic use of an ICS or LTRA effective in decreasing the morbidity associated with severe intermittent wheezing in preschool-aged children? Using a unique study design, the authors demonstrated benefit for children with symptoms and treatment predictive of asthma, indicating consideration for the early use of antiinflammatory medications. Additional study is needed to address this important question fully.
and 1.58 exacerbations in group 3). Three patients in group 1 and 9 patients in group 2 were withdrawn because of asthma deterioration after 6 months of treatment. The number of asthma-free days did not differ between groups 1 and 2 but remained better than in group 3. Growth velocity was normalized in groups 1 and 2.

CONCLUSIONS. Regular use of budesonide afforded better asthma control but had a more systemic effect than did as-needed use of budesonide.

REVIEWER COMMENTS. It is not a surprise that the inhaled corticosteroids achieved better asthma control than did cromolyn and are the preferred medications. The question addressed by this study is whether inhaled corticosteroids can be used as needed versus continuously. Although these 2 approaches did not differ in lung function or number of asthma-free days, the continuous-treatment group had significantly fewer exacerbations. An accompanying editorial (Pedersen S. Arch Dis Child. 2008;93[8]:644–645) asks, “Do the benefits of daily inhaled steroid treatment of mild asthma outweigh the risks?” and answers in the affirmative, noting that regular use is safe (6 of 7 studies found no long-term effects on growth), as well as more effective and less expensive than any other treatment.

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Preemptive Use of High-Dose Fluticasone for Virus-Induced Wheezing in Young Children

PURPOSE OF THE STUDY. To examine the efficacy and safety of preemptive, high-dose fluticasone treatment in reducing the severity of recurrent virus-induced wheezing in children.

STUDY POPULATION. Children between 1 and 6 years of age (N = 129) with moderate-to-severe, virus-induced wheezing were included. The investigators tried to exclude subjects with sensitization to aeroallergens, but 7% of the randomly assigned children developed symptoms of persistent or atopic asthma during the study period.

METHODS. The subjects received 750 μg of fluticasone propionate or placebo twice daily, beginning at the onset of an upper respiratory infection and continuing for a maximum of 10 days, over a period of 6 to 12 months. The primary outcome measured was the use of rescue oral steroid treatment. Secondary outcomes included symptoms, use of β₂-adrenergic receptor agonists, acute care visits, hospitalizations, discontinuation of study drug administration, changes in growth and bone mineral density, basal cortisol level, and adverse events.

RESULTS. Over a median period of 40 weeks, 8% of upper respiratory infections in the fluticasone group led to systemic steroid treatment, compared with 18% in the placebo group (odds ratio: 0.49). However, children treated with fluticasone, compared with the placebo group, had smaller gains in height (6.23 ± 2.62 vs 6.56 ± 2.90 cm) and weight (1.53 ± 1.17 vs 2.17 ± 1.79 kg). There were no significant differences between the groups in basal cortisol levels, bone mineral density, or adverse events.

CONCLUSIONS. In preschool-aged children with moderate-to-severe, virus-induced wheezing, preemptive treatment with high-dose fluticasone, compared with placebo, reduced the use of rescue oral steroid treatment. High-dose fluticasone treatment, however, was associated with smaller gains in height and weight. Therefore, the authors concluded that this approach should not be adopted in clinical practice until long-term adverse effects are clarified.

REVIEWER COMMENTS. The investigators showed, on one hand, improvement in the need for oral steroid treatment for children treated with high-dose fluticasone but, on the other hand, smaller gains in height and weight for these patients. The question for the rest of us is how to incorporate these new data into clinical practice. For example, the dose of fluticasone that was used was quite substantial for small children. Was this dose on the flat part of the dose-response curve for corticosteroids? Would a smaller dose give the same benefit without the detriment? Also, how do these data apply to children with clinical allergy or risk factors for allergy?

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Glen Ellyn, IL

Effect of Long-term Corticosteroid Use on Bone Mineral Density in Children: A Prospective Longitudinal Assessment in the Childhood Asthma Management Program (CAMP) Study
Kelly HW, Van Natta ML, Covar RA, et al.
Pediatrics. 2008;122(1). Available at: www.pediatrics.org/cgi/content/full/122/1/e53

PURPOSE OF THE STUDY. To evaluate the effects of multiple short courses of oral corticosteroid treatment and long-
term inhaled corticosteroid (ICS) treatment on bone mineral accretion over a period of years.

**STUDY POPULATION.** Cohort follow-up study for a median of 7 years with 877 children 5 to 12 years of age who had mild-to-moderate asthma and initially were randomly assigned in the Childhood Asthma Management Program.

**METHODS.** Serial dual-energy x-ray absorptiometry scans of the lumbar spine to assess bone mineral density were performed for all patients. Annual bone mineral accretion was calculated for 531 boys and 346 girls.

**RESULTS.** Oral corticosteroid bursts produced dose-dependent reductions in bone mineral accretion (0.052, 0.049, and 0.046 g/cm² per year with 0, 1–4, and ≥5 courses, respectively) and increases in the risk for osteopenia (10%, 14%, and 21%, respectively) in boys but not girls. Cumulative ICS use was associated with a small decrease in bone mineral accretion in boys but not girls but no increased risk for osteopenia.

**CONCLUSIONS.** Multiple oral corticosteroid bursts over a period of years can produce dose-dependent reductions in bone mineral accretion and increased risk for osteopenia in children with asthma. ICS use has the potential to reduce bone mineral accretion in male children progressing through puberty, but this risk is likely to be outweighed by the ability to reduce the amounts of orally administered corticosteroids used for these children.

**REVIEWERS COMMENTS.** One of the goals for prescribing an ICS is to decrease the chances of acute exacerbations, which often require oral corticosteroid treatment for asthma control. The findings of this long-term treatment study highlight one of the several reasons to strive to minimize repeat doses of orally administered corticosteroid in children, especially during times of peak bone mineral accretion. Interestingly, the effects of decreased bone mineral accretion with orally administered corticosteroid and ICS were not seen for girls in this study. Girls might have been less susceptible because of estrogen effects and/or being on the flat portion of their bone mineral accretion curve during the study period, but this topic will require additional study. The finding of no increased risk for osteopenia with regular use of ICS is somewhat reassuring, although most of the children in this study were receiving low doses of ICS, and additional studies with children receiving medium or high doses ICS are warranted.

**Long-term Budesonide or Nedocromil Treatment, Once Discontinued, Does Not Alter the Course of Mild to Moderate Asthma in Children and Adolescents**

**CONCLUSIONS.** During the posttrial follow-up period, asthma morbidity and medication use were not appreciably affected by earlier long-term use of budesonide or nedocromil. The reductions in prednisone course and urgent care visits seen in the budesonide group do not seem relevant, on the basis of the overall rates of these events in all groups.
REVIEWER COMMENTS. Inhaled corticosteroids are safe and effective for long-term control of asthma, but this study shows that continued benefit requires ongoing use. We must continue to consider factors such as symptoms, spirometry findings, and biochemical markers and to use our clinical judgment to determine which children will benefit from continued treatment. It is hoped that future phenotype and genotype studies will shed more light on this issue.

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Oral Prednisolone for Preschool Children With Acute Virus-Induced Wheezing
Panickar J, Lakhanpaul M, Lambert PC, et al.

PURPOSE OF THE STUDY. To determine the efficacy of a short course of oral prednisolone treatment for wheezing induced by upper respiratory viral infections in preschool-aged children.

STUDY POPULATION. The study included 700 children between 10 and 60 months of age who were hospitalized at 3 different centers in England with attacks of wheezing associated, by the judgment of an examining physician, with viral infection. Most of these patients did not have the classic phenotype of atopic asthma.

METHODS. This was a randomized, double-blind, placebo-controlled trial. In the nonplacebo arm of the study, children 10 to 24 months of age received 5 days of prednisolone treatment at 10 mg/day, whereas the older children received 20 mg/day. The primary outcome was duration of hospitalization. Secondary outcomes were Preschool Respiratory Assessment Measure scores, use of albuterol, and 7-day symptom scores.

RESULTS. There was no significant difference in the duration of hospitalization between the placebo group and the prednisolone group (13.9 vs 11.0 hours) or in the interval between hospital admission and signoff for discharge by a physician. There was also no significant difference in any of the secondary outcomes or in the number of adverse events.

CONCLUSIONS. In preschool-aged children presenting to a hospital with mild-to-moderate wheezing associated with a viral infection, oral prednisolone treatment was not superior to placebo.

REVIEWER COMMENTS. I fondly remember my numerous rotations in the emergency department during my residency at St Louis Children’s Hospital, when one of my goals was to quickly assess wheezing children and to just as quickly give them oral steroids. This report suggests that we should think twice before giving that oral steroid. However, it must be pointed out that the dose of prednisolone used in the trial was substantially less than 2 mg/kg and the lack of effect may reflect, in part, the dose. Furthermore, most of the patients in this trial did not have atopy. Wheezing children with allergies do respond to oral corticosteroid treatment. This trial does raise very important questions about commonly accepted norms of treatment, but “real-world” practice may be different.

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Efficacy and Safety of 5–Grass-Pollen Sublingual Immunotherapy Tablets in Pediatric Allergic Rhinoconjunctivitis


PURPOSE OF THE STUDY. To determine the efficacy and safety of a 300-index of reactivity sublingual immunotherapy (SLIT) tablet for children with allergic rhinoconjunctivitis.

STUDY POPULATION. Subjects were 278 children (age: 5–14 years) with seasonal grass pollen-induced allergic rhinoconjunctivitis for ≥2 years. Allergy was confirmed by a timothy grass-specific immunoglobulin E (IgE) level of at least class 2 and a wheal diameter of >3 mm in a skin-prick test containing 5 grass pollens included in the SLIT tablet (orchard, meadow, perennial rye, sweet vernal, and timothy grasses). Patients who were sensitized to other allergens present during the grass pollen season, patients who had previously received immunotherapy for grass pollen allergy, and patients with asthma who were receiving medications other than β2-adrenergic receptor agonists were excluded.

METHODS. This was a randomized, multicenter, double-blind, placebo-controlled trial conducted in 29 centers in 5 European countries. Patients received daily dosing with either the SLIT tablet or placebo beginning 4 months before and continuing throughout the grass pollen season. The primary outcome was efficacy of treatment, as assessed with the Rhinoconjunctivitis Total Symptom Score, an 18-point scale using 6 common rhinoconjunctivitis symptoms (nasal pruritus, nasal congestion, sneezing, rhinorrhea, ocular pruritus, and watery eyes) scored from 0 to 3 on the basis of severity. Daily symptoms and adverse events were recorded 1 month before and throughout the pollen season. Rescue medication use was scored from 1 to 3 on the basis of the use of antihistamines, nasally administered corticosteroids, or orally administered corticosteroids. Serum levels of IgG₄ and IgE specific for grass pollen allergens were measured before and at the end of the study.

RESULTS. A total of 278 children received either a SLIT tablet or placebo. The Rhinoconjunctivitis Total Symptom Scores showed benefit corresponding to mean and median improvements across all 6 categories of 28% and 39.3%, respectively, for the SLIT tablet over placebo (P = .01). Significant improvements in rescue medication scores (P = .0064), corresponding to mean and median improvements of 24.1% and 48.7%, respectively, and reductions in symptom scores (P < .038) were seen for the active group, compared with the placebo group. A threefold increase in grass-specific IgG₄ levels was seen for the active group, with little change for the placebo group. Changes in grass-specific IgE levels were similar between the groups. Adherence to therapy was similar between the groups (placebo: 95%; active: 94%). A total of 902 treatment-associated adverse events were noted (active: 84.9%; placebo: 82%), with most being mild to moderate in severity. Nine subjects withdrew from the study because of adverse events, including 7 in the treatment group and 2 in the placebo group.

CONCLUSIONS. Study data demonstrate that a grass pollen SLIT tablet is effective and safe in decreasing seasonal symptoms in children with allergic rhinoconjunctivitis.

The Safety of Sublingual Immunotherapy With One or Multiple Pollen Allergens in Children


PURPOSE OF THE STUDY. To evaluate the rate and type of adverse events experienced by children receiving sublingual immunotherapy (SLIT) for pollen allergy with either single or multiple allergen extracts.

STUDY POPULATION. Prospective postmarketing survey of 433 children receiving SLIT for respiratory allergies attributable to pollens.

METHODS. Consecutive children with respiratory allergies attributable to pollens who were receiving SLIT with multiple or single allergens were enrolled. Parents recorded adverse events (eye symptoms, rhinitis/ear itching, asthma, oral itching/swelling, nausea, vomiting, abdominal pain, diarrhea, urticaria, angioedema, and anaphylaxis) on a diary card. The adverse events were graded as mild, moderate, or severe.

RESULTS. Four hundred thirty-three children (male: n = 285; age range: 3–18 years) receiving SLIT were surveyed. Of them, 179 received a single allergen extract and 254 received multiple allergens. The total number of doses given was 40 169 (17 143 with single allergen). Overall, 178 adverse events were reported. Of those, 76 occurred in children receiving a single allergen extract (42.46% of patients; 4.43 of 1000 doses) and 102 in children receiving multiple allergens (40.3% of patients;
4.42 of 1000 doses; not significant). A total of 165 episodes (92.5%) were mild and self-resolving, distributed equally in the 2 groups. In 13 cases, the events were judged to be of moderate severity and medical advice was required. Three patients discontinued SLIT, despite the local adverse effects being mild. No emergency treatment was required.

CONCLUSIONS. The use of multiple allergens, compared with single allergens, for SLIT does not increase the rate of adverse events in children.

REVIEWERS COMMENTS. Although it is not commercially available in the United States, SLIT for pollen allergy has gained widespread acceptance in Europe, and evidence supporting its safety and efficacy is accumulating. The promise of SLIT is that it might provide a safer and more-convenient alternative to subcutaneous immunotherapy while maintaining efficacy. Much of the literature supporting its use has involved single allergen extracts, and recent case reports described anaphylaxis with multiple-allergen SLIT. This study, which did not evaluate efficacy, addressed the question of whether the use of multiple allergen extracts for SLIT is safe in children. In this study, the authors did not find any serious adverse events in children using either single or multiple allergen extracts. Their survey involved a limited number of patients and, although SLIT seems to be safe for children, the possibility of anaphylaxis with pollen SLIT cannot be excluded on the basis of these results.

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Safety and Immunogenicity of a Cluster Specific Immunotherapy in Children With Bronchial Asthma and Mite Allergy
Int Arch Allergy Immunol. 2009;148(3):251–260

PURPOSE OF THE STUDY. The authors evaluated whether cluster specific immunotherapy (SIT), which involves rapid allergen desensitization over a shorter time, compared with standard SIT, could safely and effectively desensitize children with allergic asthma attributable to house dust mites.

STUDY POPULATION. Children with asthma (N = 34; age: 6–18 years) with evidence of house dust mite allergies were randomly assigned to receive either cluster or standard SIT.

METHODS. Twelve individuals received standard SIT, which allowed for maintenance doses to be reached after 14 weeks of injections. The rest received multiple increasing doses per treatment day, to reach maintenance doses in 6 weeks according to the cluster SIT schedule. Immunotolerance was measured with specific immunoglobulin G (IgG) and IgG4 levels for house dust mite, antibody-blocking properties on basophil activities, and T-cell subset transcription factors (Foxp3, T-bet, and GATA-3) at weeks 1, 8, and 16.

RESULTS. Initially, cluster SIT involved 3 injections at increasing doses per treatment day up to week 4, but 5 subjects developed systemic adverse effects (mainly coughing); therefore, at week 4, the regimen was changed to 2 injections per treatment day. With that, the authors found no significant differences in local (54.2% vs 53%) and systemic (3.5% vs 4.6%) adverse effects between the cluster and standard SIT groups. The most common local adverse effects were redness and swelling <5 cm in diameter. Systemic reactions were all respiratory (cough and dyspnea), and no anaphylaxis occurred. In the cluster SIT group, serum levels of specific IgG for dust mites (< .001) and specific IgG4 for dust mites (< .001) significantly increased after 8 weeks, whereas such changes required 12 weeks in the group receiving standard SIT. In vitro basophil stimulation showed a significant decrease in cysteinyl leukotriene release in the cluster SIT group at 8 weeks; this was not reached in the standard SIT group until the 16-week time point. CD63 expression in both groups was decreased at 8 weeks. There were no significant differences in expression of Foxp3, T-bet, or GATA-3 between the 2 groups.

CONCLUSIONS. Cluster SIT was safe and showed more-rapid induction of specific immunotolerance in children, compared with conventional SIT.

REVIEWER COMMENTS. Building immunotolerance to allergens through immunotherapy (more commonly known as allergy shots) is effective but can be very time-consuming. The ideal schedule would be fast and efficacious, with minimal risk of adverse effects. The authors indicate that cluster dust mite SIT is a safe alternative for children, and they note that markers such as increased levels of specific IgG suggest that immunotolerance is being achieved. This is promising news for patients who are reluctant to undergo extensive, prolonged, immunotherapy protocols but need an alternative therapeutic option because of complications such as allergic asthma and/or poor responses to allergy medications. However, cluster SIT is not without adverse effects, and immunotherapy should always be conducted under the care of qualified physicians. Future studies should investigate the effectiveness of cluster SIT in managing allergy and asthma symptoms, as well as the possibility for step-down asthma therapy.

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Primary and Secondary Immunodeficiency

Pyogenic Bacterial Infections in Humans With MyD88 Deficiency

PURPOSE OF THE STUDY. Myeloid differentiation protein 88 (MyD88) is a key downstream adapter for receptors of the innate immune system, including most Toll-like receptors (TLRs) and interleukin 1 receptors (IL-1Rs). MyD88 deficiency in mice leads to susceptibility to a broad range of pathogens, and the goal of this study was to determine whether there are children with recurrent infections who have a deficiency in MyD88.

STUDY POPULATION. Nine children with MyD88 deficiency were identified from those evaluated for recurrent infections in immunodeficiency clinics in several different tertiary care centers.

METHODS. Fibroblasts, peripheral blood mononuclear cells, and Epstein-Barr virus-transformed B cell lines were evaluated with a number of molecular techniques, to evaluate responsiveness to stimulation via MyD88-dependent pathways such as IL-1Rs and multiple TLRs. Genetic analyses were also performed for patients and family members.

RESULTS. Nine children with autosomal recessive MyD88 deficiency suffered from life-threatening, often recurrent, pyogenic bacterial infections, including Streptococcus pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa. However, these patients were otherwise healthy, with normal resistance to other microbes. Their clinical status improved with age, but not because of any cellular leakiness in MyD88 deficiency. Cells from affected subjects were not responsive to IL-1R or TLR stimulation, and this responsiveness was restored by transfecting MyD88-deficient fibroblasts from the patients with a normal copy of the gene (complementary DNA). Genetic analysis revealed several defects associated with loss of function.

CONCLUSIONS. The authors conclude that MyD88-dependent TLRs and IL-1R are essential for protective immunity to a small number of pyogenic bacteria but are redundant for host defenses to most natural infections.

REVIEWER COMMENTS. There has been an explosion in information describing the innate immune system. The primary purpose of the innate immune system is to recognize microbial components. One major mechanism involves the binding of pathogen-associated molecules (eg, endotoxin or bacterial DNA) to innate immune receptors such as the TLR group. These receptors, which were first discovered in fruit flies, initiate intracellular signaling pathways that direct the synthesis of a wide variety of cytokines and antimicrobial pathways. MyD88 is a particularly important because it is involved in several TLR signaling pathways. These findings identify a specific pattern of increased bacterial infections associated with MyD88 deficiency. One of the advantages of identifying this disorder is that the clinical course improves with time, perhaps because elements of the adaptive immune system can compensate for the defect in innate immunity. In addition, now that the genetic defect is known, family members of affected individuals can be screened. Treatment is currently limited to supportive care, but identification of the molecular defect raises the possibility that specific therapies for MyD88 deficiency will be developed in the future.

Common Variable Immunodeficiency: 20-Yr Experience at a Single Centre

PURPOSE OF THE STUDY. To describe and to classify children with common variable immunodeficiency (CVID) according to presentation, familial incidence, infections, and memory B (MB) cell classification.

STUDY POPULATION. Participants were children <18 years of age with CVID (N = 22) at a National Health Service referral center for immunodeficiency in Barcelona, Spain.

METHODS. A retrospective chart review was used to obtain clinical and immunologic data for pediatric patients with CVID monitored between 1985 and 2005. Clinical data included documentation of infections, onset of allergic diseases, autoimmune diseases, bronchiectasis, or cancer, and familial cases of CVID and other primary immunodeficiencies. Immunologic data included immunoglobulin levels, lymphocyte subsets, and classification of MB cells in patients with >2% CD19+ cells, to determine whether they were naive or mature. Patients with normal MB cells were classified as MB2, those with low MB cells but normal nonswitched MB cells were classified as MB1, and those with no MB cells were classified MB0.

RESULTS. The median age at diagnosis was 7.8 years (range: 2.5–16 years), with the exception of 1 outlier who was diagnosed at 6 months of age on the basis of family history and infectious manifestations. There were 15 boys and 7 girls, and follow-up periods ranged from 1 to 18 years. Infections were the most common manifes-
tations before diagnosis, with respiratory and gastrointestinal symptoms being the most common. Infection rates improved with γ-globulin replacement therapy. Bronchiectasis secondary to respiratory infections was present in 7 of 22 patients and was the presenting finding for 5 of 7 patients. Allergy was diagnosed in 11 of 22 patients, but only 3 patients had positive specific allergen prick test results. CVID was diagnosed in 3 girls after they were found to have an autoimmune disease, which delayed the diagnosis for 1 patient who subsequently developed severe lung disease. Four patients had other family members with CVID or other primary immunodeficiency. Immunoglobulin G (IgG) levels (range: 80–552 mg/dL; median: 332 mg/dL) at the time of diagnosis did not correlate with the severity of clinical manifestations in children. Although results were not statistically significant, patients without MB cells (MB0 group) had more-severe complications, including bronchiectasis, persistent positive culture results, or autoimmune manifestations, compared with MB2 and MB1 groups.

CONCLUSIONS. Early diagnosis and treatment are important for patients with CVID. IgG levels at diagnosis did not correlate with the severity of clinical manifestations in pediatric patients with CVID; however, there was a trend suggesting that lack of MB cells might correlate with clinical severity and outcomes.

REVIEWERS’ COMMENTS. Contrary to findings among adult patients with CVID, IgG levels did not correlate with disease severity among children with CVID. Bronchiectasis was diagnosed in one third of pediatric patients with CVID and presented as early as 2.5 years of age. Providers should consider CVID in the differential diagnosis for young children with recurrent infections. The authors were able to demonstrate that MB cell classification correlates with the severity of clinical manifestations and may be an important marker to aid in the determination of prognoses for patients with CVID in the future.

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

PURPOSE OF THE STUDY. To investigate the long-term outcome of gene therapy for severe combined immunodeficiency (SCID) attributable to the lack of adenosine deaminase (ADA), a fatal disorder of purine metabolism and immunodeficiency.

STUDY POPULATION. The study evaluated 10 children with SCID attributable to ADA deficiency who lacked a HLA-identical sibling donor. These patients had early manifestations of the deficiency (median age: 2 months) and underwent gene therapy at a median age of 1.7 years (range: 0.6–5.6 years).

METHODS. After nonmyeloablative conditioning with busulfan, the subjects received infusions of autologous CD34+ bone marrow cells that had been transduced with a retroviral vector containing the ADA gene. Enzyme-replacement therapy polyethylene glycol-modified bovine ADA (PEG-ADA) was not given after infusion of the cells.

RESULTS. All patients were alive after a median follow-up period of 4.0 years. Transduced hematopoietic stem cells had stably engrafted and differentiated into myeloid cells containing ADA and lymphoid cells. Eight patients did not require enzyme-replacement therapy, their blood cells continued to express ADA, and they had no signs of defective detoxification of purine metabolites. Nine patients had immune reconstitution with increases in T-cell counts and normalization of T-cell function. In the 5 patients for whom intravenous immunoglobulin replacement was discontinued, antigen-specific antibody responses were elicited. Serious adverse events included prolonged neutropenia (2 patients), hypertension (1 patient), central venous catheter-related infections (2 patients), Epstein-Barr virus reactivation (1 patient), and autoimmune hepatitis (1 patient).

CONCLUSIONS. Gene therapy, combined with reduced-intensity conditioning, is a safe, effective treatment for SCID in patients with ADA deficiency.

REVIEWER COMMENTS. This group previously reported gene therapy for ADA deficiency in 2 patients, and this article includes the long-term outcomes of those patients as well as 8 others. Because the mortality rates for patients with ADA deficiency who receive transplants from unrelated or haploidentical donors are quite high, this report represents a significant advance. Because, with gene therapy for ADA deficiency, there is less selective pressure for the survival of stem cells that may have vector integrations that may lead to activation of oncogenes, it is less likely that these patients will experience the T-cell lymphoproliferative syndrome that affected some of the patients in the previously reported trials of gene therapy for X-linked SCID. It is hoped that the principles learned in these trials of gene therapy for children affected with SCID will be used in the further development of gene therapy for these and other genetic diseases.
Cutting Edge: Unusual NK Cell Responses to HIV-1 Peptides Are Associated With Protection Against Maternal-Infant Transmission of HIV-1
Tiemessen CT, Shalekoff S, Meddows-Taylor S, et al.

PURPOSE OF THE STUDY. To investigate the role of specific T cell responses in maternal-fetal HIV-1 transmission.

METHODS. CD3⁺ cell responses to HIV-1 peptide were measured in HIV-infected mothers and their infants at birth and at 6 to 10 weeks after delivery. Samples from the mother-child cohort were stimulated with HIV-1 synthetic peptides in pools representing Gag, Pol, Nef, envelope, and regulatory protein regions. A positive peptide-induced CD3⁺ response was defined as >3% of cells expressing cytokine at a level at least twofold above background levels. Additional HIV-infected women were recruited to determine whether CD3⁺ HIV-responding cells expressed markers for B cells, monocytes, T cells, or natural killer (NK) cells.

RESULTS. In the cohort of infected mothers, 54% and 22% had CD3⁺ responses to envelope and regulatory peptides, respectively. These same regions were targeted to a lesser degree in their infants (21% and 5% had CD3⁺ responses to envelope and regulatory peptides, respectively). Twenty-eight (57%) of 49 nontransmitting mothers and 13 (30%) of 44 exposed uninfected infants had detectable, HIV-specific, CD3⁺ responses. In comparison, 1 (7%) of 15 transmitting mothers and 1 (6%) of 18 infected infants had these responses. When both the mother and the infant had HIV-specific CD3⁺ responses, none of the infants became infected. One of the 22 responder mothers with a nonresponder infant transmitted HIV to her infant, and 2 of the nonresponder mothers with responder infants transmitted HIV to their infants. HIV-specific CD3⁺ cells were identified as NK cells on the basis of cell surface markers.

CONCLUSIONS. Mothers and infants who have CD3⁺ NK cells that respond to HIV-1 peptides are substantially less likely to transmit and to acquire infection, respectively. CD3⁺ NK cells respond with high specificity and strength to HIV-1 peptides from envelope and regulatory protein regions. This finding highlights the importance of innate immunity in preventing maternal-fetal transmission of HIV-1.

REVIEWERS COMMENTS. Significant research has been conducted to find ways to reduce the risk of maternal-fetal transmission of HIV-1 infection. These interventions have been very successful, with transmission rates as low as 5% in developed countries. This article describes the immune responses seen in HIV-positive mothers and HIV-exposed infants and offers a possible marker for transmission risk. Although future studies need to be conducted, it is possible not only that this robust immune response to specific HIV-1 proteins may serve as a predictor of possible vertical transmission but also that a decrease in these cell numbers may serve as a marker of disease progression. In addition, the HIV-1-specific CD3⁺ cell population may serve as a possible target for future immunotherapy for HIV infection.

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T Cell-Specific siRNA Delivery Suppresses HIV-1 Infection in Humanized Mice

PURPOSE OF THE STUDY. Since the discovery of RNA interference within mammalian cells in 2001, RNA interference has become a significant bench research tool and presents a new therapeutic modality against viral infections and cancer. The purpose of this study was to determine whether a novel method for delivery of small interfering RNAs (siRNAs) to T cells can suppress HIV viral infection.

STUDY POPULATION. A humanized mouse model of AIDS was used to demonstrate in vivo effects.

METHODS. A CD7-specific antibody conjugated to a peptide was used to deliver siRNA to target cells in mice reconstituted with human lymphocytes or CD34⁺ stem cells. Anti–chemokine receptor 5 (viral coreceptor) complexed with antiviral siRNAs was also used in HIV-infected mice.

RESULTS. Treatment controlled viral replication, prevented disease-associated CD4⁺ T cell loss, suppressed endogenous virus, and restored CD4⁺ T cell counts. In addition, it was demonstrated that antiviral siRNAs could be delivered to naive T cells and effectively suppress viremia.

CONCLUSIONS. siRNA therapy for HIV infection seems to be feasible in a preclinical animal model.

REVIEWER COMMENTS. The annual rate of new HIV infections around the globe was 2.7 million in 2007, with 14% of these cases (370,000 cases) occurring in children <15 years of age (1,013 cases per day). RNA interference holds considerable potential for antiviral therapy, but delivering effective quantities of siRNAs into the right target cells in vivo represents a considerable challenge. Several small clinical trials using siRNAs are currently underway. This study represents a significant advance for 2 reasons: (1) the findings heighten the prospect of a new HIV-1/AIDS therapy and (2) this study provides a
Timing of HAART Defines the Integrity of Memory B Cells and the Longevity of Humoral Responses in HIV-1 Vertically-Infected Children


PURPOSE OF THE STUDY. HIV infection induces a progressive decline in immune function that affects not only T-cell but also B-cell activities, including the progressive decline in memory B cells, markedly elevated serum immunoglobulin levels, impaired responsiveness to routine immunizations, and loss of specific antibodies previously generated. Treatment of adults with highly active antiretroviral therapy (HAART) reduces immunoglobulin levels and increases B-cell numbers. However, several studies indicate that the B-cell compartment does not recover completely and patients maintain impaired antibody responses to immunizations. The purpose of this study was to determine whether the timing of HAART initiation affected pediatric patients’ ability to generate and to maintain protective levels of antibodies to routine immunizations.

STUDY POPULATION. Seventy children perinatally infected with HIV were studied with 50 healthy control subjects.

METHODS. Patients and control subjects received childhood immunizations according to the national (Italian) vaccine protocol. Patients who started HAART within the first year of life were categorized as “early treated”; children treated after the first year of life were considered “late treated,” and this group was subdivided into individuals with controlled virus and those who developed virological failure. Peripheral blood cells were evaluated with standard flow cytometry for B-cell subsets, including memory B cells. Antigen-specific B-cell functions were measured with an enzyme-linked immunosorbent spot assay. Plasma antibody titers against measles, tetanus, and pneumococcal antigens were assayed with enzyme-linked immunosorbent assays.

RESULTS. Early-treated patients maintained high percentages of memory B cells, compared with levels observed in healthy control subjects; patients who started HAART later showed lower percentages. Patients treated early maintained the capacity to generate antigen-specific memory B cells, and early HAART resulted in maintenance of multiple antibody levels above protective thresholds in HIV-infected children. Of concern, 25% of patients treated late failed to generate protective levels of antibodies to measles, and this number increased to >40% among those who experienced failure of antiretroviral therapy. In addition, >60% of subjects who received late HAART failed to maintain protective levels of antibodies to antigens including measles and tetanus; similar findings were noted in antibody responses to pneumococcal antigens.

CONCLUSIONS. Early HAART is essential for maintenance of normal B-cell functions in perinatally HIV-infected children. Regardless of T-cell numbers and/or clinical status, the results of this study strongly indicate that newborns infected with HIV should be treated as early as possible to preserve immune functions.

REVIEWER COMMENTS. Although T cells are critical for generating normal antibody responses, unique subsets of B lymphocytes are also essential in this regard. Specifically, marginal-zone B cells are required for the ability to generate polysaccharide-specific, “T-cell independent” antibodies. Infants <2 years of age are deficient in this subset of B lymphocytes. This study provides strong confirmation of many clinicians’ impressions that children who begin HAART at <1 year of age and who maintain viral suppression have normal immune functions by all measures that are clinically applied to the evaluation of this population. When to initiate HAART has been a long-term question among practitioners treating adults. Increasingly, earlier treatment (ie, at CD4+ cell counts of <500 cells per μL in adult patients) is being considered. The results of this study suggest that HAART should begin as soon as a diagnosis of HIV infection is made in perinatally exposed children.

Maraviroc for Previously Treated Patients With R5 HIV-1 Infection


PURPOSE OF THE STUDY. Although there are now >20 anti-HIV medications, new agents are still needed. HIV drug resistance is highly prevalent and 15% of newly infected patients in the United States have drug-resistant virus. In addition, enhanced safety and tolerability and improved convenience would enhance adherence to antiretroviral regimens. HIV uses 1 of 2 chemokine receptors, in addition to CD4, to gain entry into a cell, chemokine receptor 5 (CCR5) and α-chemokine receptor 4 (CXCR4). HIV that uses CCR5 is the primary type of virus that is transmitted through sexual or perinatal exposure. CCR5 antagonists are a new class of anti-
retroviral agents. The purpose of this study was to evaluate a CCR5 antagonist, maraviroc, in the treatment of HIV-infected adults.

**STUDY POPULATION.** Two double-blind, placebo-controlled studies were conducted. More than 1000 patients were randomly assigned to receive either maraviroc or placebo in combination with investigator-chosen optimized background therapy. Most patients were resistant to multiple classes of antiretroviral agents; mean baseline viral loads were >72 000 copies per mL, and median CD4+ cell counts were 169 cells per mm³.

**METHODS.** Subjects were assigned to receive maraviroc or placebo in addition to optimized background therapy based on treatment history and drug resistance testing. Safety and efficacy were assessed after 48 weeks.

**RESULTS.** The demographic and baseline characteristics of patients were similar between the 2 study groups (placebo and active drug). A significantly greater proportion of individuals receiving placebo discontinued treatment, primarily because of lack of efficacy. The primary end point of the study, mean change in plasma levels of HIV RNA, was substantially greater for maraviroc-treated patients than placebo-treated patients (−1.82 log₁₀ copies per mL in the maraviroc-treated group, compared with −1.079 log₁₀ copies per mL in the placebo-treated group). Secondary end points included the proportion of subjects who achieved undetectable viral loads (<50 copies per mL of plasma) at 48 weeks. Forty-seven percent of individuals receiving maraviroc twice daily achieved viral suppression, compared with ~18% of placebo-treated patients. Finally, the improvement in circulating CD4+ T-cell counts was substantially greater in the maraviroc-treated patients (~122 cells per mm³ gained), compared with the placebo-treated subjects (69 cells per mm³ gained). Maraviroc was well tolerated. Rates of discontinuation because of adverse events related to study treatment were the same in the placebo and maraviroc groups. Rates of serious adverse events were similar among the treatment groups (~18%–20%), and rates of laboratory abnormalities were similar among the study groups.

**CONCLUSIONS.** Maraviroc was well tolerated, and adverse events were no greater than in the placebo group. Maraviroc treatment resulted in greater suppression of HIV, greater increases in CD4+ cell counts, and a greater proportion of individuals who achieved HIV RNA levels of <50 copies per mL.

**REVIEWER COMMENTS.** This study and its companion article (Fätkenheuer G, Nelson M, Lazzarin A, et al. *N Engl J Med.* 2008;359[14]:1442–1455) demonstrated that maraviroc is an effective antiretroviral agent. It achieved remarkable success in a very heavily pretreated population. Of particular importance was the need for at least 1 and preferably 2 effective agents in the optimized background regimen to maximize the effect of maraviroc. In addition, in the secondary analysis of the results, pre-existing CXCR4-using HIV essentially eliminated any benefit of maraviroc. The development of CXCR4-using HIV after primary infection with CCR5-using virus is a matter of time and chance. Approximately 50% of heavily pretreated, long-term HIV-infected adults have CXCR4-using virus and thus would be completely resistant to maraviroc therapy. Currently, maraviroc is approved for patients who are known to be resistant to multiple other drugs. Perhaps maraviroc and similar chemokine receptor blockers would best be used before the likely development of CXCR4-using virus. Studies are underway to evaluate the use of this novel agent in patients naive to antiretroviral therapy.

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**Raltegravir With Optimized Background Therapy for Resistant HIV-1 Infection**

**PURPOSE OF THE STUDY.** As described above, there are compelling reasons for expanding the anti-HIV armamentarium. Raltegravir is an inhibitor of HIV integrase, an enzyme essential in the cycle of HIV replication. Because it belongs to a novel class of antiretroviral agents, the drug should be effective against HIV that is resistant to other antiretroviral drugs. The purpose of this study was to evaluate the safety and effectiveness of raltegravir in adults with multidrug-resistant virus.

**STUDY POPULATION.** HIV-infected patients ≥16 years of age were eligible if they had plasma HIV RNA levels of >1000 copies per mL and documented resistance to ≥1 drug in each of the 3 classes of antiretroviral drugs (ie, nucleoside transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors).

**METHODS.** Two identical trials in different geographic regions were conducted to evaluate raltegravir versus placebo in combination with optimized background anti-HIV therapy. Patients were randomly assigned to receive raltegravir or placebo, in a 2:1 ratio. Clinical status was assessed regularly during the trial, and protocol-mandated laboratory studies were performed at a central laboratory. The primary end point of the study was the proportion of patients achieving HIV RNA levels of <400 copies per mL after 16 weeks of study therapy.

**RESULTS.** Subjects (*N = 699*) were enrolled in studies in the different geographic locations. Because results were very consistent between the 2 substudies, combined re-
sults are presented. Subjects receiving raltegravir were well matched to the subjects receiving placebo. Seventy-eight percent of subjects receiving raltegravir achieved the primary end point of <400 copies of HIV RNA per mL, compared with ~42% for those receiving placebo. This difference persisted through week 48 of the study (72% vs 37%). HIV RNA suppression to <50 copies per mL at 48 weeks was achieved by 62% of raltegravir-treated subjects, compared with 33% of placebo recipients. Raltegravir was very well tolerated. The most common drug-related laboratory adverse events were increased serum cholesterol, triglyceride, and amino-transferase levels in the raltegravir group and increased cholesterol and creatinine levels and decreased neutrophil counts in the placebo group. Clinical adverse events were similar between groups, and rates of discontinuation because of drug-related events were also similar in the raltegravir and placebo groups.

CONCLUSIONS. In heavily pretreated, HIV-infected patients with limited treatment options, raltegravir plus optimized background therapy provided better viral suppression than did optimized background therapy alone for ≥48 weeks.

REVIEWER COMMENTS. Since 1995, it has been apparent that treatment of HIV with single agents does not result in complete viral suppression. In that year, given the drugs that were available at the time, ≥3 antiretroviral agents were required to suppress HIV RNA levels to <50 copies per mL. It is clear from the raltegravir and maraviroc studies that the addition of a single active agent, regardless of potency or mechanism of action, is not sufficient to achieve this end. However, given the new agents now available, patients with multidrug-resistant HIV have excellent chances of achieving viral suppression, often with 2 active agents. The availability of potent new agents active against multidrug-resistant HIV is welcome news to clinicians and patients still facing the daunting task of maintaining control over a remarkably resilient microbe.

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Long-term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation


PURPOSE OF THE STUDY. HIV infection of a target cell requires the expression of CD4 and a chemokine receptor. Early after HIV transmission, the chemokine coreceptor used most often is chemokine receptor 5 (CCR5). Approximately 1% of Northern European individuals possess homozygosity for a 32-base pair deletion (Δ32) in their CCR5 genes. These individuals are exceptionally resistant to HIV infection with CCR5-expressing HIV. The purpose of this study was to determine whether HIV could be suppressed by hematopoietic stem cell transplantation (HSCT) from a donor homozygous for CCR5 Δ32.

STUDY POPULATION. One HIV-infected adult was studied.

METHODS. The patient had been diagnosed with HIV ~10 years before the development of acute myeloid leukemia. He had been treated effectively with antiretroviral agents and, at the time of the leukemia, his CD4 + T-cell count was 415 cells per mm³ and HIV RNA was undetectable. The leukemia was initially treated with chemotherapy but relapsed. The patient underwent allogeneic HSCT. The donor was chosen from a long list of potential donors who were HLA identical to the patient. The specific donor was chosen because of his homozygosity for the CCR5 Δ32 mutation.

RESULTS. Before HSCT, the patient’s virus was shown to use the CCR5 coreceptor. The patient required 2 transplants because of acute myeloid leukemia relapse. However, the patient’s antiretroviral therapy was stopped before the first transplant and was not restarted. After the second transplant, 100% chimerism of the patient’s peripheral blood was demonstrated. Strikingly, the patient’s viral load in plasma and lymphocytes remained undetectable for 20 months after HSCT and discontinuation of antiretroviral therapy.

CONCLUSIONS. This report provides “proof of concept” that HIV may be controlled (or eliminated) after HSCT with cells intrinsically resistant to HIV infection.

REVIEWER COMMENTS. The accompanying commentary (Levy JA. N Engl J Med. 2009;360[7]:724–725), titled “Not an HIV Cure, But Encouraging New Directions,” perhaps understates what happened for this single patient; it is indeed possible that he was cured of his HIV. Although this is not applicable to the vast majority of HIV-infected individuals, this approach can be adapted for more-general use. For example, ongoing studies are being performed with autologous hematopoietic stem cells that have been genetically manipulated to mimic the unfavorable conditions for the virus that occur naturally in homozygous CCR5 Δ32 individuals. Insertion of genes that downregulate CCR5 expression, interfere with HIV replication, or both is an area of intense investigation. Although the initial costs of such an approach are substantial, the long-term costs of antiretroviral drugs and other interventions likely would make this approach, if it works, cost-effective.

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Age at First Introduction of Cow Milk Products and Other Food Products in Relation to Infant Atopic Manifestations in the First 2 Years of Life: The KOALA Birth Cohort Study
Jaime Olenec and James E. Gern
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