Section on Allergy and Immunology

American Academy of Pediatrics

Founded in 1948, the Section on Allergy and Immunology is dedicated to ensuring that children receive the highest quality of allergy and immunology care. To accomplish its mission, the Section provides a number of educational, 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, online continuing medical education course on "asthma gadgets," electronic quality improvement in practice program on asthma diagnosis and management (Education in Quality Improvement for Pediatric Practice [eQIPP], which meets the American Board of Pediatrics maintenance-of-certification criteria), school nurse allergy tool kit, and a number of public education materials. The Section is also active in contributing to educational programs and resources such as *AAP News*, educational brochures, clinical reports, and many other endeavors.

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

The reviews contained in the 2011 synopsis were written by Fellows of the AAP Section on Allergy and Immunology and fellows in allergy and immunology training programs who contributed reviews with their mentors.

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

The 2010–2011 journals chosen for review were *Allergy*, *American Journal of Asthma & Allergy for Pediatricians*, *Archives of Pediatric and Adolescent Medicine*, *American Journal of Medicine*, *American Journal of Respiratory and Critical Care Medicine*, *Annals of Allergy, Asthma, and Immunology*, *Annals of Internal Medicine*, *Archives of Disease in Childhood*, *Archives of Internal Medicine*, *Blood*, *British Journal of Dermatology*, *British Medical Journal*, *Chest*, *Clinical and Experimental Allergy*, *Clinical Pharmacology and Therapeutics*, *Critical Care Medicine*, *European Journal of Pediatrics*, *European Respiratory Journal*, *Immunology*, *Journal of Allergy and Clinical Immunology*, *Journal of the American Academy of Dermatology*, *Journal of the American Medical Association*, *Journal of Applied Physiology*, *Journal of Experimental Medicine*, *Journal of Immunology*, *Journal of Infectious Diseases*, *Journal of Pediatric Gastroenterology and Nutrition*, *Journal of Pediatrics*, *Journal of Pharmacology and Experimental Therapeutics*, *Lancet*, *Nature*, *New England Journal of Medicine*, *Pediatrics*, *Medicine*, *Pediatric Allergy and Immunology*, *Pediatric Asthma, Allergy & Immunology*, *Pediatric Dermatology*, *Pediatric Infectious Disease Journal*, and *Science*.

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A Synopsis of the Synopses

This synopsis book 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 this synopsis book selected many articles that have clinical "pearls" and provide insights that are applicable for daily practice, as well as ones that challenge our previous notions and provide data that might lead to new approaches for diagnosis and treatment.

The apparent increase in atopic disease demands attention toward environmental and genetic factors and their interaction and an eye toward identifying prevention strategies. Barrier defects of the skin, reflected by genetic variants in filaggrin, are not only associated with atopic dermatitis but also with additional atopic diseases. This raises the possibility that a defective skin barrier, or immunologic changes associated with this defect, might predispose to allergen sensitization. Results of several studies support the notion that prematurity or lower birth weights might be protective against atopy, but the reason remains elusive. There are theories that obesity creates an inflammatory state that promotes atopy, as evidenced by a study from the National Health and Nutrition Survey reviewed in this supplement. An interesting novel observation was that even among lean adolescents, decreased sleep time was associated with a greater risk for atopy; fatigue is possibly being another stress on immune function. Our reviewers found a large number of studies with findings that suggest that vitamin D deficiency is related to increased atopy. Relationships were described among various studies to indicate that lower vitamin D levels or lower dietary intake is associated with more infections, more wheeze, a higher risk of atopy, and worse atopic dermatitis. Less outdoor activity, with its resulting decrease in sun exposure, and diet seem to be at fault. The indoor environment also includes indoor pollutants that might raise the risk of atopy and asthma. Additional environmental risk factors of atopy seem to be related to the hygiene hypothesis; less exposure to microbes is a risk. If we put all of the findings together, is it a surprise that children today, with so many electronic diversions that keep them indoors, sedentary, snacking, and staying up late, are suffering more atopic disease? The solution seems obvious: put down the video games, go outside and play (especially if the playground is a farm), eat a healthy diet, and get a good night's sleep.

A major step forward in food-allergy diagnosis and management is the recent publication of the new national guidelines for the diagnosis and management of food allergies from the National Institute of Allergy and Infectious Diseases.[1] Several of the studies highlighted in this synopsis supplement have provided additional support for some of the recommendations in the guidelines. For example, the authors of the guidelines substantially agree with the American Academy of Pediatrics clinical report concerning the role of diet in atopy prevention, one aspect of which is that it is not necessary to delay introduction of allergenic foods for prolonged periods in otherwise healthy infants, even ones with a family history of atopy.[2] Studies reviewed herein have revealed that later, rather than earlier, introduction of egg or milk is associated with a higher risk of allergy to those foods. In addition, results of an interesting study from China suggest that delayed ingestion of peanut might be a risk for peanut allergy. There are no specific dietary recommendations for pregnant mothers, but regarding peanut there remains some controversy about the role of maternal peanut ingestion on peanut allergy outcomes, as discussed in 2 reviewed studies that produced different results. The current data continue to be insufficient to suggest anything other than a healthful diet during pregnancy; in fact, the results of several studies have underscored the importance of a diet sufficient in vitamins, fruits, and vegetables. The National Institute of Allergy and Infectious Diseases guidelines also support the important role of the supervised oral food challenge in food-allergy diagnosis, and the results of several reports reviewed herein also support the notion that tests alone are insufficient for diagnosis and that a successful diagnosis requires additional information including a careful history and, often, an oral food challenge. An emerging food-related disorder is eosinophilic esophagitis. Several study reports we reviewed have further elucidated the nature of this illness, with its relationship to allergy,

association with feeding disorders, and potential to result in esophageal fibrosis. A consensus guideline on eosinophilic esophagitis was recently published.[3]

It is important to stay alert for diagnosing asthma. Several studies have found that having allergic rhinitis is a risk, as is atopy. Studies on the role of infection continue to raise new questions; for example, it seems that airway bacterial infections, not only viral infections, are a risk factor for wheeze. But what came first, the virus or the asthma? This remains a question with studies reviewed here, which suggest that the asthma predisposition is the defining factor. The role of swimming in chlorinated pools as a risk factor remains under study, and there were opposing conclusions from some studies highlighted here. That extreme premature birth is a significant risk for asthma seems less controversial. Diagnosis and management of asthma is also highlighted with studies that have found possible disparities in care based on race and ethnicity, even when access was similar. The potential success of guidelines-based programs that can be undertaken in the office setting is also reviewed. It has been several years since the Expert Panel Report on asthma,[4] and studies continue to address therapeutic options. Reviewed here are a number of studies on medical treatment. Some of the studies addressed topics such as suggesting a potentially broader role in some settings for use of a leukotriene-receptor antagonist, options of doubling inhaled corticosteroid doses versus adding a combination of a long-acting bronchodilator with inhaled corticosteroid for children who were symptomatic on a moderate dose of inhaled corticosteroids, and the efficacy of adding inhaled corticosteroid to albuterol for rescue. The efficacy of omalizumab is reviewed in specific settings (eg, in improving asthma control for inner-city children who were not adequately controlled with guidelines-based management).

Allergy management is proactive, and numerous studies are ongoing to prevent and treat allergic disease. Promising immunotherapy studies for food and environmental allergens are also reviewed. For example, peanut oral immunotherapy significantly increased the threshold of reactivity for the children studied, although experts caution that this therapy requires more study regarding a variety of pitfalls such as reactions to the treatment, loss of efficacy if doses are missed, and other limitations. Still, progress has been swift and promising. We also reviewed a number of studies on prebiotics and probiotics that found promising results, particularly in prevention; some favored outcomes for reducing the risk of eczema, and some had disheartening results with regard to treatment. This is an area of investigation that is still early in addressing the influence of numerous variables such as the types of probiotics or mixtures used, dosing, the timing of administration, and target populations.

Several primary immunodeficiency diseases are highlighted, which underscores the wide phenotypic diversity of these genetic diseases, and there are lessons for the pediatrician about clues for raising concern for investigating underlying immune defects with the guidance of a clinical immunologist. Dissection of the immunologic basis of these disorders provides new insights on the complexities of the immune response. For example, translational research identified mutations in interleukin 17 family genes that cause functional deficiency of this pathway that are associated with chronic mucocutaneous candidiasis. Meanwhile, the approach to treatment extends beyond antimicrobial agents with a report of successful gene therapy for Wiskott-Aldrich syndrome. Studies are also delineating effective means to prevent mother-to-infant transmission of HIV with less use of drug, but the authors also advise caution regarding cardiac toxicity of perinatal exposure to antiretroviral therapy. Finally, the risks and burden of seasonal influenza is delineated and emphasizes the need for vaccination. Studies are emerging that qualify the degree of risk of influenza vaccinations of children with egg allergy and support more liberal immunization with some caution.

On behalf of myself and our reviewers, we hope that this supplement stimulates and informs, giving you practical information for improving the care of children with allergic and immunologic diseases now, and an exciting peek out of a window toward understanding therapies on the horizon. For additional information about our Section, please visit www.aap.org/sections/allergy.

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Chair, Section on Allergy and Immunology
Editor, Best Articles Relevant to Pediatric Allergy and Immunology

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Allergy

RISK FACTORS, PREVENTION, AND THE "HYGIENE HYPOTHESIS"

Filaggrin Gene Variants and Atopic Diseases in Early Childhood Assessed Longitudinally From Birth

Bønnelykke K, Pipper CB, Tavendale R, Palmer CNA, Bisgaard H. *Pediatr Allergy Immunol*. 2010;21(6): 954–961

PURPOSE OF THE STUDY. Filaggrin coding gene (*FLG*) loss-of-function variants lead to skin-barrier dysfunction and have been associated with atopic dermatitis. These researchers sought to find associations between *FLG* variants and development of asthma, eczema, and sensitization to foods and aeroallergens in a high-risk birth cohort.

STUDY POPULATION. A total of 411 infants born to mothers with a history of asthma were followed longitudinally for a 5-year period with follow-up visits at least every 6 months. Asthma, eczema, and sensitization to allergens were diagnosed prospectively. *FLG* variants were determined in 382 white infants.

METHODS. Respiratory symptoms were recorded in daily diaries. Recurrent wheeze was defined as 5 episodes that each lasted 3 days in 6 months or daily symptoms for 4 consecutive weeks. Asthma and atopic dermatitis were diagnosed according to accepted criteria. Specific immunoglobulin E levels were determined by the ImmunoCAP test (Phadia, Uppsala, Sweden) at 1½ and 4 years of age for common food and aeroallergens. Genotyping for *FLG* variants R501X and 2282del4 was performed.

RESULTS. The mutated alleles R501X and 2282del4 were present in 18 and 25 children, respectively, and 95 of 382 children developed asthma-related phenotypes. Differentiation in development of an asthma-related phenotype was present in the first 18 months ($P = .02$). Yearly incidences of acute severe asthma exacerbations were elevated from infancy in those with *FLG* variants and persisted throughout the 5 years ($P = .01$). Yearly point-prevalence of asthma was elevated in those with *FLG* variants that also persisted throughout the 5 years ($P = .03$). *FLG* variants were associated with eczema development in the first year of life. Point-prevalence of specific immunoglobulin E sensitization was not elevated in *FLG* variants by the age of 2 but was increased by the age of 4 ($P = .0007$).

CONCLUSIONS. This study revealed that those with *FLG* variants developed eczema, asthma, and sensitization at higher rates than those without these variants in a high-risk birth cohort. The temporal pattern of *FLG*-associated atopic disease included early onset of asthma and eczema and later development of sensitization.

REVIEWER COMMENTS. We do not have a clear understanding of the genetic and environmental factors that influence the development of atopic disease. This longitudinal birth cohort revealed that those high-risk infants with *FLG* variants have higher rates of atopic disease, which suggests that skin-barrier defects have a role in this process and that this process occurs very early in life.

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Growing Up on a Farm Leads to Lifelong Protection Against Allergic Rhinitis

Eriksson J, Ekerljung L, Lötvall J, et al. *Allergy*. 2010; 65(11):1397–1403

PURPOSE OF THE STUDY. This cross-sectional study sought to examine the effect of childhood farm living and the degree of urbanization on the prevalence of allergic rhinitis into adulthood.

STUDY POPULATION. More than 30 000 questionnaires were mailed to those residents aged 16 to 75 years who lived in West Gothia, a region of Sweden.

METHODS. The administered questionnaire covered topics including history of farm living for the first 5 years of life, history of physician-diagnosed obstructive respiratory disease, rhinitis, respiratory symptoms, smoking, atopic family history, and occupational and environmental exposures. The region was divided into 4 categories on the basis of population size: metropolitan areas (700 000 inhabitants), midsized towns (10 000–100 000 inhabitants), small towns (2000–10 000 inhabitants, and rural areas (<2000 inhabitants).

RESULTS. A total of 18 087 subjects participated in the study (62% response rate). The prevalence of allergic rhinitis was lower for those who had lived on a farm during their first 5 years of life ($P < .001$). This effect was seen in all age groups including 16 to 30 years ($P < .001$), 31 to 45 years ($P = .002$), 46 to 60 years ($P = .001$), and 61 to 75 years ($P = .045$). The effect was seen most strongly in the younger age group and less so for the oldest age group. The prevalence of allergic rhinitis was increased significantly in those who lived in regions with higher populations. Again, the effect was seen most strongly in the 16- to 30-year age group ($P = .002$). This association between farm living in the first 5 years of life and decreased allergic rhinitis continued to be significant after adjusting for confounders such as gender, family history of allergic disease, smoking, degree of urbanization, and occupational exposure.

CONCLUSIONS. This large-scale study found that farm living in the first 5 years of life was associated with a lower prevalence of allergic rhinitis and that this protective effect continued throughout adulthood. Increased urbanization also was associated with an increased prevalence of allergic rhinitis until 60 years of age.

REVIEWER COMMENTS. Limitation of this study include self-report of allergic rhinitis and lack of a more expanded panel of questions regarding other childhood exposures. However, the results highlight the potential importance of the early childhood environment in shaping future burden of allergic disease. It has been theorized that the protective effect of farm living might be a result of exposure to endotoxin, a cell wall component of Gram-negative bacteria, which promotes nonallergic T-helper 1 responses and a shift away from T-helper 2 responses. These results show the persistence of this protective effect well into adulthood.

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Pre- and Post-natal Exposure to Antibiotics and the Development of Eczema, Recurrent Wheezing, and Atopic Sensitization in Children Up to the Age of 4 Years

Dom S, Droste JH, Sariachvili MA, et al. *Clin Exp Allergy*. 2010;40(9):1378–1387

PURPOSE OF THE STUDY. To investigate the relationship of indirect prenatal and postnatal antibiotic exposure and the subsequent development of eczema, recurrent wheeze, and atopic sensitization in early childhood.

STUDY POPULATION. The study population of 773 children was obtained from a prospective project regarding the Influence of Perinatal Factors on the Occurrence of Asthma and Allergies (PIPO cohort) in Belgium. Of 2006 women recruited at 20 weeks of pregnancy, 1072 agreed to participate (total cohort population: 1128 children).

METHODS. Children were included in the current study if information on antibiotic exposure and at least 1 health outcome was available. History of maternal antibiotic use during pregnancy and breastfeeding was queried at home visits during pregnancy and after delivery. Postal questionnaires queried patient antibiotic exposure at 1 year and subsequently every 6 months until the age of 4 years. Biannual questionnaires also queried the diagnoses of eczema or recurrent wheeze in children. Atopic sensitization was assessed via *Dermatophagoides pteronyssinus*–, cat-, dog-, egg-, and cow's milk–specific immunoglobulin E (IgE) at 1 and 4 years and birch- and timothy grass–specific IgE at 4 years. Atopic sensitization was defined as at least 1 positive specific IgE result. Parental *D pteronyssinus*–, cat-, dog-, birch-, timothy-, mugwort-, and *Cladosporium herbarum*–specific IgE were quantified. Gender, parental allergic history, parental educational level, pet exposure, tobacco use during pregnancy, birth weight, maternal age at birth, breastfeeding history, number of older siblings, day care attendance, environmental tobacco exposure, and lower respiratory tract infection history were also queried. Chronology of exposures and outcomes were considered independently.

RESULTS. Prenatal antibiotic exposure was significantly positively associated with eczema but not associated with recurrent wheeze or atopic sensitization. Antibiotic exposure through breastfeeding had a positive, but not statistically significant, association with recurrent wheeze. Neither eczema nor atopic sensitization was significantly associated with antibiotic exposure through breastfeeding. There was a negative association between patient use of antibiotics in the first year of life and eczema and atopic sensitization and between patient use of antibiotics after the first year of life and recurrent wheeze, eczema, and atopic sensitization.

CONCLUSIONS. Indirect exposure to antibiotics during pregnancy or through breast milk increases the risk for allergic symptoms in children, whereas direct exposure is protective.

REVIEWER COMMENTS. The authors acknowledged potential study limitations to include selection bias, selective attrition, and misclassification of the chronology of antibiotic exposure and outcomes. Future studies on both outcomes associated with indirect antibiotic exposure in children and associations between the chronology of antibiotic exposure and atopic disease outcomes in childhood are needed.

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Impaired Fetal Growth Decreases the Risk of Childhood Atopic Eczema: A Swedish Twin Study

Lundholm C, Ortqvist AK, Lichtenstein P, Cnattingius S, Almqvist C. *Clin Exp Allergy*. 2010;40(7):1044–1053

PURPOSE OF THE STUDY. Previous studies have revealed an association between high birth weight and gestational age and increased risk for subsequent atopic eczema. These researchers sought to evaluate associations between fetal growth and risk of atopic eczema or allergic rhinitis in a prospective twin cohort.

STUDY POPULATION. Data were collected via telephone interviews between October 2004 and July 2007 from

parents participating in the Swedish Twin and Medical Birth registers. Children were 9 or 12 years old. The study base included 11 020 twins; data were available for atopic eczema among 10 132 and for allergic rhinitis among 10 896 participants.

METHODS. Birth weight, gestational age, birth weight by gestational week, and gender in SD score, as a measure of fetal growth, and birth length were used as exposure variables. Exposure variables were handled as both categorized and continuous variables. To control for shared genetic and environmental factors, co-twin–control analyses were performed in twin pairs discordant for atopic eczema or allergic rhinitis.

RESULTS. The rate of atopic eczema increased with birth weight from 12.6% in twin children born at <2000 g to 17.3% in children born at ≥3500 g. The overall rate of allergic rhinitis was 8.4%, and there was no clear relationship with birth weight, gestational age, or birth length. In the cohort analyses, the odds ratio for atopic eczema was 1.62 for a 500-g increase in birth weight. The odds ratio for allergic rhinitis was 1.00 for a 500-g increase in birth weight. The co-twin–control analysis on atopic eczema resulted in an odds ratio of 3.93 for a 500-g increase in birth weight, and there was no significant difference between monozygotic and dizygotic twins. The co-twin–control analysis revealed no evidence of association between allergic rhinitis and weight.

CONCLUSIONS. The risk of childhood atopic eczema increased with increasing birth weight. In the co-twin–control analysis, odds ratios did not decrease, and odds ratios did not differ between monozygotic and dizygotic twins, which indicates that genetic or shared environmental factors do not explain this association. The study results indicate that fetal growth influences the risk of childhood atopic eczema but not allergic rhinitis.

REVIEWER COMMENTS. It is not surprising that maternal and fetal characteristics influence the development of childhood disease. In addition to fetal growth associations, the authors provided extensive descriptive data for the rates of atopic eczema and allergic rhinitis by all queried child and maternal characteristics. Additional studies of singletons are necessary to further evaluate the reasons for the association of fetal growth and atopic disease.

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Preterm Birth Reduces the Incidence of Atopy in Adults

Siltanen M, Wehlkalampi K, Hovi P, et al. *J Allergy Clin Immunol*. 2011;127(4):935–942

PURPOSE OF THE STUDY. There is evidence that the risk for atopic disease is influenced during fetal development and by early life events. This study evaluated the association between preterm birth, very low birth weight (VLBW), and atopy in young adulthood.

STUDY POPULATION. Subjects from the Helsinki Study of VLBW Adults were compared to matched controls born at ≥37 weeks' gestation. Of 255 VLBW adults (birth weight: 1120 ± 221 g; weeks of gestation: 29.2 ± 2.2) and 314 controls (birth weight: 3593 ± 471 g; weeks of gestation: 40.1 ± 1.1) invited, 166 (65.1%) and 172 (54.8%), respectively, chose to participate. The mean age at analysis was 22.4 to 22.5 years.

METHODS. Skin-prick testing was performed to birch, timothy grass, mugwort, cat, dog, and *Dermatophagoides pteronyssinus*. Total immunoglobulin E (IgE) and serum-specific IgE levels to cat, timothy, and birch were measured. Diagnosis of asthma, allergic rhinitis, and atopic dermatitis were obtained from an unvalidated questionnaire that included physician diagnosis of asthma and allergic rhinitis. The primary outcome of atopy was defined as a positive skin-test result. Other indicators of atopy included elevated total or specific IgE level. Self-reported histories of atopic diseases were secondary outcomes.

RESULTS. VLBW adults were less likely than controls to have at least 1 positive skin-test result (45.5% vs 57.9%; adjusted odds ratio [OR]: 0.48; $P = .13$). Timothy and mugwort were the only individual allergens associated with a decreased OR in the VLBW group. Adults born at VLBW were also less likely to have any elevated serum-specific IgE level (adjusted OR: 0.48) or an elevated level to cat (adjusted OR: 0.41). Of the adults born at VLBW, those born appropriate for gestational age (AGA) were statistically less likely ($P < .05$) than those born small for gestational age (SGA) to have a positive skin-test result to dog or *D pteronyssinus* or to have elevated levels of total serum IgE, serum-specific IgE to any allergen, or serum-specific IgE to birch. Within the VLBW group, each week of earlier gestational age was associated with lower risk of any positive skin-test result or any elevated serum-specific IgE level (OR: 0.82 for each measure). The decreased risk was even more apparent when the SGA adults were excluded from analysis. There was no difference in the frequency of self-reported asthma, allergic rhinitis, or atopic dermatitis between the VLBW adults and controls or between the AGA and SGA VLBW subjects.

CONCLUSIONS. Young adults born at VLBW had a greater risk of atopy based on allergen sensitization. There was no difference in the incidence of atopic disease. The results of this study support the hypothesis that the risk for atopy is influenced by early life events.

REVIEWER COMMENTS. A weakness of this study is that the incidence of atopic disease itself was based solely on self-report. As the data are reported, being born prematurely and at VLBW places an infant at a lower risk of sensitization to allergen as a young adult. However, the results do not support a decreased risk of allergy (sensitization plus symptoms with exposure).

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Vitamin D Levels and Food and Environmental Allergies in the United States: Results From the National Health and Nutrition Examination Survey 2005–2006

Sharief S, Jariwala S, Kumar J, Muntner P, Melamed ML. *J Allergy Clin Immunol*. 2011;127(5):1195–1202

PURPOSE OF THE STUDY. To examine the relationship between serum 25-hydroxyvitamin D (25[OH]D) levels and the prevalence of food and environmental allergies.

STUDY POPULATION. The study used the National Health and Nutrition Examination Survey 2005–2006, composed of a population of civilian noninstitutionalized US residents, which deliberately oversampled non-Hispanic black and Mexican American people to obtain accurate prevalence data in those subpopulations. All participants 1 year of age or older with available 25(OH)D levels and allergy-test results were included. Included in the final analysis were 3136 children and 3454 adults (>21 years old).

METHODS. Information about vitamin D supplements, milk intake in the previous month (daily, less than daily but more than weekly, and once weekly or less), and television, computer, and videogame time ("screen time") (none, <2 hours/day, 2–4 hours/day, and >4 hours/day) was collected. Allergy was determined by a questionnaire, and serum was obtained for total immunoglobulin E (IgE) and for specific IgE to dust mites, cat, dog, *Alternaria*, peanut, egg, and milk. Subjects 6 years of age or older also had ImmunoCAP (Phadia, Uppsala, Sweden) levels measured for German cockroach, selected tree, grass, and weed pollens, and shrimp. Allergy was defined as any positive IgE test result (≥0.35 kU/L) or a total IgE level in the top quintile (>191 kU/L). Seasonal and perennial allergies were defined as a positive ImmunoCAP level to a pollen or perennial allergen, respectively. 25(OH)D levels were classified as deficient (<15 ng/mL), insufficient (15–29 ng/mL), or sufficient (≥30 ng/mL).

RESULTS. Deficient 25(OH)D levels were associated with being non-Hispanic black or Mexican American, having a low socioeconomic status, >4 hours/day of screen time, lower frequency of milk-drinking, and not taking vitamin D supplements. Children and adolescents deficient in 25(OH)D had a higher prevalence of sensitization to most individual allergens, to any allergen, and to any seasonal or perennial allergen than those with insufficient or sufficient levels. The same trends were not seen in adults. Questionnaire data also revealed an association between deficient and insufficient 25(OH)D levels and prevalence of allergy symptoms in general but not to specific symptoms in children and adolescents.

CONCLUSIONS. Vitamin D deficiency is associated with a higher rate of allergic sensitization and self-reported allergy in children and adolescents.

REVIEWER COMMENTS. Results of this study support previous ones in which low vitamin D levels were implicated in higher rates of allergic disease. The noncalcemic effects of vitamin D, including its immunomodulatory effects on antigen-presenting cells and effector cells, are growing areas of research, but specific mechanisms are not yet known. "Got milk?" Although there are no data as to whether vitamin D supplementation or naturally acquired higher 25(OH)D levels can reverse allergic sensitization, these results provide 1 more reason for children to turn off the video screen and go outside to play.

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Nutrients and Foods for the Primary Prevention of Asthma and Allergy: Systematic Review and Meta-analysis

Nurmatov U, Devereux G, Sheikh A. *J Allergy Clin Immunol*. 2011;127(3):724–733

PURPOSE OF THE STUDY. Results of several individual studies have suggested an association between specific nutrient and food intake and the development of atopic disease. This study aimed to systematically review and analyze the published literature.

STUDY POPULATION. This was a systematic review and meta-analysis of published literature. Reviewed studies included pregnant women, infants, and children younger than 16 years.

METHODS. Eleven databases were systematically reviewed for studies that investigated the role of nutrients and foods for the primary prevention of atopic disorders in children.

RESULTS. There were 62 eligible reports identified from cohort, case-control, and cross-sectional studies. Serum vitamin A levels were lower in children with asthma compared with controls (odds ratio [OR]: 0.25 [95% confidence interval (CI): 0.1–0.4]). High maternal dietary

intake of vitamin D and E during pregnancy was protective for the development of wheezing (OR: 0.56 [95% CI: 0.42–0.73] and 0.68 [95% CI: 0.52–0.88], respectively). Adherence to a Mediterranean diet was protective for persistent wheeze and atopy (OR: 0.22 [95% CI: 0.08–0.58] and 0.55 [95% CI: 0.31–0.97], respectively). The authors of most (17 of 22) fruit and vegetable studies reported beneficial associations with asthma and allergic outcomes.

CONCLUSIONS. The available evidence is supportive with respect to vitamins A, D, and E; zinc; fruits and vegetables; and a Mediterranean diet for the prevention of atopic disease.

REVIEWER COMMENTS. Although the study was observational in nature, its results highlight the importance of dietary exposures in the development of atopic disease. Controlled interventional studies are warranted to determine if it is possible to prevent atopic disease with dietary modification.

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Partial Protein-Hydrolyzed Infant Formula Decreased Food Sensitization but Not Allergic Diseases in a Prospective Birth Cohort Study

Kuo HC, Liu CA, Ou CY, et al. *Int Arch Allergy Immunol*. 2011;154(4):310–317

PURPOSE OF THE STUDY. To determine whether feeding a partially protein-hydrolyzed formula in the first 6 months of life would decrease the incidence of future allergic diseases.

STUDY POPULATION. Taiwanese newborns who had at least 1 first-degree family member with a history of atopy and who were not breastfeeding participated.

METHODS. A total of 679 participants were exclusively fed with partially hydrolyzed whey formula (HF) (n = 345) or cow's milk infant formula (CM) (n = 334) for at least 6 months via an open-label protocol. They were prospectively assessed at 6, 18, and 36 months of age to determine allergic sensitization (immunoglobulin E [IgE] > 0.7 kU/L) and clinical presence of eczema, food allergy, asthma, or allergic rhinitis.

RESULTS. At 36 months, cow's milk protein sensitization in the HF group was significantly lower than that in the CM group (12.7 vs 23.4%; P = .048). There was no difference with sensitization to egg or peanut between the 2 groups. Aeroallergen sensitization and serum total IgE levels were not significantly different. Occurrence of allergic disease was significantly correlated with aeroallergen sensitization but not to food-allergen sensitization, parental atopy, or feeding types.

CONCLUSIONS. The authors concluded that although HF feeding during the first 6 months of life helped to lower cow's milk protein sensitization, it alone is not enough to decrease the development of allergic disease.

REVIEWER COMMENTS. Can controlling a susceptible infant's diet early in life help to lessen the development of atopic symptoms in later years? These findings suggest that exclusively feeding this HF for the first 6 months of life does not. Other comparative studies have found more favorable outcomes in those infants who were fed extensively hydrolyzed formula. However, more large-scale, controlled studies that follow newborns through childhood are needed to better define the advantages.

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Association Between Short Sleep Duration and the Risk of Sensitization to Food and Aero Allergens in Rural Chinese Adolescents

Zhang S, Liu X, Kim JS, et al. *Clin Exp Allergy*. 2011; 41(4):547–555

PURPOSE OF THE STUDY. To explore the association between sleep duration and sensitization to food allergens and aeroallergens.

STUDY POPULATION. There were 1534 rural Chinese adolescent twins aged 12 to 21 years drawn from an ongoing prospective study on precursors of metabolic syndrome in children in a large Chinese twin cohort. Any participant aged 12 to 21 years at a follow-up visit for the main study with complete information on sleep questionnaires and skin-prick-test (SPT) results was included.

METHODS. Subjects completed standard sleep questionnaires and SPTs to 9 food allergens and 5 aeroallergens. Total sleep time was defined as the interval from bedtime to wake-up time minus sleep latency. Sensitization was defined as having at least 1 positive SPT result. Percentage body fat was calculated, because previous studies have suggested that sleep duration and allergic sensitization are associated with adiposity.

RESULTS. Compared with subjects in the highest tertile of sleep duration, those who slept less were more likely to be sensitized to any food allergen (odds ratio [OR]: 1.9 [95% confidence interval (CI): 1.3–2.7] and 1.4 [95% CI: 1.0–1.9] for the first and second tertiles [trend test $P_{trend} = 3 \times 10^{-4}$], respectively). The corresponding ORs for sensitization to any aeroallergen were 1.5 (95% CI: 1.1–2.0) and 1.3 (95% CI: 1.0–1.7) ($P_{trend} = 8 \times 10^{-3}$). These associations were independent of percentage body

fat. In addition, there was a significant dose-response association between the number of positive SPT results and prevalence of short sleep duration (lowest tertile) ($P_{trend} = 1 \times 10^{-3}$).

CONCLUSIONS. In this sample of relatively lean rural Chinese adolescents, short sleep duration was associated with increasing risk of sensitization to food allergens and aeroallergens independent of percentage body fat.

REVIEWER COMMENTS. A methodologic concern for this study regards the possibility that allergic disease was interrupting sleep, but the authors felt that the allergic sensitization was unlikely to be explained by this confounder because the majority of them were clinically asymptomatic, and the effect persisted even when those with allergic or sleep disorders were excluded from the analysis. This intriguing and previously unreported finding provides further evidence to suggest that immune function is affected by sleep deprivation, which is already known to increase susceptibility to infection. Sleep duration is far more modifiable than many other risk factors for allergic disease and also has other undisputed benefits for overall health, and so this finding has substantial clinical and public health importance. Longitudinal studies are needed to further determine the temporal and causal relationships. In the meantime, get a good night's sleep!

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ALLERGENS AND ENVIRONMENTAL EXPOSURES

Opposing Effects of Cat and Dog Ownership and Allergic Sensitization on Eczema in an Atopic Birth Cohort

Epstein TG, Bernstein DI, Levin L, et al. *J Pediatr*. 2011;158(2):265–271

PURPOSE OF THE STUDY. To evaluate the effect of environmental exposures and allergic sensitization on the risk of developing eczema at 4 years of age.

STUDY POPULATION. This was a birth-cohort study that enrolled newborns in the Cincinnati metropolitan area born between 2001 and 2003. Enrolled infants had at least 1 parent with symptoms of asthma, allergic rhinitis, or eczema.

METHODS. On a yearly basis from the ages of 1 to 4 years, children underwent a physical examination, a clinician's assessment, and a skin-prick test (SPT) to 15 aeroallergens plus cow's milk and hen's egg. Parents completed an in-person validated survey at these times to assess environmental exposures and the parent's perception of their child's eczema. A home environmental assessment and collection of house dust samples were performed before 1 year of age.

RESULTS. Of the 636 children analyzed, 14% had eczema. The most significant predictors of eczema at age 4 were having a parent with eczema ($P = .03$), a positive SPT result to egg at 1 year of age ($P < .001$), and a positive SPT result to elm tree pollen at ages 1, 2, or 3 years ($P = .03$). Those who owned a dog before the age of 1 and were SPT-positive to dog at age 1, 2, or 3 did not have an increased risk for eczema at age 4, whereas those who did not own a dog before age 1 and were SPT-positive to dog at age 1, 2, or 3 had an almost fourfold increased risk of eczema at age 4 ($P = .002$). In contrast, children who lived with cats before age 1 and were SPT-positive to cat at ages 1, 2, and 3 years were 13 times more likely to have eczema at age 4 than those who were SPT-negative to cat ($P < .001$).

CONCLUSIONS. A history of parental eczema, SPT positivity to egg at 1 year of age, and SPT positivity to elm tree pollen at ages 1, 2, or 3 years were all found to significantly increase the risk of development of eczema at age 4 years. Dog ownership before 1 year of age significantly reduced the risk of eczema at age 4 years among children sensitized to dog. In contrast, cat ownership before 1 year of age significantly increased the risk of eczema at age 4 among cat-sensitized children.

REVIEWER COMMENTS. The prospective design of the study is a strength; however, recall bias and the relatively small total number of children with eczema and either cat or dog ownership are limitations. The protective influence of dog ownership on the development of eczema has been reported previously and deserves further investigation into the exact effects of dog antigens on the immune system. Conflicting data regarding the effects of cat ownership on the development of atopy have been reported in other study reports, and larger studies need to be performed before advice regarding pet ownership is given to parents on a routine clinical basis.

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Cockroach Exposure Independent of Sensitization Status and Association With Hospitalization for Asthma in Inner-City Children

Rabito FA, Carlson J, Holt EW, Iqbal S, James MA. *Ann Allergy Asthma Immunol*. 2011;106(2):103–109

PURPOSE OF THE STUDY. To examine the relationship between house dust mite, cockroach exposures and sensitization,

and asthma morbidity in children in an inner-city environment.

STUDY POPULATION. The subjects were patients from an allergy clinic ($n = 86$, mostly black, aged 4–17 years) with physician-diagnosed asthma and positive skin-test results to an indoor allergen and living in urban New Orleans, Louisiana. Most of the children were taking daily asthma medications, more than half had had an emergency department visit, almost 75% had had an urgent physician visit, and nearly 25% had had a hospitalization in the previous 4 months.

METHODS. This was a cross-sectional study. Sociodemographic factors and home characteristics were queried by using a structured questionnaire and by visual observation of the home at study entry. A revised Childhood Respiratory Health Questionnaire was used to measure frequency of health care utilization, asthma symptoms, activity limitation, and medication use during the previous 4 months. Indoor dust samples were collected and analyzed for the presence of dust mite and cockroach content. In vitro–specific immunoglobulin E to dust mites, cat, dog, and cockroach was measured.

RESULTS. Both dust mite and cockroach exposure were associated with sensitivity, but only cockroach showed a strong linear relationship between degree of exposure and sensitization (even low levels of exposure to dust mite were associated with sensitization). Multivariable regression analyses controlling for exposure, sensitization, oral steroid use, and ICU admission revealed that the only variable associated with multiple exposure variables was hospital admission. The odds of reporting a hospitalization in the previous 4 months, using 2 different statistical models, were 4.2- to 5.4-fold higher for children exposed to >2.0 U/g than for those exposed to <2.0 U/g Blag1. There was no increase in odds for hospitalization related to dust mite exposure.

CONCLUSIONS. Exposure to cockroach allergens is strongly associated with hospital admissions for asthmatic children living in the inner city regardless of sensitization.

REVIEWER COMMENTS. This study's results reaffirm the association between cockroach exposure and severe asthma morbidity and that this association is, to some degree, independent of sensitivity. The failure to show the same relationship for house dust mite might be a result of sample size and the lack of a relationship between exposure and sensitization in this group. It remains to be shown that remediation efforts directed toward cockroach infestation are helpful in decreasing this morbidity.

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Allergen-Specific IgE as a Biomarker of Exposure Plus Sensitization in Inner-City Adolescents With Asthma

Matsui EC, Sampson HA, Bahnson HT, et al; Inner-City Asthma Consortium. *Allergy.* 2010;65(11):1414–1422

PURPOSE OF THE STUDY. These researchers sought to understand the relationship between allergen-specific immunoglobulin E (IgE) levels, exposure to indoor allergens, and asthma severity.

STUDY POPULATION. There were 546 subjects, aged 12 to 20 years, with physician-diagnosed moderate-to-severe asthma enrolled at 10 centers around the United States as part of the Asthma Control Evaluation (ACE) study.

METHODS. Subjects underwent a 3-week run-in period in which asthma symptoms, medication use, pulmonary-function testing, and adherence data were collected. Skin testing was performed to a panel of 14 aeroallergens, and allergen-specific IgE levels to common indoor allergens were measured. A home visit was conducted to collect dust samples from the bed and bedroom floor. Subjects were then assigned to either a pharmacotherapy titrated according to National Asthma Education and Prevention Program (NAEPP) guidelines or pharmacotherapy titrated according to NAEPP guidelines and fractional exhaled nitric oxide (FeNO). Subjects were followed for 1 year, and data on exacerbations, health care utilization, and pulmonary function were collected at each visit.

RESULTS. Black subjects comprised 65% of the participants; 48% had an annual household income of less than $15 000. The majority (88%) were skin-test–positive to at least 1 aeroallergen including cockroach (61%), cat (58%), mold (52%), and dust mite (47%). There were statistically significant correlations between allergen-specific IgE levels and settled dust allergen concentrations for dust mite, cockroach, and mouse. Those with higher allergen-specific IgE levels to cockroach, mouse, cat, and dust mite had higher FeNO concentrations and peripheral blood eosinophils. Higher allergen-specific IgE levels were associated with lower lung function for all allergens, although not all were statistically significant.

CONCLUSIONS. In atopic asthmatic adolescents from the inner city, allergen-specific IgE levels were positively correlated with bedroom allergen exposure for dust mite, cockroach, and mouse allergens. Higher allergen-specific IgE levels were also associated with worse clinical and biomarker outcomes.

REVIEWER COMMENTS. Indoor allergen burden has been proposed to be the reason for the increased asthma morbidity in inner-city populations. There have also been many attempts to find specific biomarkers that might better

predict disease severity in asthma. These results indicate that for most indoor allergens, allergen-specific IgE levels might be a marker of allergen exposure and disease burden.

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TOBACCO AND AIR POLLUTION

Smoke-Free Air Laws and Asthma Prevalence, Symptoms, and Severity Among Nonsmoking Youth

Dove MS, Dockery DW, Connolly GN. *Pediatrics*. 2011; 127(1):102–109

PURPOSE OF THE STUDY. To investigate the relationship between smoke-free laws and asthma prevalence, symptoms, and severity among nonsmoking children aged 3 to 15 years.

STUDY POPULATION. The data were obtained from the National Health and Nutrition Examination Survey 1999–2006 (NHANES).

METHODS. Survey sites were designated as having or not having at least 1 smoke-free work location, restaurant, or bar law at the county or state level that encompassed the entire county population. Asthma prevalence was assessed as self-reported current asthma and as ever having asthma with current symptoms. Asthmatic symptoms included persistent wheeze, chronic night cough, and wheeze-medication use. The authors also examined asthma severity defined by asthma episode or emergency department visit for asthma.

RESULTS. Smoke-free laws were significantly related with lower odds of asthma symptoms (odds ratio [OR]: 0.67 [95% confidence interval (CI): 0.48–0.93]) among nonsmoking youth. The relationship between smoke-free laws and ever having asthma with current symptoms trended to significance (OR: 0.74 [95% CI: 0.53–1.03]). Smoke-free laws were associated with lower odds of asthma episodes (OR: 0.66 [95% CI: 0.28–1.56]) and emergency department visits for asthma (OR: 0.55 [95% CI: 0.27–1.13]), but these outcomes were not statistically significant.

CONCLUSIONS. Smoke-free laws decrease asthma symptoms, including persistent wheeze, chronic nocturnal cough, and wheeze-medication use in youthful nonsmoking populations.

REVIEWER COMMENTS. This study was limited by the county-limited definition of smoke-free laws, which is only an estimate of individual exposure to secondhand tobacco smoke outside the home. Misclassification of county smoke-free laws might not reflect individual exposure, and misclassification of current asthma is possible because self-reports were not validated by objective measures or clinical assessment. However, the findings of this study are consistent with those of other studies of secondhand smoke. In summary, the take-home message and conclusion of this important study is that smoke-free laws are associated with decreased exposure to secondhand smoke but equally with decreased respiratory symptoms as well.

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A Strong Synergism of Low Birth Weight and Prenatal Smoking on Asthma in Schoolchildren

Bjerg A, Hedman L, Perzanowski M, Lundbäck B, Rönmark E. *Pediatrics*. 2011;127(4). Available at: www.pediatrics.org/cgi/content/full/127/4/e905

PURPOSE OF THE STUDY. To study the independent and joint effects of prenatal smoking and low birth weight (LBW) on childhood asthma.

STUDY POPULATION. The study included asthmatic 11- to 12-year-old children in Sweden ($N = 3389$).

METHODS. Children were studied by questionnaire survey as part of the International Study of Asthma and Allergy in Childhood (ISAAC). A subset of 2121 children also underwent skin-prick testing.

RESULTS. Mean birth weight was 3360 g in children exposed to prenatal smoking and 3571 g in nonexposed children ($P < .001$). The association of prenatal smoking with physician-diagnosed asthma was stronger in LBW children (risk ratio: 8.8 [95% confidence interval: 2.1–38]) than in normal birth weight children (risk ratio: 1.3 [95% confidence interval: 1.0–1.8]). LBW alone was not an independent predictor of asthma.

CONCLUSIONS. There is a strong interaction of LBW and prenatal smoking on the risk of physician-diagnosed asthma, which is observed even after adjusting for known risk factors including allergic sensitization.

REVIEWER COMMENTS. This report highlights the observation that the combination of LBW and prenatal smoking increases the risk of physician-diagnosed asthma sixfold versus either LBW (no effect) or prenatal smoking (weak effect) alone. The authors speculated that smoke-induced oxidative stress in underdeveloped airways (caused by impaired fetal growth) might lead to increased asthma risk. In this regard, it has been shown that smoke exposure interacts with *ADAM33* polymor-

phisms in a way that adversely affects lung function and hyperresponsiveness.

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Indoor Particulate Matter Increases Asthma Morbidity in Children With Non-Atopic and Atopic Asthma

McCormack MC, Breysse PN, Matsui EC, et al; Center for Childhood Asthma in the Urban Environment. *Ann Allergy Asthma Immunol.* 2011;106(4):308–315

PURPOSE OF THE STUDY. Environmental control is an accepted component of asthma management in children with atopic asthma, but it is not usually a part of management in nonatopic asthma. Air pollutants, particularly particulate matter, might have a stronger effect on nonatopic asthma and might have significant indoor sources. This study examined the effect of indoor particulate matter in children with asthma.

STUDY POPULATION. Studied were 150 predominantly black children from the east Baltimore, Maryland, area aged 2 to 6 years with physician-diagnosed asthma and symptoms or medication use in the previous 6 months. Most of the children were from lower-income households.

METHODS. Integrated air sampling in the child's bedroom was performed over 3 days at baseline, 3 months, and 6 months, using PM_{10} (particulate matter that is <10 μm in diameter) and $PM_{2.5}$ (particulate matter that is <2.5 μm in diameter) samples collected with personal environmental monitors. Ambient particulate matter for the study was monitored at a central site within the study area. Each child underwent baseline skin testing to a mix of 14 aeroallergens. Atopy was defined as at least 1 positive skin-test result. At baseline, 3 months, and 6 months, caregivers completed questionnaires adapted from the International Study of Asthma and Allergies in Childhood and the Children's Health Survey for Asthma Questions. Participants completed a daily activity diary during each 3-day monitoring period, including an account of the time spent in the room where monitoring was performed.

RESULTS. Subjects were classified as nonatopic (31%) or atopic (69%). Nonatopic children were slightly younger. Indoor $PM_{2.5–10}$ concentrations were similar in atopic and nonatopic children's homes, although $PM_{2.5}$ exposure was significantly higher in the homes of children with nonatopic asthma ($P = .04$). Concentrations of $PM_{2.5}$ exceeded Environmental Protection Agency standards in 75% of the homes. There were statistically significant interactions found between both coarse and fine particulate matter levels and asthma symptoms in both atopic and nonatopic asthmatic children.

CONCLUSIONS. In-home particle concentrations are associated with asthma morbidity, including symptoms and use of rescue medications, among atopic and nonatopic children with asthma. Strategies for reducing and eliminating sources of indoor particulate matter pollution should be considered a priority in the management of nonatopic asthma.

REVIEWER COMMENTS. This study is one of few to note that the effect of indoor air pollution is at least as important in nonatopic children with asthma. As clinicians, we often discuss secondhand smoke, which is a component of indoor particulate matter, but we also should consider other sources including cooking and cleaning products.

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Microsomal Epoxide Hydroxylase Genotypes/Diplotypes, Traffic Air Pollution, and Childhood Asthma

Tung KY, Tsai CH, Lee YL. *Chest.* 2011;139(4):839–848

PURPOSE OF THE STUDY. The gene that encodes microsomal epoxide hydroxylase, (*EPHX1*, is responsible for detoxification of reactive epoxides to generate reactive oxygen species. The different polymorphisms influence *EPHX1* activity. The associations of *EPHX1* Tyr113His and His139Arg genotypes and diplotypes with asthma and wheezing outcomes were examined with a focus on the functional genetic change in glutathione S-transferase m1 (GSTM1) genotypes.

STUDY POPULATION. The study included 3741 7th-grade schoolchildren from 14 communities enrolled in the Taiwan Children Health Study.

METHODS. Asthma and wheeze status was determined by a baseline questionnaire. Children were classified as having lifetime asthma (physician-diagnosed asthma) or early-onset asthma (onset at <5 years old). Air pollution data (average hourly NO_2 level) were available from monitoring stations for the Taiwan Environmental Protection Agency. DNA was collected from oral mucosa, and genomic DNA was isolated.

RESULTS. Having the *EPHX1* Arg/His or Arg/Arg genotypes at codon 139 was significantly associated with increased risks of lifetime asthma (adjusted odds ratio [aOR]: 1.3 [95% confidence interval (CI): 1.1–1.7] and 1.5 [95% CI: 1.1–2.1], respectively). The *EPHX1* diplotypes showed significant associations with lifetime asthma (global P value = .01) and early-onset asthma (global P value = .01). The risk of *EPHX1* 139Arg allele and 113Tyr139Arg diplotype was of greater magnitude in higher-NO_2 compared with lower-NO_2 communities.

The increase of the effect from the *EPHX1* 139Arg allele with higher NO_2 exposure was most marked in the GSTP1 Val allele and GSTM1-present genotype.

CONCLUSIONS. Children with high *EPHX1* activity have an increased risk of asthma and wheezing outcomes. The risk is higher with high NO_2 exposure and a GSTP1 105Val allele or GSTM1-present genotype, which suggests that these common genetic polymorphisms and diplotypes play important roles in asthma pathogenesis among children, depending on airway oxidative stress.

REVIEWER COMMENTS. This article, although technical, sheds light on the scientific background of a basic premise in asthma: the association of air pollution on asthma risk. The results of previous studies have suggested that exposure to air pollution carries an increased risk of asthma. This study examined the genetic basis of this principle with a focus on the epoxide hydroxylase enzyme activity. An increased risk of asthma was seen in children with certain genotypes, and the risk was of higher magnitude depending on environmental NO_2 levels. These results add to the complex pathogenesis of asthma in regards to both genetic and environmental influences.

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FOOD ALLERGY

National Prevalence and Risk Factors for Food Allergy and Relationship to Asthma: Results From the National Health and Nutrition Examination Survey 2005–2006

Liu AH, Jaramillo R, Sicherer SH, et al. *J Allergy Clin Immunol*. 2010;126(4):798–806

PURPOSE OF THE STUDY. To investigate the prevalence and demographic risk factors of food allergy (FA) and its association with other atopic diseases in a population sample.

STUDY POPULATION. Data were collected from 10 348 adult and children older than 1 year, who represented the national population from 30 sites across the continental United States. Blood was collected and specific immunoglobulin E (IgE) panels were run for 79.3% of the subjects.

METHODS. Specific IgE levels to peanut, cow's milk, egg white, and shrimp were collected from subjects aged 6 years and older. Shrimp-specific IgE was not tested for subjects younger than 6 years. Food sensitization was defined as having at least 1 food-specific serum IgE level at ≥0.35 kU/L. FA risk categories included unlikely FA (between ≥0.35 and 2 kU/L), likely FA (egg white: ≥7 kU/L, or ≥2 kU/L if ≤2 years old; milk: ≥15 kU/L, or ≥5 kU/L if ≤2 years old; peanut: ≥14 kU/L; and shrimp: ≥5 kU/L), and possible FA (between 2 kU/L and the likely FA threshold level for each food). Clinical FA rates were based on the sum of 50% of possible FA and 95% of likely FA.

RESULTS. Overall food sensitization was 16.8%. Milk and egg sensitization were highest (22% and 13.9%, respectively) in children aged 1 to 5 years. Peanut sensitization was highest in older children aged 6 to 19 years (10.7%) and young adults aged 20 to 39 years (8.7%). Shrimp sensitization did not vary with age. Overall prevalence of multiple sensitizations was 4.7%. The overall estimated clinical FA rate was 2.5% ([3.1% possible FA × 0.5] + 1.0% likely FA). The highest prevalence of clinical FA was in children aged 1 to 5 years (4.2%) and lowest in adults aged 60 years or older (1.3%). Clinical FA was 1.8% in children aged 1 to 5 years for milk, egg, and peanut. Peanut (2.7%) was the most common clinical FA in older children aged 6 to 19 years. Peanut and shrimp (range: 0.9%–1.2%) were the most common clinical FA in adults aged 20 to 59, and shrimp (0.7%) was the most common clinical FA in adults aged 60 years or older. Overall prevalence of multiple clinical FA was 1.3%. Clinical FA was more prevalent in younger subjects ($P < .001$), male subjects ($P < .001$), and non-Hispanic black subjects ($P < .001$). Household income and education level were not significantly associated with clinical FA. Subjects with doctor-diagnosed asthma were at a higher risk for likely FA; this risk increased with increased asthma persistence and severity and with an emergency department visit for asthma in the previous year. The odds of doctor-diagnosed hay fever were increased for those with possible FA. Eczema was not significantly increased for any FA risk group.

CONCLUSIONS. The estimated population prevalence of clinical FA was 2.5% and was associated with childhood, male gender, and non-Hispanic black race/ethnicity. Asthma and emergency department visits for asthma were associated with likely FA.

REVIEWER COMMENTS. This is an important study that investigated the prevalence of clinical FA in children and adults in the same large population sample; it confirmed early observations of association of FA with childhood, non-Hispanic black race, and asthma. Use of objective data eliminated some limitations of previous survey studies. However, these data most likely underestimate clinical FA, because the study only accounted for 4 common allergenic foods, no clinical history is included (a small but significant percentage of patients with undetectable specific IgE might have clinical FA), and confirmation with oral food challenges was not performed. The next step will be to expand the number of foods

investigated and develop protocols for confirming clinical FA in a large sample.

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a higher rate of soy reactivity among infants with CMP FPIES.

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The Prevalence and Natural Course of Food Protein-Induced Enterocolitis Syndrome to Cow's Milk: A Large-Scale, Prospective Population-Based Study

Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. *J Allergy Clin Immunol*. 2011;127(3):647–653

PURPOSE OF THE STUDY. To prospectively determine the prevalence, clinical characteristics, and natural history of food protein–induced enterocolitis (FPIES) in association with cow's milk protein (CMP).

STUDY POPULATION. In this birth-cohort study, 13 019 of 13 234 newborns (98.4%) born over a 2-year period from June 2004 to June 2006 were enrolled.

METHODS. Information on reactions to CMP were obtained for all infants, and those with probable reactions were evaluated with skin-prick testing and oral challenge if clinically indicated. Criteria for CMP FPIES included onset at less than 9 months; vomiting, diarrhea, or both within 24 hours after the ingestion of milk in the absence of other immunoglobulin E (IgE)-mediated symptoms; and a positive challenge to milk that resulted in the symptoms listed above or removal of milk resulting in resolution of the symptoms.

RESULTS. The cumulative incidence of CMP FPIES was 0.34% (44 of 13 019). The most common symptoms were vomiting (100%), lethargy (77%), diarrhea (25%), pallor (14%), and bloody diarrhea (4.5%). All patients were diagnosed before the age of 6 months. Fifty percent of the cases resolved around the age of 1, and 90% resolved by age 3. Eight patients with FPIES had IgE-mediated milk allergy, and none had concomitant soy allergy.

CONCLUSIONS. The prevalence of FPIES is low but significant. Most patients with FPIES recover in early childhood. A significant proportion of CMP FPIES might convert to IgE-mediated milk allergy.

REVIEWER COMMENTS. This study is unique because of its large size and prospective design. It provides much needed information on the prevalence and natural history of CMP FPIES and highlights the possible overlap between FPIES, which is considered a non–IgE-mediated allergy, and IgE-mediated milk allergy. Soy might be a reasonable alternative to hypoallergenic formulas in infants with CMP FPIES, although previous US studies revealed

Can Early Introduction of Egg Prevent Egg Allergy in Infants? A Population-Based Study

Koplin JJ, Osborne NJ, Wake M, et al. *J Allergy Clin Immunol*. 2010;126(4):807–813

PURPOSE OF THE STUDY. Earlier guidelines, in which delaying the introduction of potentially allergenic foods to infancy in an effort to prevent food allergy was recommended, were based on little evidence. These researchers sought to determine if the development of egg allergy by 12 months of age is associated with the age at which egg and solids are introduced and the duration of breastfeeding.

STUDY POPULATION. Subjects aged 11 to 15 months were recruited during immunization visits as part of the Australian HealthNuts study, which was a single-center, population-based, cross-sectional study of food allergy.

METHODS. During the clinic wait period after immunization, skin-prick tests for egg white, saline, and histamine were administered. Before the results were read, a questionnaire was administered to the parents regarding age of egg introduction. A second self-administered questionnaire collected information regarding duration of breastfeeding and age of solids introduction. Infants with positive skin-prick-test results to egg (wheal size $\geq$1 mm greater than negative saline control) were offered oral food challenges within the next 4 to 8 weeks. Infants with a history of reaction to egg in the previous month and/or a positive skin-prick-test result who were currently avoiding egg were considered egg allergic and excluded from oral food challenges.

RESULTS. Of 3552 eligible infants, 2589 (73%) were recruited. Results of egg skin-prick tests were positive for 448 infants, and 340 infants underwent an oral food challenge. Overall, 231 infants (8.9%) were determined to be egg-allergic. Egg introduction at 4 to 6 months was associated with a decreased risk of egg allergy, whereas egg introduction after 10 months was associated with an increased risk of egg allergy in both low- and high-risk infants. High-risk infants with a family history of allergy or a personal history of food allergy or eczema had a much higher risk of egg allergy (odds ratio [OR]: 6.7 [95% confidence interval (CI): 4.7–9.6]). Age of introduction of cooked egg (boiled, scrambled, fried, or poached) was significantly associated with egg allergy, whereas age of introduction of baked egg

(egg-containing products such as cakes or biscuits) was not. The lowest risk for egg allergy was found in infants introduced to cooked egg at 4 to 6 months (OR: 0.2 [95% CI: 0.06–0.71]; $P = .012$). There was no association of egg allergy with duration of breastfeeding (after adjustment for family and personal history of allergy) or age of introduction of other solid foods.

CONCLUSIONS. Introduction of cooked egg (boiled, scrambled, fried, or poached) at 4 to 6 months of age might protect against egg allergy irrespective of family or personal history of allergy. Duration of breastfeeding and age of introduction of other solids does not seem to affect development of egg allergy.

REVIEWER COMMENTS. In light of the changing perception that early instead of delayed exposure of commonly allergenic foods might lead to tolerance, this study is an important step in determining how the timing of introduction and form of food introduced (eg, cooked versus baked) might influence the development of food allergy. A large population was studied, and 75% of positive skin-prick-test results were confirmed with oral food challenges; however, egg-introduction history was retrospective and might have been subject to recall bias. The next step would be a prospective study on egg introduction to confirm these observations and to determine if the protective effect is limited only to egg or affects other food allergies such as those to peanut.

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Early Exposure to Cow's Milk Protein Is Protective Against Immunoglobulin E (IgE)-Mediated Cow's Milk Protein Allergy

Katz Y, Rajuan N, Goldberg MR, et al. *J Allergy Clin Immunol.* 2010;126(1):77–82

PURPOSE OF THE STUDY. The investigators determined the prevalence of cow milk allergy, the cross-reactivity with soy, and risk factors for the development of cow milk allergy in a large-scale, population-based prospective study.

STUDY POPULATION. All infants (13 234) born from June 10, 2004, to June 30, 2006, at the Assaf-Harofeh Hospital in Zerifin, Israel, were eligible for enrollment. The feeding history was obtained for 98.4% (13 019) of these infants, mostly by telephone interview.

METHODS. In the newborn period, after routine anticipatory guidance, in which breastfeeding was encouraged and other alternative cow milk–based feeding programs were reviewed, parents were asked to either fill in a questionnaire or contact the allergy clinic immediately after any suspected adverse reaction to the initiation of cow milk–protein feeding. If no unusual event was noted, the families were asked to contact the allergy clinic 14 to 30 days after initiation of cow milk–based feeding. Any parents who noted a possible adverse reaction were interviewed by an investigator and invited for examination and testing. Final diagnosis of immunoglobulin E (IgE)-mediated cow milk–protein allergy was made independently by 2 investigators, and any disagreement (2 cases) was resolved with conjoint discussion. Skin-prick testing to cow's milk and soy was conducted, as were open cow milk challenges.

RESULTS. The cumulative incidence of IgE-mediated cow milk allergy was 0.5% (66 of 13 019). The mean age of cow milk introduction was significantly different ($P < .001$) between healthy infants (61.6 ± 92.5 days) and those with IgE-mediated cow milk allergy (116.1 ± 64.9 days). Only 0.05% of the infants who were started on regular cow milk–protein formula within the first 14 days versus 1.75% who were started on formula between the ages of 105 and 194 days had IgE-mediated cow milk allergy ($P < .001$). None of the patients with IgE-mediated cow milk allergy proved to have an IgE-mediated soy allergy.

CONCLUSIONS. In this patient population, IgE-mediated cow milk allergy is less prevalent than previously reported. Early exposure to cow milk protein seemed to be protective against cow milk allergy.

REVIEWER COMMENTS. The results of this study, as well as those of other recent investigations, go against the previous mantra that prolonged restriction of specific food allergens might be helpful in the prevention of food sensitivity in the early years. Early introduction of specific dietary proteins seems to lead to tolerance, although the exact timing and dose required have not been determined. It is remarkable that none of the subjects with IgE-mediated milk allergy proved to have soy allergy, contrary to a reported co-reactivity of 10% to 14%. Because the reported rate of IgE-mediated milk allergy is lower in this study population than has been reported previously, additional studies are required to confirm these findings.

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Peanut Oil and Peanut Allergy, Foes or Folks?

Ho MH, Lee S, Wong WH, Lau Y. *Arch Dis Child.* 2011; 95(10):856–857

PURPOSE OF THE STUDY. Peanut allergy seems to be increasing among children in Hong Kong. The authors of this study report suggested that this increase might be a result of changes in edible oils. Crude peanut oil (protein content:

100–300 μg/mL) was "ubiquitous in maternal and infant diet in Hong Kong in the past" but has now largely been replaced by olive oil.

METHODS. The consumption of various oils was estimated from data on imports. Per-capita consumption was calculated on the basis of population over time.

RESULTS. Per capita consumption of crude peanut oil fell ~30-fold over the last 15 years, whereas consumption of olive oil increased ~30-fold over the same time period.

CONCLUSIONS. It is gaining consensus that avoiding consumption of peanut abrogates development of oral tolerance and increases risk of hypersensitivity through cutaneous exposure. The timing and perhaps the dosage and the balance of cutaneous and oral exposure determine whether a child will have allergy or tolerance. Crude edible peanut oil contains immunogenicity-competent protein fractions that might deserve further studies on its implication on peanut-allergy prevention.

REVIEWER COMMENTS. The authors suggested that oral consumption of crude peanut oil (contaminated with peanut protein) might have been protecting infants in Hong Kong from peanut allergy by tolerizing them and that now, without this early enteral exposure, more are becoming sensitized through cutaneous or respiratory routes. This concept is consistent with data from other studies that suggest that early feeding of food proteins is protective against the development of allergy and that early feeding avoidance (which leaves only cutaneous or respiratory exposure) might actually cause allergy. The American Academy of Pediatrics no longer advocates delayed introduction of any food past 4 months of age. Prospective, blinded, randomized trials are underway to better characterize the relationship between route, timing, and dose of food exposure and subsequent development of allergy.

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Maternal Consumption of Peanut During Pregnancy Is Associated With Peanut Sensitization in Atopic Infants

Sicherer SH, Wood RA, Stablein D, et al. *J Allergy Clin Immunol*. 2010;126(6):1191–1197

PURPOSE OF THE STUDY. To identify factors associated with peanut sensitization.

STUDY POPULATION. The study population included 512 infants aged 3 to 15 months with likely milk or egg allergy but no previous diagnosis of peanut allergy.

METHODS. Enrollment criteria included history of immediate allergic reactions to cow's milk (and/or egg) and a positive skin-prick-test (SPT) result to milk (or egg if the clinical reaction was to egg) and/or moderate-to-severe atopic dermatitis and a positive SPT result to milk or egg. This longitudinal study was aimed at observing the development of peanut allergy; therefore, children with a known peanut allergy or known peanut-specific immunoglobulin E (IgE) level of ≥5 kU of antibody (kU_A)/L before enrollment were excluded. Maternal ingestion of peanut was queried retrospectively. In categorical analyses, frequent maternal peanut ingestion was defined as ≥2 times per week. A peanut-IgE level of ≥5 kU_A/L was used as the end point to signify a high likelihood of peanut allergy.

RESULTS. The 503 participants from whom blood samples were obtained were included. At enrollment, 140 (27.8%) of the participants were found to have a peanut-IgE level of ≥5 kU_A/L. A peanut-IgE level of ≥5 kU_A/L was associated with sensitization to egg or milk, male gender, nonwhite race, and frequent maternal peanut consumption during pregnancy. There was a dose-dependent association between frequent maternal peanut ingestion during pregnancy or breastfeeding and a peanut-IgE level of ≥5 kU_A/L, but only consumption during pregnancy was a significant predictor. Of the 71 infants who were never breastfed, frequent peanut consumption during pregnancy was related to a peanut-IgE level of ≥5 kU_A/L.

CONCLUSIONS. Maternal ingestion of peanut during pregnancy was strongly associated with peanut sensitization in infancy.

REVIEWER COMMENTS. Dietary advice for mothers during pregnancy and lactation is controversial because of conflicting results from previously published retrospective studies. This observational investigation of young atopic infants provides evidence that frequent consumption of peanut (≥2 times per week) during pregnancy is related to peanut sensitization; however, the development of clinical peanut allergy was not determined. The American Academy of Pediatrics (AAP) previously recommended peanut avoidance for pregnant and lactating women; however, the lack of scientific evidence to support such recommendations led to their withdrawal of that recommendation in 2008. Currently, neither the AAP nor the National Institute of Allergy and Infectious Diseases (NIAID) expert panel recommends maternal dietary avoidance of any foods, including peanut. The development of clinical peanut allergy among this study's cohort, as well as results of prospective investigations, will need to be examined before more definitive maternal dietary recommendations can be made.

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Maternal Antenatal Peanut Consumption and Peanut and Rye Sensitization in the Offspring at Adolescence

Kemp AS, Ponsonby AL, Dwyer T, Cochrane JA, Pezic A, Jones G. *Clin Exp Allergy*. 2011;41(2):224–231

PURPOSE OF THE STUDY. To examine the influence of antenatal peanut ingestion on peanut and rye sensitization.

STUDY POPULATION. The 373 participants were drawn from a cohort of 1437 children born in Tasmania in 1988 and 1989, selected from all births for being at elevated risk of sudden infant death syndrome. Those who were not lost to follow-up and who subsequently agreed to participate at age 8 in studies on bone density, blood pressure, high-density lipoprotein cholesterol, and vitamin D and at age 16 in a study of bone health and allergy were included.

METHODS. The mothers completed a hospital interview shortly after delivery that included a food-frequency questionnaire of diet in the third trimester and family history of asthma. Those mothers who ingested peanut at least once per month were regarded as eating peanut. Peanut and rye sensitization at age 16 were determined by using the ImmunoCAP test (Phadia, Uppsala, Sweden). An allergen-specific immunoglobulin E (IgE) level of >0.35 kU of antibody (kU_A)/L was regarded as a positive result.

RESULTS. The peanut sensitization rate was 14%. In the entire cohort ($N = 310$), there was no association between antenatal peanut ingestion and peanut sensitization ($P = .17$). However, there was a strong association between antenatal peanut ingestion and decreased risk of rye sensitization and peanut sensitization in those ($n = 201$) without a family history of asthma (rye odds ratio [OR]: 0.30 [95% confidence interval (CI): 0.14–0.63], $P = .001$; peanut OR: 0.18 [95% CI: 0.04–0.78], $P = .02$). There was an increased risk of rye sensitization in those ($n = 108$) with a family history of asthma and antenatal peanut ingestion (rye OR: 2.69 [95% CI: 1.11–6.51], $P = .03$). It was considered that these sensitizations were likely to be related to the presence of IgE antibodies to cross-reacting carbohydrate epitopes common to rye and peanut allergens, which are not the epitopes thought to typically contribute to clinical disease.

CONCLUSIONS. Antenatal peanut ingestion might influence the development of IgE antibody to cross-reacting carbohydrate epitopes in later life, and avoidance might inadvertently increase sensitization in some people. Genetic factors might modify this association.

REVIEWER COMMENTS. This study is the first to obtain prospective data on antenatal peanut consumption in a population-based cohort rather than one with a family history of allergy. Selection bias is likely to have been limited, because the subjects were initially recruited for a study of nonatopic conditions, but there was a substantial loss to follow-up that might have introduced unrecognized bias. The fact that the results were not significant overall, but were significant and meaningful when considered according to family history of asthma, adds to the evidence that the relationship between sensitization and disease, and antenatal and early life exposure to allergens, is complex and depends on multiple factors.

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Oral Food Challenges in Children With a Diagnosis of Food Allergy

Fleischer DM, Bock SA, Spears GC, et al. *J Pediatr*. 2011;158(4):578–583

PURPOSE OF THE STUDY. To assess the outcome of oral food challenges (OFCs) in a pediatric patient population placed on elimination diets often based solely on the results of food-specific immunoassays (specific immunoglobulin E [IgE] testing).

STUDY POPULATION. Included was a pediatric population of 125 children (median age: 4 years) with active atopic dermatitis (AD) and food avoidance evaluated at National Jewish Health (Denver, CO).

METHODS. This was a retrospective chart review of patients who underwent at least 1 OFC to evaluate for an IgE-mediated reaction. OFCs were conducted after reviewing clinical history, skin-prick-test (SPT) results, and serum allergen-specific IgE test results. If there was a history of a convincing reaction within the previous 6 to 12 months or if a reaction was life-threatening, then an OFC was not performed.

RESULTS. Ninety-six percent of the patients evaluated had AD, and OFCs were only undertaken once appropriate AD treatment had been started. Of the 364 OFCs performed on avoided foods, results were negative for 325 (89%). Of the 122 foods that were being avoided because of previous adverse reactions, 102 (84%) had a negative OFC result. Of the 111 foods being avoided because of immunoassay or skin-prick testing results, 103 (93%) had a negative OFC result. For foods without established decision points (ie, foods other than milk, egg, and peanut), there was a wide range of immunoassay results, and 93% had negative OFC results. Many foods were being avoided for reasons other than serum test results or a history linking the food to an observed reaction, and of those 131 OFCs, results were positive for only 11 of them.

CONCLUSIONS. Using serum food-specific IgE testing alone to diagnose food allergy, especially for children with AD,

might result in an overly restrictive food-elimination diet.

REVIEWER COMMENTS. Although the retrospective design of the study did cause some limitations, the takeaway point for pediatricians and allergists alike should be that SPTs and immunoassays alone do not definitively diagnose food allergy, especially when evaluating nonanaphylactic symptoms of food allergy (eg, AD). Serum allergen-specific IgE testing, when necessary, should be directed toward relevant allergens only. OFCs performed in a board-certified allergist's office to confirm food-allergy status remain the most reliable test for food-allergy diagnosis. Further prospective studies that examine specific IgE levels and SPT results for suspected food allergy in patients with and without AD are needed.

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Performance of a Component-Based Allergen-Microarray in the Diagnosis of Cow's Milk and Hen's Egg Allergy

D'Urbano LE, Pellegrino K, Artesani MC, et al. *Clin Exp Allergy*. 2010;40(10):1561–1570

PURPOSE OF THE STUDY. Published clinical decision points (CDPs) have improved the accuracy of current allergen-specific immunoglobulin E (sIgE) testing, but the oral food challenge (OFC) remains the gold standard. These researchers sought to evaluate the performance of an in vitro microarray-based diagnostic test for the diagnosis of cow's milk (CM) and hen's egg (HE) IgE-mediated allergy.

STUDY POPULATION. Infants and children ($N = 104$; median age: 4.9 years [range: 0.7–15.1 years]) referred to the allergy clinic with a history of CM or HE consumption and a resultant severe and/or immediate reaction were included in the study.

METHODS. Using the ImmunoCAP system (Phadia, Uppsala, Sweden), sIgE testing was performed to milk, α-lactalbumin, β-lactoglobulin, casein, egg white, and egg yolk. Microarray testing was performed to multiple known CM and HE allergen components. OFCs were performed on all subjects using pasteurized CM and boiled egg. Negative OFCs to boiled egg were followed by an OFC to raw egg. OFCs were discontinued for anaphylactic shock or objective symptoms in 2 or more systems.

RESULTS. For CM allergy, sIgE testing to milk and casein and microarray testing to Bosd8 provided the highest accuracy for predicting OFC outcomes. For HE allergy, results of sIgE testing to egg white and microarray testing to Gald1 (ovomucoid) were most accurate. For CM allergy, the milk sIgE 95% CDP (≥16.6 kU/L) resulted in a positive predictive value (PPV) of 93% and a negative predictive value (NPV) of 57% compared with the Bosd8 microarray 95% CDP (>0.60 ISU [ISAC standardized units]), which resulted in a PPV of 96% and an NPV of 78%. For HE allergy, the egg white sIgE 95% CDP (≥25.3 kU/L) resulted in a PPV of 86% and an NPV of 59% compared with the Gald1 microarray 95% CDP (>0.86 ISU), which resulted in a PPV of 94% and an NPV of 79%. Sequential use of sIgE and microarray testing for both CM and HE yielded minimally improved results.

CONCLUSIONS. Component-based allergen microarray provides improved PPV and NPV in the diagnosis of CM and HE allergy when compared with standard sIgE testing. The improved accuracy can reduce the number of OFCs that need to be performed and, more importantly, can reduce the number of positive challenge results, thereby decreasing the risk to patients.

REVIEWER COMMENTS. This well-designed, prospective study found strong performance of component-based microarray testing for food allergy. However, the modest additional accuracy of microarray testing, when balanced with its limited availability and its considerable cost, limits its practical benefit. As the authors suggested, it might presently be more suited to large tertiary care centers as a secondary screen after standard specific IgE testing has been performed.

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Serum Immunoglobulin E (IgE) Measurement and Detection of Food Allergy in Pediatric Patients With Eosinophilic Esophagitis

Erwin EA, James HR, Gutekunst HM, et al. *Ann Allergy Asthma Immunol.* 2010;104(6):496–502

PURPOSE OF THE STUDY. To determine the degree of allergic sensitization in patients with eosinophilic esophagitis by using serum immunoglobulin E (IgE) testing and comparing the results to those obtained by epicutaneous skin-prick tests (SPTs) and patch testing.

STUDY POPULATION. This was a cross-sectional study of pediatric patients ($N = 53$) referred for evaluation for biopsy-proven eosinophilic esophagitis at an allergy referral clinic at Nationwide Children's Hospital (Columbus, OH) over a 2½-year period (January 2007 to June 2009).

METHODS. Questionnaires about symptoms and treatment of eosinophilic esophagitis were completed. Serum-specific IgE antibodies to 8 common foods and

8 inhalants were measured. Epicutaneous SPTs were performed to 16 foods and 38 inhalant allergens. Patch testing to foods was also performed. IgE-mediated allergy was diagnosed if either serum-specific IgE or skin-prick test results were positive, whereas non–IgE-mediated allergy was diagnosed if a positive patch test result was found. A streptavidin-based immunoassay was performed to determine the presence of cross-reactive carbohydrate determinants and *Helicobacter pylori.*

RESULTS. Prevalence of food and inhalant allergy was 80%. The most common symptoms were dysphagia, vomiting, and abdominal pain. Food-specific IgE test results were positive to food more often than were SPT results, most commonly to milk. Serum-specific IgE detected sensitization to food in 42% of patients without a diagnosis of food allergy. Food and inhalant allergies were found with similar frequencies. Almost one-third of patients had multiple sensitivities (tree nuts, peanut, pollen, soy, and grains). Recent studies revealed allergy to plant and mammalian-derived cross-reactive carbohydrate determinants, and 3 patients were found to have a positive result (2 to bromelain and 1 patient to galactose-α-1,3-galactose). Patch-testing results were positive for more than one-third of the patients, most commonly to rye, without correlation to either serum-specific IgE or SPT results.

CONCLUSIONS. The majority of patients with eosinophilic esophagitis are atopic. The use of serum-specific IgE to foods might be useful, in particular to milk.

REVIEWER COMMENTS. The treatment of patients with eosinophilic esophagitis is challenging. The authors found that almost half of the patients were identified to have sensitization to a previously undiagnosed food allergen. Although the clinical significance of the serum-specific IgE might be argued, elimination diets for most patients with eosinophilic esophagitis leads to improvement. This study provides insight into another diagnostic modality, frequently used in the diagnosis of other allergic conditions, that might aid clinicians in the diagnosis and treatment of patients with eosinophilic esophagitis. However, more correlation with response to elimination of specific foods is needed.

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Esophageal Subepithelial Fibrosis and Hyalinization Are Features of Eosinophilic Esophagitis

Li-Kim-Moy JP, Tobias V, Day AS, Leach S, Lemberg DA. *J Pediatr Gastroenterol Nutr*. 2011;52(2):147–153

PURPOSE OF THE STUDY. The overlap of clinical and histologic findings between eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD) can lead to difficulty distinguishing these 2 conditions. These researchers sought to determine if subepithelial fibrosis could be a more specific distinguishing histologic feature of EoE.

STUDY POPULATION. From 358 esophageal biopsies collected from 1995–2008 in a children's hospital in Sydney, Australia, 27 children with EoE and 24 children with GERD were identified. Seventy percent of the patients were male and ranged from 7 months to 16 years of age.

METHODS. EoE was defined as ≥15 eosinophils per high-powered field, whereas GERD biopsies had <15 eosinophils per high-powered field. Retrospective chart reviews were performed to assess clinical symptoms, and the presence of subepithelial fibrosis was assessed with esophageal biopsy specimens.

RESULTS. Subepithelial fibrosis was observed in 24 (89%) children with EoE and in 9 (38%) children with GERD ($P < .0001$). Fibrosis in EoE was not associated with lymphoid tissue and was less likely to occur in younger children (1.84 vs 7.02 years; $P = .02$).

CONCLUSIONS. Subepithelial fibrosis was a common finding in children with EoE; it occurred in 89% of the children. Fibrosis was more likely to occur in older children and children with longer symptom duration.

REVIEWER COMMENTS. The finding of subepithelial fibrosis in children with EoE has long-term implications. If EoE pathophysiology has any similarity to asthma (which this article suggests), then early recognition and treatment to prevent fibrosis and remodeling of the esophagus are crucial. Esophageal remodeling might explain why some children with EoE have persistent symptoms despite reduction in eosinophils and why this disease is rarely short-lived.

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Feeding Dysfunction in Children With Eosinophilic Gastrointestinal Diseases

Mukkada VA, Haas A, Creskoff Maune N, et al. *Pediatrics*. 2010;126(3). Available at: www.pediatrics.org/cgi/content/full/126/3/e672

PURPOSE OF THE STUDY. Feeding dysfunction (FD) is a symptom complex commonly associated with neurologic diseases, developmental delays, and, occasionally, gastroesophageal reflux disease. Symptoms might range from abnormal feeding behavior and immature diet preferences to sensory and motor skill deficits. The purpose of this study was to define the prevalence and feeding

characteristics of FD in children with eosinophilic gastrointestinal diseases (EGIDs).

STUDY POPULATION. The study included children previously evaluated in the multidisciplinary EGID program at Children's Hospital National Jewish Health (Aurora, CO) between January and December 2008.

METHODS. Retrospective analysis of medical records ($N = 200$) assessed patients for EGID and FD (determined by feeding therapists using a feeding assessment that addressed symptoms, observation of functional skills, learned behaviors, mealtime dynamics with caregivers, and developmental skills).

RESULTS. Thirty-three (16.5%) patients (age range: 14–113 months) were identified as having both EGID and FD. Food sensitivity was noted in 88% of the patients, and 52% of them had clinical evidence of other allergic disease. Twenty-five of the 33 patients (76%) had eosinophilic esophagitis, defined by ≥15 eosinophils per high-powered field. Learned maladaptive feeding behaviors were the predominant form of FD and were noted in 93.9% of the children; gagging or vomiting was seen in 84.8% of them. Twenty-one percent were diagnosed with failure to thrive, and nearly 70% required individual or group feeding therapy.

CONCLUSIONS. Feeding difficulties are prevalent in children with EGIDs and might persist even after eosinophilic inflammation is treated.

REVIEWER COMMENTS. This study highlights the importance of assessing for FD in children with EGIDs and vice versa, because appropriate management of both disease states might enhance outcomes. The authors were able to examine the records of a relatively large number of patients. Potential limitations of the study were its retrospective design, lack of a universally accepted feeding-assessment protocol, and possible referral bias.

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STUDY POPULATION. Children aged 1 to 18 years who had had an esophagogastroduodenoscopy (EGD) over an 8-year period (1999–2007) were assessed. The study was conducted at a children's hospital in Indianapolis, Indiana.

METHODS. A retrospective chart review was performed to identify children with EE-A, defined as EoE with ≥10 eosinophils per high-powered field in a gastric biopsy. Clinical characteristics and response to swallowed fluticasone between children with EE-A and children with EE-N were compared by using 2-sample t and χ^2 tests.

RESULTS. A total of 356 children with EoE were identified: 41(12%) met criteria for EE-A. When compared to a randomly selected group of 50 children with EE-N, there was no difference regarding gender, age, presenting symptoms, atopy history, or esophageal histology. Both groups had similar responses to swallowed fluticasone (significant reductions in the number of esophageal eosinophils). In 11 children with EE-A treated with swallowed fluticasone, 9 (82%) had a reduction in the number of gastric eosinophils (to <5 eosinophils per high-powered field). No differences were observed between responders and nonresponders.

CONCLUSIONS. Twelve percent of the children with EoE had an increased number of gastric eosinophils; however, the presence of increased numbers of gastric eosinophils does not portend a worse clinical presentation or result in a reduced response to swallowed fluticasone.

REVIEWER COMMENTS. Just when we thought we were starting to understand EoE, gastroenterologists are now identifying children with clinical symptoms and an increased number of eosinophils in areas distal to the gastroesophageal junction. Although the authors admitted that they did not have a study group of patients with only eosinophilic gastritis, the lack of differences between EE-N and EE-A was reassuring. This study's results offer another twist in the continuing story of eosinophilic gastrointestinal disorders.

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Incidental Gastric Eosinophils in Patients With Eosinophilic Esophagitis: Do They Matter?

Ammoury RF, Rosenman MB, Roettcher D, Gupta SK. *J Pediatr Gastroenterol Nutr*. 2010;51(6):723–726

PURPOSE OF THE STUDY. Some patients with eosinophilic esophagitis (EoE) demonstrate an increased number of eosinophils in gastric mucosa. These researchers sought to assess clinical and therapeutic differences in children with EoE and either no gastric eosinophils (EE-N) or an increased number of gastric eosinophils (EE-A).

Safe Vaccination of Patients With Egg Allergy With an Adjuvanted Pandemic H1N1 Vaccine

Gagnon R, Primeau MN, Des Roches A, et al; PHAC-CIHR Influenza Research Network. *J Allergy Clin Immunol.* 2010;126(2):317–323

PURPOSE OF THE STUDY. Influenza vaccines are produced from embryonated hens' eggs and contain residual, variable amounts of egg protein. This study attempted to better characterize reaction risk in a large population of egg-allergic persons.

STUDY POPULATION. Patients with egg allergy were recruited from consulting allergists for the purpose of being vaccinated against pandemic H1N1 influenza virus in the fall of 2009. A minority of them had previously been vaccinated for seasonal influenza without reaction. Egg allergy was defined as a minimum of 1 sign or symptom occurring within 60 minutes of ingesting egg, confirmed by either a positive skin-test result or an egg-specific immunoglobulin E (IgE) level of ≥0.35 kU/L. Also included in this group were persons who had no history of egg protein ingestion but who had both a positive egg skin-test result and positive serology results (specific IgE ≥ 2 kU/L if <2 years of age and ≥7 kU/L if ≥2 years). A control group with egg tolerance was included.

METHODS. This study involved 2 stages, the first of which was conducted by allergists in the population described above. Because the results suggested minimal risk, an expanded program of vaccination was undertaken for patients who self-reported egg allergy. Vaccine was administered in the study population in a single dose to patients deemed at low risk (mild gastrointestinal/skin reactions) and in 2 doses (10% and 90%) at 30-minute intervals for those deemed at higher risk (asthma or cardiovascular reactions). Patients were observed for 60 minutes after vaccination. After the first stage revealed limited risk of anaphylaxis in the first 900 egg-allergic patients, special clinics began a rapid vaccination program with a mandatory surveillance protocol.

RESULTS. Among 830 patients with confirmed egg allergy, 9% had vaccine administered in divided doses. No patient had an anaphylactic reaction. Nine patients had minor allergic symptoms. The proportion of patients who presented with signs/symptoms compatible with an allergic reaction was similar (3.1%) in the control group and the group of patients with egg allergy. In the second stage of expanded vaccination of 3640 additional patients, 2 were treated with epinephrine, although neither of them fulfilled study criteria for anaphylaxis.

CONCLUSIONS. Vaccination of patients with egg allergy with adjuvanted pandemic H1N1 vaccine seems to be safe, and the results of this study are in line with those of previous studies performed with seasonal influenza vaccine. Vaccines in this study had low levels of ovalbumin. Further studies might assess the risk after administering vaccine with the higher ovalbumin levels found in seasonal vaccine.

REVIEWER COMMENTS. The authors pointed out that patients with the most severe egg-allergy histories might have avoided vaccination altogether. There is still no published study of this much smaller, highest-risk group. However, these results add to others that indicate that vaccination can safely proceed in most children with egg allergy, particularly with vaccines that now have lower egg content.

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Variations in Quality of Life Among Caregivers of Food Allergic Children

Springston EE, Smith B, Shulruff J, et al. *Ann Allergy Asthma Immunol*. 2010;105(4):287–294

PURPOSE OF THE STUDY. To better understand the relationship between pediatric food allergy and caregiver quality of life.

STUDY POPULATION. Caregivers of food-allergic children were recruited through targeted Web pages on food-allergy resource and social media sites to complete an anonymous Web-based Food Allergy Quality of Life-Parental Burden (FAQL-PB) questionnaire.

METHODS. Caregivers completed the validated FAQL-PB questionnaire to measure the effect of food allergy on caregiver health-related quality of life. This focused on areas most affected including family/social activities, health, and emotional concerns. To assess caregiver knowledge and the child's history of food allergy, they also completed the validated Chicago Food Allergy Research Survey for Parents. Descriptive statistics were used to evaluate how troublesome different aspects of quality of life were for them (minimally, moderately, or extremely troubled).

RESULTS. Data were compiled from 1126 caregivers across the United States. Of these caregivers, 90.1% were white, 95.0% were female, and 75.3% had a 4-year college degree or more. There was wide variation in the impact of food allergy on caregiver quality of life with the exception of consistency of caregivers feeling troubled with regard to social limitations resulting from their child's food allergy. Poor quality of life was associated with caregivers being more knowledgeable about food allergies and being familiar with epinephrine administration and the child having had food-allergy–related emergency department visits in the previous year, having multiple food allergies, and having milk or wheat allergy (versus not).

CONCLUSIONS. Caregiver quality of life varies greatly; however, severity, the number of food allergies, and specific food allergies to milk or wheat were associated with lower caregiver quality of life.

REVIEWER COMMENTS. Although this study had limitations including the uniform, educated, upper-income population and the lack of information regarding the time since

the food-allergy diagnosis, there are clear lessons to be learned. As physicians, we need to support families, address their concerns, and discuss ways to minimize risk while allowing social interactions.

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Bullying Among Pediatric Patients With Food Allergy

Lieberman JA, Weiss C, Furlong TJ, Sicherer M, Sicherer SH. *Ann Allergy Asthma Immunol*. 2010;105(4):282–286

PURPOSE OF THE STUDY. To determine the scope and characteristics of bullying, teasing, or harassment of food-allergic patients because of their food allergies.

STUDY POPULATION. A specialized questionnaire developed by experts in food allergy and bullying was administered to teenagers and adults with food allergies and parents/caregivers of children with food allergies at conferences of the Food Allergy & Anaphylaxis Network in 2009.

METHODS. The anonymous questionnaire included 11 demographic questions and 16 questions about bullying, teasing, and harassment.

RESULTS. Most of the 353 completed surveys were taken by parents of food-allergic children. Of the food-allergic children, 61% were male, 95% were white, and 55% were 4 to 11 years old. Overall, 24% were reported to have been bullied, teased, or harassed about their food allergies, and 86% reported multiple episodes. Most (82%) of the episodes occurred at school (80% by classmates and 21% by teachers/staff). A total of 57% reported physical events, and 66% reported sadness or depression related to the events.

CONCLUSIONS. Food-allergic children experience bullying that is common, frequent, and repetitive, and there are resultant physical and emotional risks.

REVIEWER COMMENTS. This study was limited by a possibly biased and homogenous sample. Because bullying and food allergy are increasing in society, it becomes even more important to understand the burden of bullying in people with food allergy and to work to develop educational programs and strategies for preventing this from occurring. As clinicians, we need to screen our food-allergic patients for maltreatment so that we can identify and support them.

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ATOPIC DERMATITIS

Trends in Eczema in the First 18 Years of Life: Results From the Isle of Wight 1989 Birth Cohort

Ziyab AH, Raza A, Karmaus W, et al. *Clin Exp Allergy*. 2010;40(12):1776–1784

PURPOSE OF THE STUDY. To prospectively describe the changes in eczema prevalence and the influence of gender and atopy from birth to 18 years of age within a single cohort of children.

STUDY POPULATION. All children enrolled in the 1989 Isle of Wight, United Kingdom, birth cohort ($N = 1536$) were recruited, and 1456 children consented to participate in the study. Ninety-nine percent of the population was white and lived in a semirural region with no heavy industry.

METHODS. Subjects were assessed for eczema at 1, 2, 4, 10, and 18 years of age with a detailed questionnaire and physical examination. Atopy was evaluated through skin testing to select indoor and outdoor aeroallergens and to foods commonly implicated in allergy. Only 1- and 2-year-old subjects who were symptomatic with their eczema were skin-tested, whereas all 4-, 10-, and 18-year-old subjects were skin-tested. χ^2 tests were performed to estimate the difference in eczema occurrence and resolution rates during the observation periods.

RESULTS. Eczema data were obtained from >80% of the subjects at all times points. No differences in the prevalence of eczema were found in boys compared with girls between 1 and 10 years of age. However, at 18 years of age, the prevalence of eczema was significantly higher in girls compared with boys ($P < .001$). This shift after puberty was driven both by an increase in the development of nonatopic eczema in girls ($P = .012$) and by an increase in the resolution of atopic eczema in boys ($P = .044$). Focusing on a subset of 160 subjects with onset of eczema at ages 1 or 2 years, 16.9% had persistent eczema at 18 years of age. Recurrence was documented in 17.5% of those who had remission at 4 years of age and 10.9% of those who had remission at 10 years of age. Finally, 41.9% of this subset had complete resolution through 18 years of age.

CONCLUSIONS. Although the prevalence of eczema seems to be independent of gender and atopic status in childhood, the prevalence of eczema in girls after puberty becomes greater than that of boys as a result of an increase in nonatopic eczema in girls and a decrease in atopic eczema in boys. Overall, the prevalence of eczema decreased with age; only 16.9% had persistent eczema at 18 years of age.

REVIEWER COMMENTS. Because of the homogeneity of the study population, one should be cautious in extrapolating the

data to mixed populations such as in the United States. However, the large cohort size and long observation period are key strengths of this longitudinal study, the results of which provide insight into the natural history of this chronically relapsing and remitting disease.

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Correlation Between Serum 25-Hydroxyvitamin D Levels and Severity of Atopic Dermatitis in Children

Peroni DG, Piacentini GL, Cametti E, Chinellato I, Boner AL. *Br J Dermatol.* 2011;164(5):1078–1082

PURPOSE OF THE STUDY. To determine if low levels of vitamin D correlate with the severity of atopic dermatitis (AD).

STUDY POPULATION. Thirty-seven children (20 boys and 17 girls) with AD, between the ages of 8 months and 12 years, were evaluated in an outpatient clinic in Verona, Italy.

METHODS. The Severity Scoring of Atopic Dermatitis (SCORAD) index was used to determine the severity of AD in these children. Serum 25-hydroxyvitamin D (25[OH]D) levels were determined by using a chemiluminescent method. Values were used as a continuous variable, and vitamin D amounts were also categorized, in a descriptive analysis, as sufficient (≥30–40 ng/mL), insufficient (20–30 ng/mL), or deficient (<20 ng/mL). The ImmunoCAP test (Phadia, Uppsala, Sweden) was used to assay for specific immunoglobulin E (sIgE) to *Staphylococcus aureus* enterotoxins and to *Malassezia furfur*. Skin-prick testing was performed for common environmental and food allergens, and mean diameters were added together to create a total allergy score.

RESULTS. Using the SCORAD index, subjects were classified as having severe (9 of 37), moderate (13 of 37), or mild (15 of 37) AD. Mean serum 25(OH)D levels were found to be significantly higher in patients with mild AD (36.9 ± 15.7 ng/mL) compared with those with moderate (27.5 ± 8.3 ng/mL) or severe AD (20.5 ± 5.9 ng/mL). Although not statistically significant, the prevalence of patients with sIgE to microbial antigens increased with the severity of AD and the presence of vitamin D deficiency. There was no significant difference in the total allergy scores between those with mild, moderate, and severe AD.

CONCLUSIONS. Vitamin D deficiency might be related to the severity of AD.

REVIEWER COMMENTS. These results support the idea that vitamin D deficiency might be related to the severity of AD and adds to the current body of epidemiologic studies. The study also reinforces that studies that evaluate treatment of vitamin D deficiency and treatment with vitamin D for the management of AD are needed.

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Infant Eczema, Infant Sleeping Problems, and Mental Health at 10 Years of Age: The Prospective Birth Cohort Study LISAplus

Schmitt J, Chen CM, Apfelbacher C, et al; LISA-plus Study Group. *Allergy.* 2011;66(3):404–411

PURPOSE OF THE STUDY. This study investigated the relationship between infant eczema, infant sleeping problems, and the risk of mental health problems at 10 years of age.

STUDY POPULATION. Included were newborns (N = 1578) recruited as a birth cohort between 1997 and 1999 from 4 German maternity hospitals.

METHODS. Participants were followed regularly from birth until 10 years of age. Parental questionnaires were used to gather information regarding physician-diagnosed eczema, parent-reported sleeping problems secondary to pruritus, and known environmental risk factors for atopy. Mental health at 10 years of age was measured by using the validated German Strengths and Difficulties Questionnaire to determine possible/probable versus unlikely mental health problems. Multivariate logistic regression analyses adjusted for environmental and lifestyle factors (exclusive breastfeeding, single parents, and day care attendance), allergic comorbidity, and family history of eczema. Participants with infant eczema with sleep problems or sleep problems caused by pruritus were compared to children with no reported sleep problems and no eczema (reference group).

RESULTS. Of the 1578 participants eligible for analysis at the age of 10 years, 266 had infant eczema (first 2 years of life), 92 had parent-reported sleep problems caused by pruritus, 54 had infant eczema with sleep problems, 385 had ever been diagnosed with eczema, and 1162 never had eczema or sleeping problems (reference group). Children with eczema and/or sleeping problems did not differ significantly in regards to gender, study site, or breastfeeding status compared with those in the reference group. When adjusted for environmental exposures, demographic confounders, and comorbid atopic airway disease, children with infant eczema were at increased risk of hyperactivity/inattention at 10 years of age (odds ratio [OR]: 1.78 [95% confidence interval (95% CI): 1.02–3.09]). Infant eczema with concurrent sleeping problems was related to emotional problems (OR: 2.63 [95% CI: 1.20–5.76]) and conduct problems (OR: 3.03

[95% CI: 1.01–9.12]) at 10 years of age. Participants who had sleep problems but did not have eczema had statistically significant increased rates of hyperactivity/inattentiveness (OR: 3.09 [95% CI: 1.00–9.55]).

CONCLUSIONS. Infant eczema, if associated with concurrent sleeping problems caused by pruritus, seems to be a risk factor for the development of certain mental health problems.

REVIEWER COMMENTS. The impact of infant eczema and sleep on future mental health problems had not previously been studied in a prospective design. These results are consistent with those from previous cross-sectional and retrospective studies in which infant eczema and mental health problems were linked, and the results are also in concordance with those of previous studies that revealed early childhood sleep problems as a predictor of future anxiety, conduct, and hyperactivity problems. The mechanisms that connected eczema with mental health problems are currently unknown. The authors make an intriguing suggestion that sustained pro-inflammatory cytokine exposure might have an effect on brain development; however, other biopsychosocial possibilities should be examined, including socioeconomic factors and stigmatization by peer groups for children with eczema that could explain the associations revealed in this study.

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ALLERGIC RHINITIS

Does Allergic Rhinitis Exist in Infancy? Findings From the PARIS Birth Cohort

Herr M, Clarisee B, Nikasinovic L, et al. *Allergy*. 2011;66(2):214–221

PURPOSE OF THE STUDY. To examine the relationship of allergic rhinitis (AR)-like symptoms and atopy in infants aged 18 months or younger.

STUDY POPULATION. The study used data from the PARIS (Pollution and Asthma Risk: An Infant Study) birth cohort, which includes healthy, term, singletons born in one of a select group of hospitals in Paris, France. A free 18-month health screening examination was offered to the 3436 children who remained in the study at 1 year of age (82.3% of the original cohort).

METHODS. A standardized questionnaire was administered by a pediatrician to assess for AR-like symptoms, specifically the occurrence of runny nose, sneezing, or nasal blockage, within the previous 12 months not associated with a viral infection. Blood eosinophil counts, total immunoglobulin E (IgE), and allergen-specific IgE were measured.

RESULTS. Included in the analysis were 1850 children who had data regarding AR-like symptoms and measurements of at least 1 biological marker from the 18-month visit. There was a 9.1% prevalence of AR-like symptoms in the population. There was no difference in eosinophil counts or total IgE between infants with AR-like symptoms and those without them; however, eosinophilia (defined as >470 eosinophils per μL) and sensitization to inhalant allergens, particularly dust mite, was significantly associated with AR-like symptoms. No such relationship was seen for food-allergen sensitization. Parental history of AR was a predictor of increased risk of AR-like symptoms, but parental history of asthma or eczema was not a predictor.

CONCLUSIONS. These findings suggest that AR might begin in infancy, as early as 18 months of age, and AR-like symptoms are associated with biological markers of atopic disease and parental history of AR.

REVIEWER COMMENTS. Results of previous studies have suggested an association between chronic inflammation from AR and medical complications including irreversible damage to the nasal mucosa in patient groups including children. Identification of AR markers in infancy might help to identify patients at increased risk for these complications as well as the development of asthma and other atopic disease. Findings also suggest that implementation of targeted medical therapy and environmental interventions for allergic disease might be reasonable approaches for managing nasal symptoms in infancy for those at risk. In addition, early testing might provide an opportunity for anticipatory guidance to parents as their child travels the atopic march.

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Is Physician-Diagnosed Allergic Rhinitis a Risk Factor for the Development of Asthma?

van den Nieuwenhof L, Schermer T, Bosch Y, et al. *Allergy*. 2010;65(8):1049–1055

PURPOSE OF THE STUDY. To define the prospective risk of asthma in patients diagnosed with allergic rhinitis (AR) in a primary care population. The association between these 2 diseases has been shown previously in smaller groups and in cross-sectional studies.

STUDY POPULATION. This study used a database that tracks >35 500 patients from 4 primary care practices in the Netherlands. The AR group consisted of all patients

diagnosed with AR before the age of 50 ($n = 2279$). The control group consisted of 2 people without AR matched to each patient according to age, gender, socioeconomic status, and the practice to which they were assigned ($n = 4558$). The mean age in both groups was 25 years, and the mean length of follow-up was 8.4 years.

METHODS. This is a historic cohort study. Cox proportional hazard analyses were used to assess the relative risk of asthma in patients with AR relative to controls.

RESULTS. In the AR group, 356 patients were also diagnosed with asthma: 198 before the AR diagnosis was made and 158 after it was made. Of those not yet diagnosed with asthma, the hazard ratio for developing asthma relative to controls was 4.86 (95% confidence interval: 3.50–6.73; $P < .001$). Atopic eczema and socioeconomic status were not found to significantly affect the risk of asthma.

CONCLUSIONS. Physician-diagnosed AR is an independent risk factor for a future diagnosis of asthma. A significant number of patients developed asthma before the diagnosis of AR, which suggests that, although there is a link between AR and asthma, the risk is not necessarily prospective. The assessment of which came first is limited by the fact that AR is often self-treated and might not be diagnosed by a physician.

REVIEWER COMMENTS. Data were not broken down according to age group, but the calculated hazard ratio is comparable to that of previous studies that only evaluated adults. Most AR cases were diagnosed by subjective symptoms, so this group undoubtedly contained many people with nonallergic rhinitis. In addition, the control group might have included some with AR who self-treated without being diagnosed by a physician. Because of these factors, the derived hazard ratio might be an underestimate. According to the authors, this is the largest prospective investigation of the association between AR and asthma in a primary care population with such a wide age range and length of follow-up. If so, this study provides the best definition to date of the risk of asthma for patients with AR in the primary pediatric population.

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Allergic Rhinitis as a Predictor for Wheezing Onset in School-aged Children

Rochat MK, Illi S, Ege MJ, et al; Multicentre Allergy Study (MAS) Group. *J Allergy Clin Immunol.* 2010;126(6):1170–1175

PURPOSE OF THE STUDY. To determine if rhinitis in early childhood is an independent predictor of wheezing between the ages of 5 and 13 years.

STUDY POPULATION. The study followed 1314 healthy children, from birth to the age of 13 years, as part of the German Multicenter Allergy Study.

METHODS. This was a prospective, multicenter birth-cohort study that used standardized questionnaires, interviews, and objective sensitization methods. To better characterize the association between sensitization and rhinitis on the incidence of wheeze, 4 rhinitis phenotypes were defined: (1) allergic rhinitis (rhinitis plus sensitization); (2) nonallergic rhinitis (rhinitis without sensitization); (3) atopy without rhinitis (sensitization only); and (4) none (control group). The occurrence of rhinitis, wheezing, and sensitization was assessed over time through the age of 13 years. Airway hyperresponsiveness was assessed at the age of 7 years, and specific allergen immunoglobulin E (IgE) was measured yearly.

RESULTS. Of the 1314 children recruited at birth, 83.1% were followed to the age of 2 years, 76.4% to 5 years, 71.5% to 7 years, and 58.3% to 13 years. Overall, the period prevalence of wheezing varied depending on the rhinitis phenotypes and the age of stratification. A difference existed between children sensitized versus those who were not at the age of 2 years. The greatest incidence of wheeze was seen in children who had atopy without rhinitis (relative risk: 1.70; $P = .007$), whereas the incidence was lower in the nonallergic rhinitis and control groups. In contrast, all 4 rhinitis phenotypes at the age of 5 years tracked proportionally, and the nonallergic rhinitis group showed significantly higher period prevalence than the patients who had atopy without rhinitis. Overall, the probability of wheezing between the ages of 5 and 13 years was significantly increased in children with allergic rhinitis (relative risk: 3.85; $P < .01$). This association was not attributable to the type or severity of sensitization or atopic dermatitis during the first 2 years.

CONCLUSIONS. Allergic rhinitis in the preschool age group was shown to be associated with the onset of wheezing after the age of 5 years.

REVIEWER COMMENTS. On the basis of findings from this study, preschool-aged children with rhinitis might benefit from early assessment of allergic sensitization to identify those who are at high risk of wheezing. Furthermore, identification of these children could lead to targeted treatment and early intervention to prevent asthma in school-aged children.

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Asthma

PATHOPHYSIOLOGY

Paracetamol in Pregnancy and the Risk of Wheezing in Offspring: A Systematic Review and Meta-analysis

Eyers S, Weatherall M, Jefferies S, Beasley R. *Clin Exp Allergy*. 2011;41(4):482–489

PURPOSE OF THE STUDY. To review the evidence from studies that investigated the association between paracetamol (acetaminophen) use in pregnancy and childhood asthma.

STUDY POPULATION. The meta-analysis included randomized controlled trials (RCTs) and observational studies published before October 2010 that compared women who used paracetamol during pregnancy with a placebo (RCT) or control (observational) group and evaluated the effect of paracetamol use during pregnancy on offspring using wheeze or asthma as a primary outcome. Only studies that presented raw data, or from which raw data were available from the authors on request, were used.

METHODS. Articles were searched for in health research databases, in previous meta-analyses, and in the reference lists of relevant studies. Articles were examined, and raw data were extracted. If appropriate data were not included in the studies, the lead author was contacted in an attempt to obtain the raw data. The primary outcome variable was wheeze in the 12 months before the last interview, defined as "current wheeze." For tabulated raw data, not adjusted for confounders, random-effects odds ratios were pooled by the inverse variance weighted method.

RESULTS. Six studies were included: 5 prospective cohort studies and 1 cross-sectional study. The age range of the children in these studies was 30 to 84 months. The pooled random-effects odds ratio for the risk of current wheeze in the children of women who were exposed to any paracetamol during any stage of pregnancy was 1.21 (95% confidence interval: 1.02–1.44).

CONCLUSIONS. The use of paracetamol during pregnancy is associated with an increased risk of childhood asthma.

REVIEWER COMMENTS. The results of this meta-analysis confirm the association seen in individual studies over recent years between early paracetamol (acetaminophen) exposure and wheeze. In contrast with studies of the association between paracetamol use in early postnatal life and wheeze, studying paracetamol exposure in utero vastly decreases the potential for confounding by indication. The authors' decision to use the unadjusted odds ratio is well justified but leaves open the possibility that the effect seen might be a result of confounding to some extent. Given the almost ubiquitous use of paracetamol, and the recent increase in rates of atopy, untangling the true association between paracetamol and atopy is a topic that should, and undoubtedly will, have significant attention devoted to it in the coming years.

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Cord-Blood 25-Hydroxyvitamin D Levels and Risk of Respiratory Infection, Wheezing, and Asthma

Camargo CA Jr, Ingham T, Wickens K, et al; New Zealand Asthma and Allergy Cohort Study Group. *Pediatrics*. 2011;127(1). Available at: www.pediatrics.org/cgi/content/full/127/1/e180

PURPOSE OF THE STUDY. Previous studies have provided support for the role of low vitamin D levels in the increasing prevalence of asthma. This study examined the relationship between cord-blood levels of vitamin D and respiratory infection, wheezing, and asthma.

STUDY POPULATION. Cord blood from study participants (N = 922) was collected as part of a prospective birth cohort of 1105 children recruited by a random sample of midwives in the New Zealand Asthma and Allergy Cohort Study. Questionnaires were administered by study nurses at birth, 3 months, and 15 months and then annually between the ages of 2 and 5 years.

METHODS. Cord-blood 25-hydroxyvitamin D (25[OH]D) levels were measured and categorized as ≥75, 25 to 75, or <25 nmol/L. The primary outcomes were the incidence of respiratory infection, cumulative wheeze, and incidence of asthma by 5 years of age based on answers to the questionnaires. Multiple confounding covariates were accounted for, including season of birth, ethnicity, and environmental tobacco smoke exposure. The linear regression or the Kruskal-Wallis test for continuous variables and the Wilcoxon-Mann-Whitney test for categorical variables were used to test for trend across vitamin D levels. Multivariable logistic regression models were used to test the association between cord-blood 25(OH)D levels and infection outcomes at 3 months of age.

RESULTS. Data were available for 882 (96%) children at 3 months of age and 823 (89%) children at 5 years of age. The median 25(OH)D cord-blood level was 44 nmol/L. An inverse association was found between cord-blood 25(OH)D levels and risk of respiratory infection by 3 months of age. Newborns with 25(OH)D levels of <25 nmol/L had an increased risk of respiratory infections (odds ratio [OR]: 2.04) and other viral infections (OR: 2.36) compared with those with levels of

≥75 nmol/L. There was an inverse linear association between vitamin D level and cumulative wheezing by 5 years of age but no association with asthma incidence. Every 10 nmol/L increase in cord-blood 25(OH)D level lowered the cumulative risk of wheezing by the age of 5 years (adjusted OR: 0.95).

CONCLUSIONS. This birth-cohort study revealed an inverse association between 25(OH)D cord-blood levels and the risk of respiratory and other viral infections by the age of 3 months and cumulative risk of wheezing by the age of 5 years. The 25(OH)D cord-blood levels were not associated with the risk of incident asthma.

REVIEWER COMMENTS. The measurement of vitamin D in cord blood, but not at follow-up visits, is a major limitation of this study. Recall bias that resulted from the use of parent questionnaires to detect the outcomes of interest is another limitation. It remains unclear whether low vitamin D levels in utero cause increased respiratory infections and wheezing or if this low level is a marker for likely low vitamin D levels in the future. Further studies are needed to clarify this issue. This study adds to the body of evidence that suggests that low vitamin D levels might play a role in wheezing and respiratory infections in infants and children.

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Dairy Food, Calcium and Vitamin D Intake in Pregnancy, and Wheeze and Eczema in Infants

Miyake Y, Sasaki S, Tanaka K, Hirota Y. *Eur Respir J.* 2010;35(6):1228–1234

PURPOSE OF THE STUDY. Previous studies have provided mixed results regarding a relationship of intake of dairy products with allergic disorders. This study examined the association between maternal consumption of dairy products, calcium, and vitamin D during pregnancy and risk of wheeze and eczema in Japanese children at 16 to 24 months of age.

STUDY POPULATION. A total of 763 mother-child pairs in the Osaka Maternal and Child Health Study (OMCHS) were included.

METHODS. The OMCHS is a prospective cohort study. Participants mailed each of 3 questionnaires to the data center. The first survey was performed on pregnant women between the 5th and 39th weeks of gestation, and the second and third surveys were collected from 2 to 9 and 16 to 24 months after delivery, respectively. Symptoms of wheeze and eczema were based on the criteria of the International Study of Asthma and Allergies in Childhood.

RESULTS. Higher maternal intake of total dairy products, milk, cheese, and calcium during pregnancy was significantly related to a decreased risk of infantile wheeze but not eczema (adjusted odds ratios [ORs] between extreme quartiles were 0.45 [95% confidence interval (CI): 0.25–0.79], 0.5 [95% CI: 0.28–0.87], 0.51 [95% CI: 0.31–0.85], and 0.57 [95% CI: 0.32–0.99], respectively). Children whose mother had consumed ≥4.3 μg/day of vitamin D, using a cutoff point at the 25th percentile, had a significantly reduced risk of wheeze and eczema (adjusted ORs were 0.64 [95% CI: 0.43–0.97] and 0.63 [95% CI: 0.41–0.98], respectively). However, the inverse associations between maternal intake of calcium in the highest quartile and ≥4.3 μg/day of vitamin D and infantile wheeze were not statistically significant after further control for maternal intake of docosahexaenoic acid or vitamin E.

CONCLUSIONS. Higher consumption of total dairy product, milk, cheese, calcium, and vitamin D during pregnancy might reduce the risk of infantile wheeze. Also, higher maternal vitamin D intake during pregnancy might be protective against eczema.

REVIEWER COMMENTS. The role of vitamin D in atopy and other immune disorders is a hot area of research. The results of this study help to place the importance of diet in pregnancy for atopy in a non-Westernized society. However, the need for long-term follow-up and questionnaire-based definitions for wheeze and eczema were a limitation of this cohort study. Confounders include undisclosed sources of vitamin D and calcium. The relationship between actual vitamin D levels and supplement use during pregnancy is still not conclusive. Additional studies to clarify the multifactorial causes of allergic disorders are desirable, and current randomized double-blind placebo-controlled trials that evaluate vitamin D supplements during pregnancy and wheeze/asthma outcomes are ongoing.

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Vitamin D Serum Levels and Markers of Asthma Control in Italian Children

Chinellato I, Piazza M, Sandri M, Peroni D, Piacentini G, Boner AL. *J Pediatr.* 2011;158(3):437–441

PURPOSE OF THE STUDY. Recent data indicate that increased serum concentrations of 25-hydroxyvitamin D are asso-

ciated with higher percent-predicted forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). These researchers sought to establish the relationship between serum vitamin D levels, pulmonary function, and asthma control.

STUDY POPULATION. This was a cross-sectional analysis of Italian children aged 5 to 11 years with asthma (intermittent or persistent) consecutively evaluated at a university hospital–based outpatient clinic in Verona, Italy, in the winter and spring of a single year.

METHODS. Asthma control was classified according to the Global Initiative for Asthma (GINA) guidelines. Children and parents completed the Childhood Asthma Control Test questionnaire. Pulmonary-function testing was performed according to American Thoracic Society guidelines. A single measurement of each child's serum vitamin D level (25-hydroxy cholecalciferol) was obtained.

RESULTS. Of the 75 asthmatic children, 7 (9.4%) had sufficient vitamin D levels (≥30 ng/mL), 28 (37.3%) had insufficient levels (20–30 ng/mL), and 40 (53.3%) had deficient levels (<20 ng/mL). A statistically significant positive correlation ($P = .011$) was found between serum levels of vitamin D and asthma-control scores according to the questionnaire. Serum levels of 25-hydroxyvitamin D were associated with percent-predicted FVC ($P = .04$), but correlation between percent-predicted FEV_1 and vitamin D levels was not significant.

CONCLUSIONS. Deficient and insufficient vitamin D serum levels were found in most asthmatic children in this study. There was a positive association between vitamin D levels and asthma control, and it was observed that lower vitamin D levels were associated with reduced asthma control. These data suggest that higher vitamin D levels are positively associated with pulmonary function, particularly FVC; however, the correlation is relatively weak.

REVIEWER COMMENTS. This study raises the question of whether vitamin D deficiency negatively affects asthma control and pulmonary function. Although the cross-sectional design reveals a correlation between vitamin D insufficiency/deficiency and poor asthma control, it does not prove a causal relationship. As suggested by the authors, interventional studies are warranted to evaluate the effect of vitamin D supplementation in poorly controlled asthmatic patients.

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Swimming Pool Attendance, Asthma, Allergies, and Lung Function in the Avon Longitudinal Study of Parents and Children Cohort

Font-Ribera L, Villanueva CM, Nieuwenhuijsen MJ, Zock JP, Kogevinas M, Henderson J. *Am J Resp Crit Care Med*. 2011;183(5):582–588

PURPOSE OF THE STUDY. Several retrospective studies have identified attending chlorinated swimming pools during childhood as a risk factor for developing asthma and allergies later in life. These researchers collected data on a large birth cohort of children in the United Kingdom.

STUDY POPULATION. Data were available for 5738 children from an initial cohort of 14 062 live births.

METHODS. Data on swimming were collected by questionnaire at ages 6, 18, 38, 42, 57, 65, and 81 months. Data on asthma and allergic conditions were collected at 7 and 10 years. Spirometry and allergy skin testing were performed between the ages of 7 and 8 years. Multiple confounders were considered in the statistical models.

RESULTS. Fourteen percent of the children swam before 4 years of age, and 50% attended pools at least once per week between 4 and 7 years of age. From birth to 7 years of age, children with a high versus low cumulative swimming-pool attendance rate had an adjusted odds ratio of 0.88 (95% confidence interval [CI]: 0.56–1.38) and 0.5 (95% CI: 0.28–0.87) for asthma ever and current asthma, respectively, and a 0.2-SD (95% CI: 0.02–0.39) increase in forced midexpiratory flow. Children with a history of asthma ever, with a high versus low cumulative swimming exposure rate, had an odds ratio of 0.34 (95% CI: 0.14–0.80) for current asthma at the age of 10 years.

CONCLUSIONS. Among those with previous asthma, swimming was associated with decreased asthma symptoms at the age of 10 years. It was also associated with increased lung function at 7 years of age. Swimming did not affect the incidence of asthma.

REVIEWER COMMENTS. The results of this study are a nice addition to the previously available data regarding the impact that exposure to swimming pools and their chemical irritants has on asthma. Swimming was not found to increase asthma or asthma symptoms; in fact, it was protective in some aspects. One weakness of this study was its inability to determine if swimming was linked to other healthy lifestyle characteristics that affected the outcomes.

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Infant Swimming in Chlorinated Pools and the Risks of Bronchiolitis, Asthma and Allergy

Voisin C, Sardella A, Marcucci, Bernard A.
Eur Respir J. 2010;36(1):41–47

PURPOSE OF THE STUDY. Recent studies postulated that chlorine used to disinfect swimming pools can cause airway changes and make the lungs more sensitive to infection and asthma. This study evaluated the associations between infant swimming and bronchiolitis and its sequelae among young school-aged children.

STUDY POPULATION. A total of 430 children aged 5 to 6 years in 30 kindergartens located mainly in the area of Brussels and Liege (Belgium) who were participating in a prospective study on the respiratory impact of air pollution were included.

METHODS. Parents completed a questionnaire regarding the child's health history, respiratory symptoms (asthma, bronchitis, bronchiolitis, and pneumonia), and swimming practices (type of pools, type of disinfection method used, frequency of attendance, age started).

RESULTS. Attendance at indoor or outdoor chlorinated pools ever before the age of 2 years was associated with an increase risk of bronchiolitis (odds ratio: 1.68 [95% confidence interval (CI): 1.08–2.68]; $P = .03$). Associations persisted, and were even strengthened, by the exclusion of other risk factors. Among children with no parental antecedents of atopic diseases or no day-care attendance, odds ratios for bronchiolitis were 4.45 (95% CI: 1.82–10.9; $P = .001$) and 4.44 (95% CI: 1.88–10.5; $P = .007$), respectively, after >20 hours spent in pools during infancy. Infant swimmers who developed bronchiolitis also showed higher risks of asthma and respiratory allergies later in childhood.

CONCLUSIONS. Swimming-pool attendance during infancy is associated with a dose-dependent increase in risk of bronchiolitis and interacts with bronchiolitis to increase the risk of respiratory allergies later in childhood.

REVIEWER COMMENTS. Recent findings raised the question of safety of infant swimming. One theory regards the possibility that compounds from the pool reduce lung Clara cell protein (CC16), which protects from inflammation in acute respiratory syncytial virus infection. To date, cross-sectional studies have found inconsistent results in association with swimming-pool attendance and respiratory diseases. However, epidemiologic studies that use data from self-limited questionnaires can be prone to recall bias. Swimming pools have a variety of chlorine compounds in the water and microaerosols, as well as other pollutants such as nitrogenous substances from bathers. These are points to clarify in these studies. Prospective longitudinal studies are needed to characterize and confirm an association between chlorinated pools and outcome in allergic and respiratory diseases.

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Association of Bacteria and Viruses With Wheezy Episodes in Young Children: Prospective Birth Cohort Study

Bisgaard H, Hermansen MN, Bønnelykke K, et al. *BMJ.* 2010;341:c4978

PURPOSE OF THE STUDY. Viral infections have been consistently associated with wheezing episodes, but no studies have suggested a role for bacterial infection. This study evaluated the association between wheeze in young children and the presence of bacteria in the airways.

STUDY POPULATION. Infants ($N = 411$) from the Copenhagen Prospective Study on Asthma in Childhood with a maternal history of asthma were recruited at 4 weeks of age. Exclusion criteria were premature birth (<36 weeks' gestation), history of mechanical ventilation, congenital disease, or respiratory tract symptoms.

METHODS. Participants were prospectively examined for common airway pathogenic bacteria and viruses from the ages of 4 weeks to 3 years. The children visited the research clinic every 6 months and as needed for acute respiratory tract symptoms. Asthma-like symptoms and treatment were recorded in diary cards. Hypopharyngeal aspirates were obtained for routine bacterial cultures, and nasopharyngeal aspirates were obtained for virus identification.

RESULTS. A total of 984 samples (361 children) were analyzed for bacteria, 844 (299 children) were analyzed for viruses, and 696 (277 children) were analyzed for both viruses and bacteria. Colonization shifted from a majority having *Staphylococcus aureus* in the first months of life to later having *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Wheezy episodes were significantly associated with these 3 pathogens (odds ratio [OR]: 2.9 [95% confidence interval (CI): 1.9–4.3]; $P < .001$). Wheezy episodes were significantly associated with viral infection (OR: 2.8 [95% CI: 1.7–4.4]; $P < .001$). The association was unaffected by bacteria as a covariate and with no significant interactions.

CONCLUSIONS. Acute wheezy episodes in children up to the age of 3 years were significantly associated with bacterial infection. This association was independent of viral infection, which suggests that bacteria might contribute independently.

REVIEWER COMMENTS. This is the first prospective clinical cohort study that used standard bacterial cultures and

sensitive molecular methods for virus detection, and the results suggest that bacteria might contribute to wheezing episodes in children at high risk. Interventional strategies geared toward these microorganisms might be useful to further our understanding of wheezing and asthma development in these children. Given the paucity of information on evidence-based strategies in young children for treating wheezing episodes, clinical trials for evaluating antimicrobial agents and other interventions for wheezing episodes should be considered and are currently being evaluated among large clinical trial networks.

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Causal Direction Between Respiratory Syncytial Virus Bronchiolitis and Asthma Studied in Monozygotic Twins

Poorisrisak P, Halkjaer LB, Thomsen SF, et al. *Chest*. 2010;138(2):338–344

PURPOSE OF THE STUDY. To compare the long-term outcome of asthma, allergy, and pulmonary function in monozygotic twin pairs discordant for severe respiratory syncytial virus (RSV) disease.

STUDY POPULATION. There were 37 monozygotic twin pairs discordant for RSV hospitalization at a mean age of 10.6 months evaluated in the study. The twins were born between January 1, 1994, and December 31, 2003, and enrolled through the Danish Twin Registry.

METHODS. Hospitalization was used as a marker of disease severity. Participants were studied at a mean age of 7.6 years. The study included clinical examinations, lung-function testing, fractional exhaled nitric-oxide levels, determination of an asthma diagnosis, use of asthma medication, and results of skin-prick tests to common inhalant allergens.

RESULTS. The prevalence of asthma among the twins was 18%. The twins did not differ with respect to current asthma, use of inhaled corticosteroids or β_2 agonists, atopic dermatitis, fractional exhaled nitric oxide, baseline lung function, bronchial responsiveness, or sensitization ($P > .1$ for all comparisons).

CONCLUSIONS. There was no significant difference within cohabiting monozygotic twin pairs discordant for hospitalization for RSV bronchiolitis in infancy on the development of asthma and allergy, which argues against a specific viral effect.

REVIEWER COMMENTS. This study examined the question of which came first: not the chicken or the egg but whether severe RSV bronchiolitis causes wheezing or whether someone with a predisposition to asthma suffers a more severe response to RSV. This study's results argue against a specific effect of severe RSV infection in the development of asthma and allergy. Another recent study report based on 8280 twin pairs showed that a model in which asthma "causes" RSV hospitalization fit significantly better than a model in which RSV hospitalization "causes" asthma. We guess the chicken came first.

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Allergic Sensitization Is Associated With Rhinovirus-, but not Other Virus-, Induced Wheezing in Children

Jartti T, Kuusipalo H, Vuorinen T, et al. *Pediatr Allergy Immunol*. 2010;21(7):1008–1014

PURPOSE OF THE STUDY. Building on recent studies that have suggested a link between early wheezing caused by rhinovirus and the development of asthma, these researchers sought to characterize the relationship of respiratory viral infections with atopy in hospitalized wheezing children.

STUDY POPULATION. The authors studied a subgroup from among a previously described cohort of 293 hospitalized wheezing Finnish children aged 3 months to 16 years who had comprehensive virology performed ($N = 247$; median age: 1.6 years). Subjects with recent oral corticosteroid use, chronic disease, or ICU treatment were excluded.

METHODS. Respiratory viral infections were evaluated through a nasopharyngeal aspirate and blood sample at baseline and after 2 to 3 weeks. A combination of viral culture, antigen detection, immunoglobulin G (IgG) and IgM measurement, and polymerase chain reaction was used to evaluate for respiratory syncytial virus, human rhinovirus, enteroviruses, human bocavirus, and a broad panel of additional respiratory viruses. Atopy was assessed through serum-specific IgE testing to several common food allergens, cat, dog, horse, birch, mugwort, timothy grass, mold, and dust mite.

RESULTS. Allergen-specific IgE sensitization was closely related to sole rhinovirus infection (odds ratio: 3.5; $P = .0002$). In contrast, sole respiratory syncytial virus infection was negatively associated with sensitization (odds ratio: 0.087; $P = .027$). No significant associations with atopy were found with the remaining viruses or with those with multiple concurrent viral infections.

CONCLUSIONS. Acute wheezing in early childhood caused by human rhinovirus is associated with an increased risk

of allergic sensitization and, therefore, an increased risk of developing future asthma.

REVIEWER COMMENTS. A limitation of this study lies in the fact that all subjects were hospitalized for their wheezing, thereby representing a minority of children with rhinovirus infection. Nevertheless, when considering the asthma predictive index, the evidence presented from this study suggests that a history of rhinovirus infection, especially severe infection, could be considered an additional risk factor for the development of asthma.

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Association of Childhood Obesity With Atopic and Nonatopic Asthma: Results From the National Health and Nutrition Examination Survey 1999–2006

Visness CM, London SJ, Daniels JL, et al. *J Asthma*. 2010;47(7):822–829

PURPOSE OF THE STUDY. Previous work has suggested that obesity is related to asthma through an allergic inflammation pathway. These researchers sought to examine the role of C-reactive protein (CRP) in the association between obesity and asthma among a nationally representative sample of US children and young adults.

STUDY POPULATION. The sample came from the 1999–2006 National Health and Nutrition Examination Survey (NHANES) and specifically included children aged 2 to 19 who had information on BMI and asthma status (N = 16 074).

METHODS. Atopy was measured by using allergen-specific serum immunoglobulin E; asthma status was measured through self-report of diagnosis by a physician; and BMI was calculated on the basis of height and weight measurements. Multiple logistic regression analysis was used to examine the association between BMI and asthma status.

RESULTS. Nearly 10% of the children reported current asthma. A higher proportion of atopic compared with nonatopic children reported current asthma (15.8% vs 6.4%; odds ratio [OR]: 2.71 [95% confidence interval (CI): 1.98–3.72]). There was a strong relationship between BMI and CRP levels (r = 0.41). Obese children had a 1.68 odds (95% CI: 1.33–2.12) of having current asthma. Among nonatopic children, those in the obese category were more than twice as likely to have current asthma (OR: 2.46 [95% CI: 1.21–5.02]); however, there was no association between overweight or obesity and asthma among atopic children. Increased CRP levels were associated with an increased odds of having asthma among nonatopic children (OR: 1.45 [95% CI: 1.16–1.81]) but not among atopic children (OR: 0.97 [95% CI: 0.65–1.44]).

CONCLUSIONS. The association of overweight and obesity with asthma was stronger among nonatopic children. Overweight might lead to systematic inflammation that, in turn, leads to an increased risk of asthma in nonatopic people.

REVIEWER COMMENTS. There is growing evidence that the rise in both obesity and asthma might be related. This study was cross-sectional and limits our understanding of the causal relationship between obesity and asthma. However, it contributes to advancing the evidence in this area by examining the mechanisms through which obesity and asthma might be related—in this case, through nonallergic disease. Future studies can build on these findings by examining these associations prospectively.

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Risk of Asthma in Young Adults Who Were Born Preterm: A Swedish National Cohort Study

Crump C, Winkleby, Sundquist J, Sundquist K. *Pediatrics*. 2011;127(4). Available at: www.pediatrics.org/cgi/content/full/127/4/e913

PURPOSE OF THE STUDY. To evaluate whether those who were born prematurely were more likely to be prescribed asthma medications in young adulthood than those who were born at term.

STUDY POPULATION. This was a national cohort study of all singleton infants born in Sweden from 1973 through 1979 (N = 622 616) and followed to ages 25.5 to 35.0 to determine whether asthma medications were prescribed in 2005–2007.

METHODS. Asthma-medication data were obtained from all outpatient and inpatient pharmacies throughout Sweden. Outcome was defined as prescription of (1) both a β_2 agonist inhalant and a glucocorticoid inhalant or (2) a combination inhalant containing a β_2 agonist and other drugs for obstructive airway diseases.

RESULTS. Young adults who were born extremely prematurely (23–27 weeks' gestation) were 2.4 times more likely to be prescribed asthma medications than those who were born at term (95% confidence interval: 1.41–4.06). No association was found between later prematurity (28–32 or 33–36 weeks' gestation) and asthma medications in young adulthood.

CONCLUSIONS. Extreme preterm birth (23–27 weeks' gestation) but not later preterm birth is associated with an increased risk of asthma, at least in young adulthood.

REVIEWER COMMENTS. This is the first study with adequate statistical power to evaluate the risk of asthma beyond adolescence in people who were born extremely prematurely. A meta-analysis of 19 previous studies revealed an overall odds ratio of 1.07 for risk of asthma when comparing people born at gestational ages of <37 weeks to those born at ≥37 weeks (*J Allergy Clin Immunol.* 2006;118[4]:823–830), but this study did not disclose specific data for extremely preterm children. One possible explanation for the findings in the Crump et al study is that preterm birth and asthma might share common genetic determinants. The results of at least 2 previous studies suggest that maternal asthma might be associated with preterm delivery (*Thorax.* 1995;50[5]:525–530 and *Am J Obstet Gynecol.* 2001;184[2]:90–96). Other studies reported that maternal asthma is associated with an increased risk of asthma in their children (*Am J Respir Crit Care Med.* 1998;157[4 pt 1]:1073–1078 and *Environ Health Perspect.* 2001;109[6]:579–582).

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Lung Function and Respiratory Symptoms at 11 Years in Children Born Extremely Preterm: The Epicure Study

Fawke J, Lum S, Kirkby J, et al. *Am J Respir Crit Care Med.* 2010;182(2):237–245

PURPOSE OF THE STUDY. More extremely preterm (EP) infants (≤25 weeks' gestational age) are surviving. What becomes of these children in terms of lung function?

METHODS. This was a national cohort study that involved all infants born at ≤25 completed weeks' gestation in the United Kingdom and Ireland between March and December 1995 ($N = 182$). At the age of 11 years, parents completed a questionnaire and the children performed spirometry. Schoolmates born at term matched for age, gender, and ethnic origin served as controls. Current asthma was defined as "use of asthma medication or wheeze in the past 12 months by children with a doctor diagnosis of asthma, or use of asthma medication and wheeze in the past 12 months even if no prior diagnosis of asthma."

RESULTS. Twice as many EP-born children (25% vs 13%; $P < .01$) had current asthma. Baseline spirometry was reduced (forced expiratory volume in 1 second [FEV_1] 83% vs 100% of predicted; $P < .001$) and bronchodilator responsiveness (>12% increase in FEV_1) was increased (27% vs 8%; $P < .001$) in EP-born children. These changes were most marked in those with previous bronchopulmonary dysplasia. Fifty-six percent of EP-born children had abnormal baseline spirometry results, but fewer than half of them were receiving any medication.

CONCLUSIONS. After extremely preterm birth, impaired lung function and increased respiratory morbidity persist into middle childhood, especially among those with bronchopulmonary dysplasia. Many of these children might not be receiving appropriate treatment.

REVIEWER COMMENTS. A large percentage of children who survive being born extremely prematurely go on to have persistent asthma in childhood. An even higher percentage of them have abnormal spirometry results, and many show reversibility with bronchodilator; however, only half of them are on asthma medication, which indicates that they are receiving inadequate treatment. These children deserve close monitoring through history and spirometry to diagnose and treat asthma.

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DIAGNOSIS AND MANAGEMENT

Changing Trends in Asthma in 9–12 Year Olds Between 1964 and 2009

Malik G, Tagiyeva N, Aucott L, McNeill G, Turner SW. *Arch Dis Child.* 2011;96(3):227–321

PURPOSE OF THE STUDY. This study is a continuation of the Aberdeen Schools Asthma Survey; the first survey was completed in 1964. Subsequent surveys were repeated in 1989, 1994, 1999, and 2004. This survey reports lifetime prevalence of asthma, eczema, hay fever, and wheeze in the previous 3 years. Trends over a 10-year period (1999, 2004, and 2009) were analyzed.

STUDY POPULATION. Children aged 9 to 12 years in Aberdeen, United Kingdom, were invited to participate in this study.

METHODS. Questionnaires were distributed to children by school staff, completed by parents at home, returned to school staff, and then collected by the research team. The same questionnaire that was used in 2004 was used for this study. In addition, International Study of Allergy and Asthma in Children (ISAAC) questions were included.

RESULTS. A total of 2253 children were eligible for the study, and 1196 (53%) of the surveys were returned. The average age of the children was 10.8 years, and 588 (49%) of them were male. Of 31 eligible primary schools, 26 participated in the study. The number of schools that participated was similar to the number that participated

in the surveys in 2004. The lifetime prevalence of asthma rose from 24.3% in 1999 to 28.4% in 2004 but decreased to 22.1% in 2009 ($P < .001$). The prevalence of wheeze in the previous 3 years decreased from 27.9% in 1999 to 25.2% in 2004 and 22.2% in 2009 ($P < .001$). The lifetime prevalence of eczema rose between 1999 and 2004 (21.4%–34.1%), and there was a small decline in 2009 (33.5%) ($P < .001$). Similar trends were seen for hay-fever prevalence. There was a significant change in prevalence for girls compared with boys for asthma, eczema, and wheeze in the previous 3 years.

CONCLUSIONS. Asthma, eczema, and hay fever remain common health conditions for children in the United Kingdom, but after many years of increasing prevalence, the number of affected children seems to finally be decreasing.

REVIEWER COMMENTS. From 1964 to 2004, the prevalence of asthma, eczema, hay fever, and wheeze in the previous 3 years had increased in the United Kingdom. Since 2004, there has been a decline in the prevalence of these health conditions. A similar trend has also been reported in other countries, and we hope that rates will continue to decline worldwide. Although this study was not designed to explain why asthma prevalence has decreased, the authors did comment on reasons that might account for the decline, including revised guidelines for diagnosing and managing asthma and bans on smoking in public places.

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Predictive Factors for Airway Hyperresponsiveness in Children With Respiratory Symptoms

Yavuz ST, Civelek E, Tuncer A, Sahiner U, Sekerel BE. *Ann Allergy Asthma Immunol*. 2011;106(5):365–370

PURPOSE OF THE STUDY. Asthma diagnosis can be challenging to make in children without persistent symptoms. Factors that contribute to this challenge include poor perception of dyspnea by children with asthma and their families and a lack of objective findings of reversible airway obstruction.

STUDY POPULATION. This study was a retrospective analysis of Turkish children aged 6 to 18 years with suspected asthma whose spirometry results had not met standard criteria for obstructive physiology and who completed a methacholine challenge (MCC).

METHODS. Parents completed a standardized questionnaire regarding symptoms before the MCC. Investigated symptoms included wheezing, daytime cough, nocturnal cough, exercise-induced cough, dyspnea, and exercise-induced dyspnea. Patients with a decrease in forced expiratory volume in 1 second (FEV_1) of 20% after exposure to a concentration of ≤8 mg/mL of methacholine were considered positive for airway hyperresponsiveness (AHR). Statistical analysis was used to analyze the association between demographic, symptomatic, and spirometric parameters with AHR on MCC.

RESULTS. The study included 111 children who ranged in age from 6 to 18 years (median: 10.2 years), and 53% of them were male. AHR was detected in 67 patients (60.3%). Patients with AHR were younger than those without AHR (9.9 vs 12.1 years). They tended to have both nocturnal and exercise-induced cough (26.9% vs 6.8%; $P = .008$; positive predictive value [PPV]: 85.7%; negative predictive value [NPV]: 45.5%). The combination of nocturnal and exercise-induced cough along with borderline bronchodilator response (change in FEV_1 of 7%–11%) was highly predictive of AHR (11.7% vs 0%; PPV: 100%; NPV: 44.2%). Peripheral blood eosinophilia (≥500/μL) was found in 23.4% of the patients with AHR and in 4.7% of those without AHR ($P = .009$; PPV: 88.2%; NPV: 45.5%). The combination of eosinophilia and borderline bronchodilator response was more frequent in patients with AHR in comparison with those without AHR (10.3% vs 0%; PPV: 100%; NPV: 44.1%). In contrast, those with AHR were less likely to report dyspnea (20.9% vs 38.6%) or exercise-induced dyspnea (26.9% vs 47.7%) than those without AHR.

CONCLUSIONS. These data are useful when applied to a selected population of diagnostically challenging patients for whom MCC is not practical or feasible.

REVIEWER COMMENTS. The results of this study, similar to others, confirm that there is no one symptom, demographic variable, or diagnostic test that reliably predicts AHR and asthma but, rather, a combination of them that can be helpful. It should be noted that patients with AHR had increased levels of eosinophilia, which has been reported in adult populations too. It is interesting to note that these data failed to detect an association between wheezing and AHR, which was seen in previous studies. The authors attributed this result to the lack of a correlate for wheezing in Turkish, which is useful to consider in an increasingly international world in which physicians commonly see patients who do not speak the same language and might not be familiar with this concept either.

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Risk Factors and Predictive Clinical Scores for Asthma Exacerbation in Childhood

Forno E, Fuhlbrigge A, Soto-Quirós ME, et al. *Chest.* 2010;138(5):1156–1165

PURPOSE OF THE STUDY. To develop and verify a clinical score to be used by primary care providers to identify children at high risk of exacerbation.

STUDY POPULATION. The clinical score was developed and validated by using 615 unrelated Costa Rican children (6–14 years old) from a family-based study of asthma genetics. The score was then evaluated by using a second group of children, a cohort of North American children from the Childhood Asthma Management Program (CAMP) (5–12 years old).

METHODS. Severe asthma exacerbation, defined as any hospitalization, urgent visit, or systemic steroid course for asthma in the previous year, was the primary outcome. A scoring questionnaire was developed and verified in the initial cohort. On the basis of their clinical score, children were categorized into 1 of 3 groups: low risk (score ≤ 5); average risk (score 6–8); and high risk (score ≥ 9). Effectiveness of the scoring system was then evaluated in the Costa Rican validation set and in the CAMP cohort.

RESULTS. Multivariate analysis in the validation set showed that each 1-point increment in the clinical score was associated with a 1.6-fold increase in the risk for an exacerbation. Relative to children at average risk, the odds ratio for an exacerbation was 0.2 (95% confidence interval [CI]: 0.1–0.4) among children in the low-risk group and 5.4 (95% CI: 1.5–19.2) among children in the high-risk group. Comparable results were obtained from the CAMP cohort. Compared with children at average risk for an exacerbation, the hazard ratios for exacerbations among children in the low- and high-risk groups were 0.6 (95% CI: 0.5–0.7) and 1.9 (95% CI: 1.4–2.4), respectively, at 1-year follow-up, and there were similar results at 2 years.

CONCLUSIONS. The asthma clinical score yielded consistent results in the exploratory and validation sets, which indicates good reproducibility. The scoring system shows potential as a simple diagnostic tool that can easily be used in primary care settings worldwide.

REVIEWER COMMENTS. Although the exclusion of pulmonary-function data might seem like a limiting factor of the study, many primary care providers do not have access to pulmonary-function testing results. The goal of this study was to create a useful clinical tool that could predict exacerbations in the absence of pulmonary-function or laboratory data. The practical usefulness of the proposed scoring system depends on its simplicity and clarity. The results of this study demonstrate the development of a simple clinical score that effectively identifies children at high risk for exacerbations. Additional studies among different cohorts are needed to fine-tune the score and evaluate its practical usefulness as a diagnostic tool in primary care settings.

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Differences in Prevalence, Treatment, and Outcomes of Asthma Among a Diverse Population of Children With Equal Access to Care: Findings From a Study in the Military Health System

Stewart KA, Higgins PC, McLaughlin CG, Williams TV, Granger E, Croghan TW. *Arch Pediatr Adolesc Med.* 2010;164(8):720–726

PURPOSE OF THE STUDY. To assess possible racial and ethnic differences in asthma prevalence, treatment patterns, and outcomes among a diverse population of children with equal access to health care.

STUDY POPULATION. In the Military Health System (MHS), children 2 to 17 years of age were enrolled throughout 2007 in TRICARE Prime, a voluntary health maintenance organization–type benefit provided by the US Department of Defense. More than 75% of children in the MHS are enrolled in TRICARE Prime.

METHODS. This was a retrospective cohort analysis. The sponsor parent's race and ethnicity were used as a proxy for the child's race and ethnicity. Outcome measures included the prevalence of diagnosed asthma (using *International Classification of Diseases, Ninth Revision* [ICD-9] codes), "potentially avoidable" asthma hospitalizations, asthma-related emergency department visits, visits to asthma specialists, and use of asthma medications among children 2 to 4, 5 to 10, and 11 to 17 years of age.

RESULTS. The cohort in the final analysis included 822 900 children aged 2 through 17 years. After adjusting for differences in demographic characteristics and socioeconomic status, black and Hispanic children of all ages were more likely to have an asthma diagnosis than white children (ranging from an odds ratio [OR] of 1.16 [95% confidence interval (CI): 1.09–1.24] to 2.00 [95% CI: 1.93–2.07]). Black children of all ages and Hispanic children aged 5 to 10 years were more likely to have any asthma hospitalization or asthma-related emergency department visit (ranging from an OR of 1.24 [95% CI: 1.1–1.37] to 1.99 [95% CI: 1.37–2.88]) and were less likely to visit a specialist (ranging from an OR of 0.71 [95% CI: 0.61–0.82] to 0.88 [95% CI: 0.79–

0.98]) compared with white children. Black children in all age categories were more likely to have filled any prescription for inhaled corticosteroids compared with white children (ranging from an OR of 1.11 [95% CI: 1.02–1.21] to 1.11 [95% CI: 1.04–1.19]).

CONCLUSIONS. Despite universal health insurance coverage offered through the MHS, the authors found evidence of racial and ethnic differences in asthma prevalence, treatment, and outcomes.

REVIEWER COMMENTS. This study corroborates the presence of racial and ethnic disparities in asthma within a cohort offered universal health care coverage. Black children were not only more likely to be diagnosed with asthma, but they were also found to have poorer control of asthma. It was surprising that black children were also more likely to have filled prescriptions for inhaled steroids compared with white children. The authors suggested that the higher rates of filled prescriptions might be attributed to the higher likelihood of receiving these prescriptions for asthma medications during and after emergency department visits and/or hospitalizations. Actual use and administration of these medications were not evaluated. The study's findings suggest that eliminating racial and ethnic disparities in health care likely requires a multifaceted approach beyond universal health insurance coverage.

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Status of Asthma Control in Pediatric Primary Care: Results From the Pediatric Asthma Control Characteristics and Prevalence Survey Study (ACCESS)

Liu AH, Gilesenan AW, Stanford R, Lincourt W, Ziemiecki R, Ortega H. *J Pediatr.* 2010;157(2):276–281

PURPOSE OF THE STUDY. To determine the prevalence of uncontrolled asthma by using validated instruments in a representative sample of pediatric primary care offices.

STUDY POPULATION. Patients were recruited from pediatric outpatient offices across the United States. Eligible patients for this study included children who were between the ages of 4 and 17 years, had a history of asthma as diagnosed by a heath care provider, used an asthma medication in the previous year, and were able to read, write, and comprehend English.

METHODS. This was a multisite cross-sectional study of patients with asthma who visited a pediatric health care provider for any reason between January and May 2008. The questionnaires given to the patients included the Childhood Asthma Control Test (C-ACT) for those between the ages of 4 and 11 years and the Asthma Control Test (ACT) for those between the ages of 12 and 17 years. Uncontrolled asthma was defined as a C-ACT or ACT score of <19. Each visit was also classified as either respiratory- or non–respiratory-related.

RESULTS. The overall prevalence of uncontrolled asthma was 46% (35% in patients with nonrespiratory complaints and 54% among those seen for a respiratory complaint). For patients evaluated for respiratory reasons, more children with uncontrolled asthma had missed ≥ 1 school day in the previous 4 weeks because of asthma (67% vs 29%; $P < .0001$). For patients seen for nonrespiratory reasons, more children with uncontrolled asthma had missed ≥ 1 day of school in the previous 4 weeks (53% vs 24%; $P < .0001$).

CONCLUSIONS. The number of missed school and work days resulting from uncontrolled asthma was not only greater for patients seen in a pediatric office for respiratory-related issues but also for non–respiratory-related reasons. This result highlights the burden and impact of uncontrolled asthma seen in all patients in pediatric clinics. Providers should consider evaluating asthma control on a regular basis regardless of the reason for the visit.

REVIEWER COMMENTS. The ACT and C-ACT tools were designed to use only for children already diagnosed with asthma. The cutoff score of ≤ 19 is not an absolute indicator of uncontrolled asthma but should serve to alert the provider that asthma might not be well controlled. A report of using C-ACT scores to identify children with very poorly controlled asthma has been published previously (*J Allergy Clin Immunol*. 2010;126[2]:267–273).

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Translation of a Pediatric Asthma-Management Program Into a Community in Connecticut

Cloutier MM, Wakefield DB. *Pediatrics.* 2011;127(1):11–18

PURPOSE OF THE STUDY. National Asthma Education and Prevention Program (NAEPP) guidelines have been widely disseminated, but their adoption by primary care clinicians has been problematic. This study evaluated an asthma-management program based on NAEPP guidelines.

STUDY POPULATION. Children aged 6 months or older in Connecticut were enrolled in community pediatric offices by trained community personnel.

METHODS. Pediatric office health care providers and personnel in 6 Connecticut communities were trained in an asthma-management program entitled "Easy Breathing," which was based on NAEPP guidelines. Quality parameters encompassed enrollment census, relevant use of anti-inflammatory medications, and provision of a written action plan. Utilization of medical services was confirmed for Medicaid-covered children and compared by using relative rates and 95% confidence intervals (CIs) before and after enrollment.

RESULTS. There were 51 practices and 297 health care providers who enrolled 32 680 children from 2002 to 2007; 10 467 of these children had asthma according to history, 4354 of whom were insured by Medicaid. Children with persistent asthma according to history had a decline in the number of hospitalizations (relative rate: 0.51 [95% CI: 0.39–0.65]) and emergency department encounters (relative rate: 0.70 [95% CI: 0.68–0.84]) but no decline in the number of outpatient visits (relative rate: 0.99 [95% CI: 0.9–1.10]). The use of inhaled corticosteroids doubled with an increment in relevant utilization of anti-inflammatory medications to 96%, and a written action plan was provided to 94% of enrolled children with asthma.

CONCLUSIONS. The authors concluded that general pediatricians can effectively institute an asthma-management program, using NAEPP guidelines, that enhances asthma care for a large population of children.

REVIEWER COMMENTS. The limitations of this study that affect its generalizability were (1) claims data were only available for Medicaid-insured children, (2) the intermittent character of state funding, and (3) the fact that both the number of outpatient visits and the filled-prescription rate were low. Therefore, the actual number of children who both filled prescriptions and received them is unknown. However, these results indicate that a disease-management program for pediatric asthma can be implemented successfully in a community pediatric setting with a subsequent significant decrease in the number of hospitalizations and emergency department visits in a large Medicaid-insured population of children.

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Genetic Variations in Nitric Oxide Synthase and Arginase Influence Exhaled Nitric Oxide Levels in Children

Salam MT, Bastain TM, Rappaport EB, et al. *Allergy*. 2011;66(3):412–419

PURPOSE OF THE STUDY. Elevated fractional exhaled nitric oxide (FeNO) has been shown to be a sensitive biomarker for airway inflammation in children with asthma. This study examined whether a relationship could be demonstrated between genetic variants in nitric-oxide synthase and arginase genes and FeNO in asthma.

STUDY POPULATION. Subjects aged 5 to 7 years were recruited from 13 Southern California communities for a Children's Health Study cohort established in 2003. Although FeNO data were available irrespective of race/ethnicity, genetic data were only available from Hispanic and non-Hispanic white children, and data from 2773 children were available for the combined analysis.

METHODS. FeNO measurements were made with breath-sample collections that followed American Thoracic Society guidelines and took place in 2 consecutive school years. Variations in 5 genetic loci were characterized by tag single-nucleotide polymorphisms. Repeated-measures analysis of variance was used to evaluate the association between these genetic variants and FeNO.

RESULTS. Sequence variations in the *NOS2A* and *ARG2* loci were globally associated with FeNO ($P = .0002$ and 0.001, respectively) but in opposite directions regarding FeNO levels. The *ARG2* association was tagged by intronic variant rs3742879 with stronger association with lower FeNO levels. The directional change noted between FeNO levels and the above-mentioned genetic variants was more pronounced in the children with asthma than in those without asthma.

CONCLUSIONS. Variants in the nitric-oxide synthesis pathway genes jointly contribute to the differences in FeNO concentrations. Some of these genetic influences were stronger in children with asthma. Further studies are required to confirm these findings.

REVIEWER COMMENTS. Exhaled nitric oxide has become a more widely used tool in asthma patient care and clinical research settings. This report points out that there are genetic variants that could influence the interpretation of FeNO results. More studies are needed to determine the potential role of these genetic variants in the pathogenesis of asthma.

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MEDICAL THERAPIES

Leukotriene Antagonists as First-Line or Add-on Asthma-Controller Therapy

Price D, Musgrave SD, Shepstone L, et al. *N Engl J Med*. 2011;364(18):1695–1707

PURPOSE OF THE STUDY. To evaluate the real-world efficacy of leukotriene-receptor antagonists (LTRAs) for the

treatment of asthma by comparing LTRAs with both inhaled glucocorticoids for first-line therapy and long-acting β_2 agonists (LABAs) for add-on therapy.

STUDY POPULATION. Patients aged 12 to 80 years were considered eligible if they had a Mini Asthma Quality of Life Questionnaire (MiniAQLQ) score of ≤6 or an Asthma Control Questionnaire (ACQ) score of ≥1. Trials were conducted at 53 primary care sites in the United Kingdom.

METHODS. Patients were randomly assigned to an LTRA (n = 148) or inhaled glucocorticoid (n = 158) in the first-line therapy trial and an LTRA (n = 170) or an LABA (n = 182) in the step-up therapy trial. Patients were managed by their primary care provider during the 2-year trial period, and treatments were given in an open-label fashion. After the initial visit, patients were followed either by telephone or in the clinic at months 2, 6, 12, 18, and 24. Patients' MiniAQLQ score was the primary outcome measure. Secondary outcome measures included the ACQ score, the Royal College of Physicians 3-item asthma questionnaire score, the Mini Rhinoconjunctivitis Quality of Life Questionnaire score, and the frequency of asthma exacerbations that required oral glucocorticoids or hospitalization.

RESULTS. Over the 2-year treatment period, the mean MiniAQLQ score increased by 0.8 to 1.0 in both trials. Assessment of data at 2 months revealed noninferiority between LTRAs and inhaled glucocorticoids for first-line therapy on the basis of the primary outcome of MiniAQLQ score. At 2 years, results approached equivalence between the treatment groups in both trials; however, the data could not prove noninferiority. There were no significant differences between treatment groups regarding all other secondary outcome measures at both 2 months and 2 years. There was no significant difference in adherence rates in either trial.

CONCLUSIONS. Results at 2 months suggest comparable efficacy between LTRAs and inhaled glucocorticoids as first-line controller therapy and equivalence to LABAs as add-on therapy. Equivalence at 2 years was not proved for either trial.

REVIEWER COMMENTS. Although LTRAs are a comparable option for both first-line and step-up therapy in asthma, true long-term equivalence has not been demonstrated. Results of previous randomized trials that examined LTRA use tend to support inhaled glucocorticoids as the preferred choice for first-line therapy and LABAs as the preferred choice for step-up therapy. The authors of a Cochrane review of 27 randomized controlled trials, mainly in adults with mild-to-moderate asthma, concluded that inhaled corticosteroid was more effective than LTRAs. A meta-analysis of 18 randomized controlled trials in children younger than 18 years with similar asthma found that inhaled corticosteroid was more effective than montelukast for preventing severe asthma exacerbations. The absence of a placebo group makes it difficult to judge whether the changes observed in MiniAQLQ score in either group from baseline are truly clinically meaningful. However, this study does provide a better, although not perfect, real-world perspective, with data approaching equivalence for LTRA use as both first-line and step-up therapy for asthma. Results from previous randomized controlled trials combined with data from this pragmatic study might not change how we currently practice but can guide us in our decision-making process more effectively in the real-world clinic setting.

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Effect of Addition of Single Dose of Oral Montelukast to Standard Treatment in Acute Moderate to Severe Asthma in Children Between 5 and 15 Years of Age: A Randomised, Double-Blind, Placebo Controlled Trial

Todi VK, Lodha R, Kabra SK. *Arch Dis Child.* 2010;95(7):540–543

PURPOSE OF THE STUDY. Montelukast has both anti-inflammatory and bronchodilator properties. Does giving a single dose at the time of an emergency department (ED) visit for an asthma exacerbation improve outcomes compared with standard therapy alone?

METHODS. One hundred seventeen children who presented to an ED with moderate-to-severe asthma exacerbations defined as a Modified Pulmonary Index Score of ≥9 were randomly assigned to receive either montelukast (n = 60) or placebo (n = 57) in addition to standard therapy, which included nebulized albuterol and ipratropium and oral corticosteroids.

RESULTS. The percentage of children whose Modified Pulmonary Index Score decreased to <9 within 4 hours was no different in the montelukast (55%) and placebo (63%) groups (P = .37). There were no differences in the improvement in lung function or hospitalization rates.

CONCLUSIONS. Single-dose oral montelukast added to standard therapy of inhaled bronchodilators and systemic glucocorticoids did not provide additional clinical benefit for children with acute moderate-to-severe asthma.

REVIEWER COMMENTS. Because montelukast can act quickly and works in a different way than other bronchodilators,

it was worth investigating whether it would have additive benefit for acute asthma, but this study found that it does not.

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The Back to School Asthma Study: The Effect of Montelukast on Asthma Burden When Initiated Prophylactically at the Start of the School Year

Weiss KB, Gern JE, Johnston NW, et al. *Ann Allergy Asthma Immunol.* 2010;105(2):174–181

PURPOSE OF THE STUDY. To determine the efficacy of prophylactic montelukast therapy in reducing asthma morbidity at the start of the school year.

STUDY POPULATION. Patients 6 to 14 years of age with a diagnosis of asthma for a minimum of 1 year were recruited for this international study that took place in 39 US states and 3 Canadian provinces from June 2006 through November 2006.

METHODS. This was a randomized, multicenter, double-blind, placebo-controlled study for patients who received either 5-mg montelukast or placebo beginning on the night before school started and continued for an 8-week period. Patients were randomly assigned during a screening period from 2 to 12 weeks before the school start date. Patients were interviewed by telephone to review symptoms, use of study medications, and need for additional β agonists 4 weeks after starting school. A final study visit at 8 weeks was conducted to document daytime symptoms, "awake all night," inhaled corticosteroid use, increased β-agonist use, and visits to a health care professional or facility for asthma. Inclusion criteria included treatment of asthma within 6 months of screening and patients having at least 1 exacerbation of asthma symptoms in the previous year that were associated with a cold. Exclusion criteria included forced expiratory flow volume in 1 second below 60% of that predicted, use of systemic steroids within 4 weeks of randomization, and more than 3 hospitalizations for asthma in the previous year. Patients on treatment with a long-acting β agonist or leukotriene receptor antagonist within 10 days of randomization were also excluded.

RESULTS. Of 1162 patients (580 randomly assigned to the montelukast group and 582 randomized to the placebo group), no significant difference was seen for the percentage of days with worsening asthma. A trend for montelukast to reduce worsening asthma days in those who began school after August 15 was seen but was not significant. A nonsignificant trend in older children and boys favoring treatment with montelukast was also seen.

CONCLUSIONS. The use of montelukast did not significantly reduce the number of days with worsening asthma when begun as prophylactic therapy at the start of the school year.

REVIEWER COMMENTS. The start of the school year presents a challenge for asthmatic children, who have greater disease burden with respiratory illnesses. In the group of children treated with montelukast, the percentage of days with worsening asthma was stable, whereas this percentage increased in weeks 3 to 4 in the placebo group and subsequently decreased for the remainder of the study. Because this study did not answer the need to prevent morbidity from asthma during the fall, additional studies are needed to address this concern.

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Combination Therapy Salmeterol/Fluticasone Versus Doubling Dose of Fluticasone in Children With Asthma

Vaessen-Verberne AA, van den Berg NJ, van Nierop JC, et al; COMBO Study Group. *Am J Respir Crit Care Med.* 2010;182(10):1221–1227

PURPOSE OF THE STUDY. To determine if the addition of a long-acting bronchodilator is noninferior to doubling the dose of inhaled corticosteroids in children whose asthma is not controlled with use of low-to-moderate doses of inhaled corticosteroids alone.

STUDY POPULATION. Children aged 6 to 16 years who were using fluticasone propionate (100 μg twice daily) to treat their asthma were enrolled in this study ($N = 257$). A 4-week run-in period was used to monitor these children. Those who were still symptomatic despite regular use of fluticasone propionate were included in the randomization of study groups ($n = 158$). The study was conducted at multiple pediatric medical centers throughout Europe.

METHODS. Symptomatic children were randomly assigned to 1 of 2 treatment groups: fluticasone propionate (200 μg twice per day) or salmeterol/fluticasone propionate (50/100 μg twice per day), used for a 26-week treatment period. Lung-function measurements were recorded at the start of the run-in period, at time of randomization, and at all visits during the treatment period. The provocative dose of methacholine that causes a 20% decrease (PD_{20}) in the forced expiratory volume in 1 second (FEV_1) and exhaled nitric-oxide levels were measured at the start and end of the treatment period. The number of symptom-free days and asthma exacerbations were logged at each clinic visit. Exacerbations were classified as mild, moderate, or severe on the basis of the medical interventions needed.

RESULTS. There was no significant difference between the treatment groups in the percentage of symptom-free days. Each treatment group had an increase in symptom-free days by ~25% while on treatment compared to baseline ($P < .001$). Furthermore, no significant difference was seen in the percentage of days in which rescue salbutamol was used; both groups had a gradual decline in use of the salbutamol. A combined ranked assessment of all exacerbations among the treatment groups revealed no statistically significant difference between the 2 groups. Lung-function parameters did not differ between groups other than a slightly greater effect on maximal expiratory flow seen in the salmeterol/fluticasone group during the first week of treatment. The 2 groups did not differ in statural growth or number of adverse events.

CONCLUSIONS. The results of this study indicate that the combination of a long-acting bronchodilator with inhaled corticosteroid has equal efficacy in controlling symptoms and preserving lung function when compared with doubling the dose of inhaled corticosteroids in children who were symptomatic on a moderate dose of inhaled corticosteroids. Therefore, combination of a long-acting bronchodilator is likely an appropriate alternative in step-up therapy.

REVIEWER COMMENTS. This study provides us with an adequate alternative step 3 treatment option. The results of this study are in line with those of previous work. Further study is now needed to evaluate whether there might be specific asthma phenotypes that respond more favorably to 1 treatment option versus another. The fear of increased severe asthma exacerbations and asthma-related deaths associated with use of long-acting β_2 agonists in children is still present. Further data from large numbers of children are needed to make a more definite conclusion about this possible risk.

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Once- vs Twice-Daily Budesonide/Formoterol in 6- to 15-Year-Old Patients With Stable Asthma

Eid SE, Noonan MJ, Chipps B, Parasuraman B, Miller CJ, O'Brien CD. *Pediatrics*. 2010;126(3). Available at: www.pediatrics.org/cgi/content/full/126/3/e565

PURPOSE OF THE STUDY. To compare the clinical effectiveness and tolerability of once-daily budesonide/formoterol pressurized metered-dose inhaler (pMDI) versus budesonide pMDI in asthmatic children aged 6 to 15 years old.

STUDY POPULATION. Children aged 6 to 15 years with stable mild-to-moderate asthma were enrolled if they had had symptoms for ≥6 months, bronchodilator response, and forced expiratory volume in 1 second (FEV_1) of 60% to 90% of that predicted at baseline.

METHODS. The study was a multicenter, 12-week double-blind, parallel-group, active-controlled, randomized study. Enrolled patients had a 4- to 5-week run-in with budesonide/formoterol 80/9 μg twice per day and albuterol as needed for rescue. Patients whose asthma was stable after the run-in period were age-stratified and randomly assigned to receive budesonide pMDI 80 μg (2 inhalations daily), budesonide/formoterol 80/4.5 μg (2 inhalations once daily), or budesonide/formoterol 40/4.5 μg (2 inhalations twice daily). Primary outcome data were evening peak expiratory flow rate (PEF). PEF and predose FEV_1 were recorded in an electronic diary by patients or caregivers in the morning and evening. Patients were immediately withdrawn from study if they met predefined worsening asthma symptom criteria. At the end of the study, physicians and caregivers were asked about health status and ability to manage asthma symptoms using a 5 point scale. Health-related quality of life (HRQoL) was assessed by questionnaire.

RESULTS. Of 719 enrolled patients, 522 were randomly assigned. The most common cause of withdrawal before randomization was worsened asthma symptoms or function. Once- and twice-daily budesonide/formoterol pMDI were superior to budesonide pMDI daily as assessed by morning PEF, morning predose FEV_1, or evening PEF. Although the twice-daily budesonide/formoterol group had improved evening PEF during the study versus being unchanged in the once-daily budesonide/formoterol group, there were no statistical differences between these groups. Evening predose FEV_1 increased in the twice-daily budesonide/formoterol group versus decreasing in the once-daily budesonide/formoterol group or budesonide group. Twice-daily budesonide/formoterol resulted in significantly less daytime rescue-medication use versus the once-daily medication study groups and resulted in significantly less nighttime rescue-medication use versus budesonide alone. Patients with at least 1 predefined event of worsened asthma episodes were significantly fewer in the twice-daily budesonide/formoterol group versus once-daily medication groups; however, this was seen entirely in the 6- to 11-year age group. Physician perception of ease of asthma management significantly favored the twice-daily budesonide/formoterol group, but the results of other subjective assessments of asthma control, health status, HRQoL, adverse events, and objective safety data were similar across all groups.

CONCLUSIONS. Once-daily dosing of budesonide-formoterol pMDI resulted in significantly higher evening PEF and most of the assessed pulmonary variables compared with once-daily budesonide pMDI. However, there were no significant differences between once-daily budesonide/

formoterol and once-daily budesonide in measures for asthma control, asthma symptoms, or HRQoL measures. Twice-daily versus once-daily budesonide/formoterol resulted in improved evening predose FEV_1, daytime rescue-medication use, rescue-medication–free days, and worsening asthma events. There were no differences in safety variables between the 3 treatment groups.

REVIEWER COMMENTS. This study was designed by scientists employed by a pharmaceutical company and conducted by a large group of clinicians. It adds to the data regarding safety of inhaled corticosteroid (ICS)/long-acting β_2 agonist (LABA) combinations in young children. In the twice-daily budesonide/formoterol group, the mean evening PEF and evening predose FEV_1 continued to increase during the study, which raises the question of whether the patients achieved true baseline status at the time of randomization. A longer run-in might have lead to different results in the comparisons between twice-daily and once-daily budesonide/formoterol. The authors warned that stepping-down from twice-daily budesonide/formoterol to once-daily dosing might lead to increased asthma symptoms without a change in safety profile but did not discuss potential long-term harm from ongoing unnecessary LABA/ICS use. Current product information and national asthma guidelines should continue to be followed regarding ICS/LABA use in children, but in individual patients for whom twice-daily dosing is not feasible, once-daily dosing (with careful monitoring) might be appropriate.

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Use of Beclomethasone Dipropionate as Rescue Treatment for Children With Mild Persistent Asthma (TREXA): A Randomized, Double-Blind, Placebo-Controlled Trial

Martinez FD, Chinchilli VM, Morgan WJ, et al. *Lancet*. 2011;377(9766):650–657

PURPOSE OF THE STUDY. To determine the effectiveness of inhaled beclomethasone dipropionate when used as a rescue treatment for symptoms in children with mild persistent asthma.

STUDY POPULATION. Children and adolescents aged 5 to 18 years with well-controlled mild persistent asthma were enrolled from 5 clinical centers in a 44-week, randomized, double-blind, placebo-controlled trial.

METHODS. Participants who remained well controlled during the 4-week run-in period were stratified according to clinical center and age group and randomly assigned to 1 of 4 treatments: twice-daily beclomethasone with beclomethasone plus albuterol as rescue (combined group); twice-daily beclomethasone with placebo plus albuterol as rescue (daily beclomethasone group); twice-daily placebo with beclomethasone plus albuterol as rescue (rescue beclomethasone group); and twice-daily placebo with placebo plus albuterol as rescue (placebo group). Twice-daily treatment was 1 puff of beclomethasone (40 μg) or placebo, and rescue treatment for symptoms was 2 puffs of beclomethasone or placebo for every 2 puffs of albuterol (180 μg). The primary outcome, time to first exacerbation that required oral prednisone, and secondary outcome, linear growth, were analyzed according to intention to treat.

RESULTS. Of the 843 participants enrolled, 288 were assigned to a treatment group (combined, $n = 71$; daily, $n = 72$; rescue, $n = 71$; placebo, $n = 74$). Baseline characteristics were similar between included and excluded participants and among those in the 4 treatment groups. The frequency of exacerbations was lower in the combined (31% [95% confidence interval (CI): 21%–43%]; $P = .07$), daily (28% [95% CI: 18%–40%]; $P = .03$), and rescue (35% [95% CI: 24%–47%]; $P = .07$) groups compared with the placebo group (49% [95% CI: 37%–61%]). The frequency of treatment failure was 5.6% (95% CI: 1.6%–14%; $P = .012$) in the combined, 2.8% (95% CI: 0%–10%; $P = .009$) in the daily, and 8.5% (95% CI: 2%–15%; $P = .024$) in the rescue groups compared with 23% (95% CI: 14%–43%) in the placebo group. Compared with the placebo group, linear growth was 1.1 cm (SD: 0.3 cm) less in the combined and daily groups ($P < .0001$) but no different in the rescue group ($P = .26$).

CONCLUSIONS. Daily inhaled corticosteroids are the most effective treatment for children with mild persistent asthma. For children not taking a daily inhaled corticosteroid, inhaled beclomethasone used as a rescue medication with albuterol can lower the risk of exacerbations and treatment failures more effectively than albuterol alone but to a lesser extent than daily inhaled beclomethasone. Children with mild persistent asthma should not be treated with only rescue albuterol.

REVIEWER COMMENTS. This study differs from previous trials of inhaled corticosteroids during asthma exacerbations in that it evaluated the benefit of adding a low-dose inhaled corticosteroid as rescue medication whenever albuterol was needed for treatment of symptoms. The results confirm the relative effectiveness of low-dose daily inhaled corticosteroids, which remain the first-line maintenance therapy for children with mild persistent asthma. Compared with rescue albuterol alone, the results also suggest a possible benefit without increased risk of growth impairment from inhaled corticosteroids added as rescue medication for children not taking a daily inhaled steroid. Among children with well-controlled

mild persistent asthma, the ongoing need for and adherence to inhaled steroid controller therapy must be regularly assessed on an individual basis. These results might be useful when trying to balance the greater effectiveness and greater potential for adverse effects of daily inhaled steroid controller therapy in these patients.

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Effectiveness of Omalizumab in Reducing Corticosteroid Burden in Patients With Moderate to Severe Persistent Allergic Asthma

Karpel J, Massanari M, Geba G, Fianifard F, Inhaber N, Zeldin R. *Ann Allergy Asthma Immunol.* 2010;105(6): 465–470

PURPOSE OF THE STUDY. To assess whether the addition of omalizumab to inhaled corticosteroid (ICS) therapy reduces the steroid burden during long-term treatment and improves clinical outcomes.

STUDY POPULATION. Patients ($N = 1071$) were aged 12 to 75 years with moderate-to-severe persistent allergic asthma that was inadequately controlled with ICSs. Eight percent of the patients were aged 12 to 18 years. All patients had confirmed allergic asthma, an immunoglobulin E (IgE) level between 30 and 700 IU/mL, and a baseline forced expiratory volume in 1 second (FEV_1) between 40% and 80%. Data were pooled from 1 US and 1 international randomized, double-blind placebo-controlled multicenter trial.

METHODS. After a 4- to 6-week ICS stabilization run-in period, patients were randomly assigned to receive omalizumab or placebo. The ICS steroid dose was held constant for the first 16 weeks of treatment and then tapered by 25% every 2 weeks as tolerated for a total of 12 weeks. Patients were then maintained for 24 weeks on continued randomized treatment as well as the lowest possible dose of ICSs established during the steroid-reduction period, and clinically appropriate dose adjustments of ICSs were permitted during this period. Measured outcomes included steroid burden (change from baseline ICS dose and number of oral corticosteroid [OCS] bursts) as well as clinical outcomes.

RESULTS. Baseline characteristics were similar between the 2 groups: patients used an average of 670 μg/day of inhaled beclomethasone and nearly 5 rescue puffs of albuterol daily, and their average IgE levels were in the 190s (IU/mL). At the end of the 3 study phases, there were statistically significant differences between the omalizumab and placebo groups in inhaled steroid dose (all $P < .001$) and number of OCS bursts (all $P < .001$). There were also significant reductions in frequency of exacerbations, improvements in FEV_1 and quality of life, and reduction in peripheral blood eosinophilia in those on omalizumab compared with those on placebo ($P < .001$).

CONCLUSIONS. Omalizumab use reduces corticosteroid burden and improves clinical outcomes in patients with moderate-to-severe persistent asthma.

REVIEWER COMMENTS. The results of this study add to a growing body of literature that substantiates the addition of omalizumab to the medical regimen of those with moderate-to-severe asthma. The high annual cost of this medication ($10 000–$30 000) and the need for supervised administration make it more suited to those who require frequent acute care for their asthma, frequent doses of oral steroids, or high-dose inhaled steroids. The study included a small but significant percentage of pediatric patients aged 12 to 17, for whom reduction in the amount of systemic steroid exposure is of arguably greater value. Ongoing studies are examining the safety of this medication in younger children.

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Randomized Trial of Omalizumab (Anti-IgE) for Asthma in Inner-City Children

Busse WW, Morgan WJ, Gergen PJ, et al. *N Engl J Med.* 2011;364(11):1005–1015

PURPOSE OF THE STUDY. To evaluate the effectiveness of omalizumab in improving asthma control of inner-city children who are not adequately controlled on guideline-based therapy.

STUDY POPULATION. Inner-city children, adolescents, and young adults ($N = 419$) with persistent allergic asthma were included in this study. Eligible patients were required to have a physician's diagnosis of asthma or documentation of asthma symptoms for longer than 1 year before entry into the study and evidence of uncontrolled asthma. All patients had at least 1 positive skin-test result to a perennial allergen, weighed between 20 and 150 kg, and had a total serum immunoglobulin E (IgE) level between 30 and 1300 IU/mL.

METHODS. Participants ($n = 419$) were randomly assigned to receive subcutaneous injections of omalizumab or placebo every 2 or 4 weeks for a 60-week treatment period. Omalizumab doses were calculated on the basis of patient weight and total serum IgE level; the minimum monthly dose was 0.016 mg/kg body weight/IU IgE/mL. Routine clinic visits were scheduled every 3 months. Asthma-control assessment was based on Na-

tional Asthma Education and Prevention Program (NAEPP) guidelines. The primary outcome evaluated at each injection visit was the number of symptomatic days in the previous 2 weeks. Numerous secondary outcomes were evaluated.

RESULTS. Compared with placebo, omalizumab treatment significantly reduced the mean number of symptomatic days per 2-week interval from 1.96 to 1.48, which is a 24.5% difference ($P < .001$). Significantly fewer exacerbations occurred during the treatment period in the omalizumab group; 30.3% of patients had an exacerbation compared with 48.8% of patients in the placebo group ($P < .001$). Similarly, the percentage of hospitalizations caused by asthma was 1.51% vs 6.3% in the placebo group ($P = .02$). Asthma control in the omalizumab group required significantly lower doses of inhaled glucocorticoids ($P < .001$) and long-acting β_2 agonists ($P = .003$). Finally, posthoc analysis revealed that omalizumab prevented the seasonal spikes in exacerbations seen in the placebo group. No differences in safety were seen.

CONCLUSIONS. Omalizumab improved asthma control in inner-city children, adolescents, and young adults when added to their previous guideline-based therapy.

REVIEWER COMMENTS. Omalizumab is an effective treatment option for patients with asthma and allergies whose conditions are not adequately controlled on guideline-based therapy. In this study, the effectiveness of omalizumab was shown at all levels of asthma severity. According to NAEPP guidelines, omalizumab is indicated for patients older than 11 years as a step 5 or 6 treatment option. Further data on the long-term safety of omalizumab in children is needed before we can fully advocate adjusting these current recommendations. Overall, this study provides us with further proof that the allergic component of asthma plays a key role in controlling this population's asthma. Further research to investigate the potential use of omalizumab for preventing seasonal peaks would also be beneficial at this time.

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Cost-effectiveness of Metered-Dose Inhalers for Asthma Exacerbations in the Pediatric Emergency Department

Doan Q, Shefrin A, Johnson D. *Pediatrics.* 2011;127(5). Available at: www.pediatrics.org/cgi/content/full/127/5/e1105

PURPOSE OF THE STUDY. To compare the incremental cost and effects (eg, averted admission to hospital) of using a metered-dose inhaler (MDI) against wet nebulization to deliver bronchodilators for the treatment of mildly to moderately severe asthma in pediatric emergency departments (EDs).

STUDY POPULATION. The population was obtained from a Cochrane systematic review in which the efficacy of using MDIs versus nebulizers for the delivery of albuterol to children who presented to the ED with asthma were compared.

METHODS. Cost data were obtained from hospitals and regional authorities involved in the Cochrane review studies. The incremental cost-effectiveness ratio was determined, and Monte Carlo simulations were used to perform probabilistic sensitivity analyses.

RESULTS. Using MDIs in the ED versus wet nebulization might result in a net savings of $154.95 (Canadian dollars [CAN$]) per patient. Models suggest that using MDIs is both more effective and less costly than wet nebulization. Sensitivity analyses revealed that MDIs would remain the better strategy even if the net cost of using an MDI was CAN$70 more expensive than using nebulized bronchodilators.

CONCLUSIONS. Using MDIs with spacers instead of wet nebulizers to deliver albuterol to treat children with mild-to-moderate asthma exacerbations in the ED could lead to significant cost savings.

REVIEWER COMMENTS. Although not statistically significant ($P = .062$), the MDI protocol was more likely to prevent hospital admission than using nebulized bronchodilators. Each hospitalization averted would save CAN$2499. At the same time, using albuterol MDI (CAN$262.73) versus albuterol via nebulizer (CAN$417.68) for acute asthma in the ED would also be less expensive (net cost savings: CAN$154.95). The authors noted that these results are only generalizable to single-payer health care models similar to those assessed in Canada.

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Cost-effectiveness Analysis of Fluticasone Versus Montelukast in Children With Mild-to-Moderate Persistent Asthma in the Pediatric Asthma Controller Trial

Wang L, Hollenbeak CS, Mauger DT, et al; Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. *J Allergy Clin Immunol.* 2011;127(1):161–166

PURPOSE OF THE STUDY. To compare the cost-effectiveness of 2 commonly used asthma controllers, fluticasone and

montelukast, in a population of pediatric patients with mild-to-moderate persistent asthma.

STUDY POPULATION. A total of 154 patients (aged 6–14 years) who participated in the Pediatric Asthma Controller Trial (PACT) were included in the study.

METHODS. This study extracted data from the PACT study, a randomized controlled, double-blind, multicenter trial that studied treatment regimens in children with mild-to-moderate persistent asthma. Both effectiveness and cost measures were used to determine a cost-effectiveness analysis of the 2 controller medications: fluticasone (100 μg twice daily) and montelukast (5 mg daily), given for 48 weeks. Effectiveness measures included (1) asthma-control days (ACDs), (2) improvement in forced expiratory volume in 1 second (FEV_1), and (3) the number of exacerbations avoided. Cost measures were taken from (1) direct costs from a third-party payer's perspective, including the sum of costs from asthma-related medication, emergency department visits, and regular physician's office visits, and (2) societal costs, which were the direct costs plus productivity losses from asthma-related missed school or work. Cost-effectiveness analysis was then used to compare the effectiveness of the different treatments relative to their costs. Cost-effectiveness analysis was also performed for subgroups on the basis of the phenotypic factors of exhaled nitric oxide (eNO) and the provocative concentration that causes a 20% decrease (PC_{20}) in the forced expiratory volume in 1 second (FEV_1).

RESULTS. Of the 154 patients analyzed, 79 received fluticasone and 75 received montelukast. There were no statistical differences in demographics among the participants. When effectiveness measures were compared, fluticasone showed significantly higher effectiveness with respect to ACDs, improvement in FEV_1, and the number of asthma exacerbations ($P < .01$). Direct costs during the study period were \$759 for fluticasone and \$1189 for montelukast ($P < .001$). Societal costs were \$1075 for fluticasone and \$1673 for montelukast ($P < .001$). Thus, fluticasone was shown to be more cost-effective. In the subgroup analysis, fluticasone was more cost-effective compared with montelukast for the subgroups with high eNO levels (eNO $\geq$ 25 ppb) and more-responsive PC_{20} ($PC_{20} < 2$ mg/mL).

CONCLUSIONS. In children with mild-to-moderate persistent asthma, fluticasone had lower cost and higher effectiveness when compared with montelukast, especially in patients with more airway inflammation and more responsivity to methacholine.

REVIEWER COMMENTS. Few evaluations exist for the cost-effectiveness of asthma controller regimens for children. The results of the study were consistent with the National Asthma Education and Prevention Program guidelines, which recommend inhaled corticosteroid monotherapy as the preferred asthma controller option for mild-to-moderate persistent asthma in children.

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Relationship of Asthma Management, Socioeconomic Status, and Medication Insurance Characteristics to Exacerbation Frequency in Children With Asthma

Ungar WJ, Paterson JM, Gomes T, et al. *Ann Allergy Asthma Immunol.* 2011;106(1):17–23

PURPOSE OF THE STUDY. To identify factors associated with severe asthma exacerbations in children as measured by the number of emergency department (ED) visits and hospitalizations.

STUDY POPULATION. Asthmatic children aged 1 to 18 years were enrolled from specialty and family practice hospital-based outpatient clinics and 2 EDs in Ontario, Canada, from November, 1, 2000, through March 31, 2003.

METHODS. Data regarding demographics, socioeconomic status, drug plan characteristics, health status, health utilization, and symptom data were collected during this retrospective cohort study. These data were compared with data on asthma ED visits and hospitalizations in the full group and a subgroup with prescription drug coverage.

RESULTS. Complete data were available from 490 patients. Fewer exacerbations were associated with medium/high income, older children, recruitment from a physician's office or asthma clinic, and having an action plan. Previous ED visits, pet ownership, nebulizer use, asthma education, and younger age were associated with more exacerbations. A history of food, medication, and insect allergies were associated with 52% more exacerbations. In the drug-plan subgroup, girls had 26% fewer exacerbations, and the rate of asthma exacerbations increased by 14% for every 1% increase in the proportion of income spent on prescription medicines.

CONCLUSIONS. Exacerbations that required urgent care were associated with asthma history, disease-management factors, and socioeconomic status. Because families with drug plans paid a higher proportion of household income for asthma medicines, there was a significant association with more exacerbations.

REVIEWER COMMENTS. This study demonstrates what clinicians see in clinical practice: cost-shifting often leads to rationing and underuse of needed medicines by our patients. We need to assess medication use and educate

and assist families in understanding the rationale for a particular medication regimen to increase compliance and decrease exacerbations.

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IMMUNOTHERAPY, IMMUNOMODULATION, PREBIOTICS/PROBIOTICS

A Randomized Controlled Study of Peanut Oral Immunotherapy: Clinical Desensitization and Modulation of the Immune Response

Varshney P, Jones SM, Scurlock AM, et al. *J Allergy Clin Immunol.* 2011;127(3):654–660

PURPOSE OF THE STUDY. To determine if peanut oral immunotherapy (OIT) was safe and effective in inducing desensitization in peanut-allergic children. Previous studies on peanut OIT did not include a placebo control.

STUDY POPULATION. Studied were 28 children aged 1 to 16 with peanut allergy defined by clinical history of reaction after ingestion, an elevated peanut immunoglobulin E (IgE) level of >15 kU/L, or an IgE level of >7 kU/L if a significant reaction had occurred within the previous 6 months. All subjects had had a positive skin-prick test result to peanut.

METHODS. Subjects began with an initial dose escalation, with build-up visits every 2 weeks, until a maintenance dose of 4000 mg was reached. Home dosing was continued daily between build-up visits. An oral food challenge (OFC) to peanut occurred around week 48, after at least 1 month of maintenance. Skin-prick testing, cytokine production, and peanut IgG_4 and IgE and T-regulatory cell levels were assessed during treatment.

RESULTS. Peanut OIT significantly increased the amount of peanut tolerated at the OFC compared with placebo (mean: 5000 vs 280 mg, respectively; $P < .001$). Three peanut OIT-treated subjects withdrew because of adverse allergic effects. The peanut-OIT group showed a reduction in skin-test size and interleukin 5 and interleukin 13 levels and increases in peanut IgG_4, and IgE, and T-regulatory cell levels.

CONCLUSIONS. The results of this study clearly showed that peanut OIT induces desensitization as well as marked changes in the immune response in subjects with peanut allergy.

REVIEWER COMMENTS. This study is novel in that it is the first placebo-controlled study of peanut OIT. The study found dramatic efficacy for OIT in inducing desensitization to peanut, as well as concomitant immunologic changes. If OIT is going to become a mainstay of therapy for food allergy, future research will need to address adverse effects of OIT, the optimal duration of OIT, and the efficacy of OIT in inducing long-term tolerance. The sublingual route of immunotherapy for peanut was evaluated in a companion study reported on in the same issue and also showed promise for efficacy and safety (Kim EH, Bird JA, Kulis M, et al. *J Allergy Clin Immunol.* 2011;127[3]:640–646).

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Immunologic Effects of Sublingual Immunotherapy: Clinical Efficacy Is Associated With Modulation of Programmed Cell Death Ligand 1, IL-10, and IgG_4

Piconi S, Trabattoni D, Rainone V, et al. *J Immunol.* 2010;185(12):7723–7730

PURPOSE OF THE STUDY. To evaluate an optimal treatment regimen for sublingual immunotherapy (SLIT) and investigate the underlying mechanism.

STUDY POPULATION. There were 62 Italian patients aged 19 to 60 years enrolled from a clinic in Milano, Italy, between February and September 2009. Inclusion criteria were a clinical history that suggested ragweed sensitization, a positive skin-prick-test result to ragweed pollen, and a clinical report of asthma and/or rhinoconjunctivitis.

METHODS. The patients were randomly assigned to 1 of 4 treatment arms: preseasonal SLIT (5 months); seasonal SLIT (3 months); prolonged SLIT (5 months × 3 years); or no SLIT. Subjects on SLIT were treated with a median Amba1 (major ragweed allergen) dose of 120 mg/day. Clinical outcomes were recorded in daily diaries by the subjects during pollen season. Immunologic outcomes were assessed just before the initiation and completion of the SLIT regimen in the treatment groups and at the beginning and end of the study in the control groups. Clinical efficacy was evaluated with a visual analog scale. Lymphocyte subsets were evaluated by flow cytometry. Peripheral blood mononuclear cells were isolated and incubated with and without Amba1, and their cytokine profiles were analyzed by flow cytometry. Amba1-specific immunoglobulin G_4 (IgG_4) was measured by an enzyme-linked immunosorbent assay.

RESULTS. Clinical outcomes improved in all SLIT regimens compared with controls. This improvement was significantly better in the prolonged-SLIT (5 months × 3 years) compared to the other SLIT regimens. Cytokine analysis of $CD4^+$ T lymphocytes, $CD19^+$ B lymphocytes, and $CD14^+$ monocytes revealed the following: interleukin 4 (IL-4)–producing cells were reduced in all SLIT regimens compared with controls, and IL-10–producing cells were

increased in all SLIT regimens compared with controls. These results were statistically significant compared with controls in all but $CD4^+$ IL-4–producing cells, and the results were similar across all treatment arms. All SLIT regimens resulted in an increase in Amba1-specific IgG_4, and this increase was most impressive in the prolonged-SLIT treatment arm.

CONCLUSIONS. Although all SLIT regimens resulted in an improvement in clinical efficacy, prolonged SLIT was the most effective. The reduction in IL-4 and increase in IL-10 production is consistent with observations from subcutaneous immunotherapy studies and provides insight into the mechanism of SLIT. These cytokine changes might serve as an objective marker of efficacy of SLIT for patients on treatment.

REVIEWER COMMENTS. Further evaluation of SLIT is of particular importance in the pediatric population because of its less invasive method of administration compared with injection immunotherapy and its improved safety profile. However, more studies are needed before the therapy makes it to US practice.

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Efficacy and Safety of Timothy Grass Allergy Immunotherapy Tablets in North American Children and Adolescents

Blaiss M, Maloney J, Nolte H, Gawchik S, Yao R, Skoner SP. *J Allergy Clin Immunol.* 2011;127(1):64–71, 71.e1–71.e4

PURPOSE OF THE STUDY. To investigate the efficacy and safety of timothy grass allergen immunotherapy (AIT) treatment using sublingual tablets in children and adolescents with grass pollen–induced allergic rhinoconjunctivitis (ARC).

STUDY POPULATION. Three hundred forty-five subjects, aged 5 to 17 years, with a clinical history of physician-diagnosed grass pollen–induced ARC with or without asthma were studied.

METHODS. This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter, phase III study. Subjects were randomly assigned (1:1) to once-daily sublingual grass AIT treatment (2800 bioequivalent allergen units; 15 μg of Phlp5) or placebo. Treatment began ~16 weeks before the grass pollen season (GPS) and continued through the entire GPS for a total treatment period of 23 weeks. The total combined score was a summation of the daily symptom score and daily medication score, which were predefined. Immune parameters were measured over time. Safety was measured on the basis of reported adverse events.

RESULTS. The mean total combined scores for the entire GPS were significantly less in the grass-AIT group than in the placebo group by 26% ($P = .001$). The mean daily symptom score was significantly less in the grass-AIT group than the placebo group by 25% ($P = .005$). The improvements in scores for ocular and nasal symptoms were 28% and 23%, respectively, were noted in the AIT group ($P = .003$). The median daily medication score was significantly reduced in the grass-AIT group by 81% ($P = .006$). There was a significant improvement in quality of life in the AIT group that was greatest at the peak of the season (38%) when compared with the entire season (18%). Treatment with grass AIT did not significantly reduce asthma symptom scores. Levels of Phlp5-specific immunoglobulin G_4 (IgG_4)- and IgE-blocking factor were similar between the 2 groups at baseline and increased over time in the grass-AIT group ($P < .001$). Grass AIT was generally well tolerated, but 82% experienced some adverse events, primarily oral and throat pruritus and/or irritation. One subject in the AIT group received epinephrine for dose-related angioedema, dysphagia, and cough.

CONCLUSIONS. Allergen immunotherapy using sublingual grass pollen tablets is effective in the treatment of grass pollen–induced ARC with anticipated and acceptable adverse effects.

REVIEWER COMMENTS. This is the first North American study to show effective symptom control and an acceptable safety profile in children and adolescents with grass pollen–induced ARC by using a sublingual tablet for dose delivery. There was no increase in the outcome of asthma attacks, and there was improvement in quality of life at the peak of the allergy season. These results show promise for future therapy targeting children and adolescents for immunotherapy using an effective, safe, and easy-to-deliver alternative to traditional subcutaneous injection immunotherapy.

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Prevention of Allergy in Infants of Allergic Mothers by Probiotic *Escherichia coli*

Lodinová-Zádníková R, Prokesová L, Kocourková I, Hrdý J, Zizka J. *Int Arch Allergy Immunol.* 2010;153(2):201–206

PURPOSE OF THE STUDY. To study the effect of after-birth oral colonization by a probiotic *Escherichia coli* strain in infants of allergic mothers to reduce occurrence of allergy later in life.

STUDY POPULATION. There were 158 term breastfed infants followed from birth, 113 of whom were born to allergic mothers. Allergic mothers selected for the study met criteria that included clinical manifestation of allergy for more than 24 months, positive allergy-test results, and response to allergy treatment.

METHODS. The infants were divided into groups of colonized infants of allergic mothers (56), control infants of allergic mothers (57), and control infants of healthy mothers (45). Infants of allergic mothers were randomly assigned to 1 of the first 2 groups. Incidence rates of bacterial pathogens in stool and levels of anti–*E coli* immunoglobulins and serum cytokines were determined, and secretory immunoglobulin A was monitored in stool filtrates and maternal milk. Clinical evaluation of infants aged 4 days, 3 and 6 months, and 1, 2, 3, and 5 years were carried out, and clinical symptoms of allergy were monitored. One milliliter of the probiotic *E coli* strain (0.8×10^9 lyophilized *E coli*, serotype O83:K24:H31) was administered orally to infants of allergic mothers within 48 hours after birth and subsequently 3 times per week over a period of 4 weeks. Control infants of allergic and healthy mothers were monitored in these intervals as well.

RESULTS. The *E coli* strain was not found in stool samples before its administration. At the 5-year conclusion of the study, allergy symptoms were found in 14 of 45 (31%) infants of control allergic mothers, 7 of 42 (16%) infants of healthy mothers, and 2 of 46 (4%) infants of allergic mothers who were colonized at birth with probiotic *E coli*. The incidence of allergy at 5 years was significantly lower in the colonized infants of allergic mothers compared with the infants of control allergic mothers ($P < .001$). The incidence reduction in the colonized group compared with that in the infants of healthy mothers was not significant. Allergic phenotype and higher interleukin 4 and 13 and lower interferon γ and transforming growth factor β levels dominated in the allergic group, but the values observed were not quantitatively different.

CONCLUSIONS. After birth, targeted colonization of the intestine by a probiotic *E coli* strain might be an effective means of allergy prevention for infants of allergic mothers.

REVIEWER COMMENTS. As allergic diseases continue to increase in prevalence around the world, primary prevention of allergic disease has been elusive. Although previous studies have found that probiotics might be an effective intervention for eczema, there is little evidence to show that probiotics are beneficial for preventing other allergic diseases. With a significant reduction in clinical signs of overall allergies in the group treated with probiotics, the results of this study raise an interesting therapeutic option, although when examining the types of allergies that these children had, the effect seems to have been primarily for skin-related allergic disease. Further studies will need to evaluate the true effectiveness of these probiotics in allergy prevention.

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Probiotics in Pregnant Women to Prevent Allergic Disease: A Randomized, Double-Blind Trial

Dotterud CK, Storrø O, Johnsen R, Oien T. *Br J Dermatol.* 2010;163(3):616–623

PURPOSE OF THE STUDY. To determine if probiotics given to pregnant and nursing women in a nonselected population could prevent allergic disease in the first 2 years of life.

STUDY POPULATION. There were 278 children (138 on probiotics, 140 on placebo) from a population of 415 women in Trondheim, Norway.

METHODS. This was a randomized, double-blind, placebo-controlled study. Women were given 250 mL of probiotic milk or placebo milk per day from 36 weeks' gestation to 3 months after delivery while breastfeeding. The probiotic milk contained *Lactobacillus rhamnosus*, *Lactobacillus acidophilus* La-5, and *Bifidobacterium animalis* subsp lactis Bb-12. At 2 years, all children were assessed for atopic dermatitis (AD), asthma, allergic rhinoconjunctivitis, and atopic sensitization (positive skin-prick-test result or elevated specific immunoglobulin E [IgE] level). The intention-to-treat analysis was enabled by multiple imputations, and the complete-case analysis included all subjects who completed end-point exams.

RESULTS. Using intention-to-treat analysis, the odds ratio (OR) for the cumulative incidence of AD was 0.51 for those in the probiotic group compared with those in the placebo group (95% confidence interval [CI]: 0.30–0.87]; $P = .013$). The effect was stronger for non–IgE-associated AD (OR: 0.43 [95% CI: 0.23–0.81]; $P = .009$). There was no effect on IgE-associated AD (OR: 0.90 [95% CI: 0.37–2.17]; $P = .812$). No significant effect was found for asthma, allergic rhinoconjunctivitis, or atopic sensitization. In complete-case analysis, there was a significant difference in the cumulative incidence of AD between the probiotic and placebo groups (log rank, $P = .022$), and the relative risk was 0.61 (95% CI: 0.41–0.91; $P = .013$; number needed to treat to benefit: 8). The hazard ratio was 0.58 (95% CI: 0.36–0.93) in the probiotic group compared with that in the placebo group ($P = .024$). There was a significantly ($P = .044$) reduced risk of having moderate AD compared with the placebo group.

CONCLUSIONS. In a nonselected population of mothers, consumption of probiotics decreased the cumulative incidence of AD but had no effect on asthma, allergic rhinoconjunctivitis, or atopic sensitization.

REVIEWER COMMENTS. This study found that probiotic bacteria given to the mother during pregnancy and early lactation might prevent AD in the child. Previous randomized controlled trials that used various probiotics have involved administration directly to all or the majority of children. The results of this study are exciting in that treatment of the mother over a limited period of time seemed to make a difference in the cumulative incidence of AD and severity of atopic dermatitis in affected children.

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Synbiotics Prevent Asthma-Like Symptoms in Infants With Atopic Dermatitis

van der Aa LB, van Aalderen WM, Heymans HS, et al; Synbad Study Group. *Allergy*. 2011;66(2):170–177

PURPOSE OF THE STUDY. Infants with atopic dermatitis (AD) are at high risk of developing asthma. These researchers sought to examine the effect of early intervention with synbiotics, a combination of probiotics and prebiotics, on the prevalence of asthma-like symptoms in infants with AD.

STUDY POPULATION. Ninety term infants less than 7 months of age with AD were recruited from 2005 to 2007 in the Netherlands. Inclusion criteria included an AD score (Severity Scoring of Atopic Dermatitis [SCORAD]) of >15, exclusive formula feeding at the time of enrollment, no other major medical problems, and no use of probiotics or immunomodulatory medications during the 4 weeks before enrollment.

METHODS. In a double-blind, placebo-controlled multicenter trial, infants were randomly assigned to receive an extensively hydrolyzed formula with *Bifidobacterium breve* M-16V and a galacto-oligosaccharide/fructo-oligosaccharide mixture or the same formula without the synbiotics during a 12-week period. After 1 year, the prevalence of respiratory symptoms and asthma medication use was evaluated by using a validated questionnaire, and the total serum immunoglobulin E (IgE) level and level of specific IgE against aeroallergens were determined.

RESULTS. Seventy-five children completed the 1-year follow-up evaluation. The prevalence of "frequent wheezing" and "wheezing and/or noisy breathing apart from colds" was significantly lower in the synbiotic than in the placebo groups (13.9% vs 34.2% [absolute risk reduction (ARR): −20.3%] and 2.8% vs 30.8% [ARR: −28.0%], respectively). Significantly fewer children in the symbiotic than in the placebo group had started to use asthma medication after baseline (5.6% vs 25.6% [ARR: −20.1%]). There were no differences in total IgE levels between groups. However, no children in the synbiotic group and 5 children (15.2%) in the placebo group developed an elevated IgE level against cat (ARR: −15.2%).

CONCLUSIONS. This study found a significant benefit in the prevention of asthma-like symptoms in infants with AD followed for 1-year after a 12-week trial of a synbiotic mixture.

REVIEWER COMMENTS. Results of this prospective study support the concept that a specific probiotic and prebiotic mixture might be effective in reducing the prevalence of asthma-like symptoms in the near term. Variable results have been noted in other studies that used only probiotics. Larger clinical studies and a longer longitudinal follow-up period to determine whether this mixture might ultimately prevent the development of asthma are needed.

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Reduced Occurrence of Early Atopic Dermatitis Because of Immunoactive Prebiotics Among Low-Atopy-Risk Infants

Grüber C, van Stuijvenberg M, Mosca F, et al; MIPS 1 Working Group. *J Allergy Clin Immunol*. 2010;126(4):791–797

PURPOSE OF THE STUDY. To determine whether the supplementation of prebiotics and immunoactive oligosaccharides can prevent the development of atopic dermatitis in infants.

STUDY POPULATION. Term weaned infants younger than 8 weeks without a family history of atopy in a parent or sibling were recruited from several northern European study centers.

METHODS. This was a double-blind, placebo-controlled, randomized, prospective study. Infants were randomly assigned to the prebiotics group (PG), control group (CG), or exclusively breastfed group (BG). Infants in the PG received a nonhydrolyzed cow's milk–based formula with a specific mixture of short- and long-chain oligosaccharides (ratio 9:1, 85% of mixture) and pectin-derived acidic oligosaccharides (15% of mixture). The PG and CG received a starter formula for the first 6 months of life, and then a follow-on formula was

offered. Parents were contacted every 2 weeks until the infants turned 1 year old, and clinical visits were conducted at 2, 4, 6, and 12 months of life.

RESULTS. Of 1187 infants screened, 1130 infants (95%) were recruited. The cumulative incidence of atopic dermatitis in the PG (5.7% [SE: 1.2%]) was significantly less than that in the CG (9.7% [SE: SE 1.5%]; $P = .04$) and similar to the lower range in the BG (7.3% [SE: SE 1.6%]). Median time to the development of atopic dermatitis was similar in the PG (15.1 weeks [range: 5.1–49 weeks]) and the CG (16.8 weeks [range: 4.4–50.3 weeks]) but longer in the BG (22.5 weeks [range: 4.4–50.3 weeks). In a Cox regression model, the rate of atopic dermatitis was 44% lower in the PG versus CG ($P = .04$). The disease-free survival period was greater in the PG versus that in the CG ($P = .0377$). The number needed to treat with prebiotic supplementation to prevent 1 case of atopic dermatitis was 25 infants. Atopic dermatitis in the PG at the age of 12 months tended to be less severe than in the CG (median SCORAD score: 8 vs 12; $P = .08$). T-helper 2–specific thymus and activation-regulated chemokine levels, total immunoglobulin E levels, and percentage sensitized to hen's egg or cow's milk were not significantly different in all 3 groups.

CONCLUSIONS. Prebiotic supplementation in low-risk infants reduced the risk of atopic dermatitis by 44% in the first year of life and might be an effective preventive measure in formula-fed infants. Severity of atopic dermatitis was not significantly affected.

REVIEWER COMMENTS. These results might have far-reaching public health implications, because the study focused on preventing food allergy in infants who might not otherwise be identified by personal or family history of atopy. Prebiotics are generally considered safe and might be an alternative to hydrolysate formula or probiotics, which have shown variable results in infants at low risk. It is interesting to note that prebiotics might be less effective once disease has started and does not seem to have an effect on sensitization or other allergic diseases. The next step would be to investigate whether the benefit is transient or persistent and what mechanism might be responsible for the observed effects.

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Efficacy of Probiotic *Lactobacillus* GG on Allergic Sensitization and Asthma in Infants at Risk

Rose MA, Stieglitz F, Köksal A, Schubert R, Schulze J, Zielen S. *Clin Exp Allergy*. 2010;40(9):1398–1405

PURPOSE OF THE STUDY. Previous studies have yielded conflicting data regarding the effects of probiotics on the prevention and treatment of allergic diseases. This prospective study examined the impact of dietary supplementation with *Lactobacillus rhamnosus* strain GG (ATCC 53103) on allergic sensitization, asthma, and atopic eczema.

STUDY POPULATION. Children ($N = 131$) between the ages of 6 and 24 months with a history of at least 2 physician-diagnosed episodes of wheezing within the previous year and a first-degree relative with atopic disease were recruited from a clinic of the Children's Hospital at Goethe University (Frankfurt, Germany) and were randomly assigned to double-blind supplementation with *L rhamnosus* or placebo twice daily for 6 months.

METHODS. Clinical monitoring was performed before intervention and at 3, 6, 9, and 12 months. Outcome measures included the Severity Scoring of Atopic Dermatitis (SCORAD) index, asthma symptom scores defined by cough, wheeze, and need for intervention, and allergic sensitization. Serum samples were taken at 0, 6, and 12 months. Serum levels of egg, milk protein, lactalbumin, cat, horse, dust mite, birch, timothy, and *Alternaria*-specific immunoglobulin E were used as markers of allergic sensitization. Serum eosinophils, eosinophil cationic protein, and transforming growth factor β were also measured.

RESULTS. There were no significant differences in SCORAD indices or asthma-related events between the intervention and placebo groups. In a subgroup of patients with previous aeroallergen sensitization, asthma symptom scores were significantly lower in the placebo group. In a subgroup of patients with previous food-allergen sensitization, patients who received probiotics had fewer rescue-free days and required more inhaled β agonists. Cumulative levels of aeroallergen-specific immunoglobulin E were lower in patients assigned to probiotic supplementation. In the subgroup sensitized to aeroallergens, median eosinophil cationic protein values were lower in the probiotic group. Transforming growth factor β was significantly reduced in the probiotic group.

CONCLUSIONS. In young children with a history of recurrent wheeze and a family history of atopic disease, oral supplementation with *L rhamnosus* had mild negative effects on clinical respiratory status in children with antecedent allergic sensitization. Probiotic supplementation had no beneficial effects on atopic eczema. Probiotic supplementation was associated with mild changes in laboratory assessments of allergic sensitization.

REVIEWER COMMENTS. In the current study, probiotic supplementation did not alleviate clinical symptoms of asthma or atopic eczema. In contrast, probiotic supplementation was associated with increased respiratory symptoms in patients with food and aeroallergen sensitivity. Potential

confounders include increased exposure to tobacco smoke and increased respiratory symptoms before the study in the children randomly assigned to the probiotic group. Additional studies are required to assess probiotic use in children with a personal or family history of atopic disease.

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The Efficacy and Safety of a Chinese Herbal Product (Xiao-Feng-San) for the Treatment of Refractory Atopic Dermatitis: A Randomized, Double-Blind, Placebo-Controlled Trial

Cheng HM, Chiang LC, Jan YM, Chen GW, Li TC. *Int Arch Allergy Immunol.* 2011;155(2):141–148

PURPOSE OF THE STUDY. To determine if the Chinese herbal product Xiao-Feng-San (XFS) taken orally could significantly improve symptoms of severe intractable atopic dermatitis.

STUDY POPULATION. A total of 71 Taiwanese subjects (age range: 8.4–22.6 years [median: 13.1 years]) with history of severe, refractory atopic dermatitis and poor response to eczema medications (topical steroids, oral antihistamines) were enrolled.

METHODS. This was a prospective, double-blind, placebo-controlled trial in which patients were randomly assigned at a ratio of 2:1 to receive XFS or placebo over 8 weeks. There were 47 (median age: 12.2 years) given XFS and 24 (median age: 13.6 years) given placebo. Participants were matched according to gender, height, weight, BMI, age, duration of illness, and symptom scores. Patients were given varying doses depending on age. Laboratory studies were performed and total lesion score, erythema score, surface damage score, pruritis score, and sleep scores were calculated at 4-week intervals up to 12 weeks.

RESULTS. A total of 56 subjects completed the entire study. There was a statistically significant improvement in total lesion scores among those in the treatment group compared to those of the placebo group (79.7 $\pm$ 5.8% vs 13.5$\pm$ 7.64%; $P < .001$). There was also statistically significant improvement in all symptom scores for those on treatment compared to those on placebo. Four weeks after the treatment was discontinued, the mean improvement in the clinical lesion score for the XFS group was still significantly better than that of the placebo group. Patients reported no adverse effects except unpalatability for some. Treatment did not affect total serum immunoglobulin E level, eosinophil counts, or interleukin 5, interleukin 13, or eosinophil cationic protein levels.

CONCLUSIONS. The traditional Chinese herbal medication XFS might be an alternative choice of therapy for severe, refractory, extensive, nonexudative atopic dermatitis.

REVIEWER COMMENTS. Severe and widespread atopic dermatitis can be frustrating to treat for patients, parents, and physicians. Patients often ask their physicians if there are alternative approaches to controlling atopic diseases. XFS is a common Chinese herbal preparation of 12 herbs, some with known anti-inflammatory effects, that might provide a complementary option for adults and children who require systemic steroids to control their eczema flares. However, more scientific evaluation of XFS to determine its mechanism of action, safety profile, applicability, and palatability need to be considered before widespread use is accepted.

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PRIMARY IMMUNODEFICIENCY, HIV, AND INFECTIOUS DISEASES

Chronic Mucocutaneous Candidiasis in Humans With Inborn Errors of Interleukin-17 Immunity

Puel A, Cypowyj S, Bustamante J, et al. *Science.* 2011; 332(6025):65–68

PURPOSE OF THE STUDY. Chronic mucocutaneous candidiasis disease (CMCD) is characterized by recurrent or persistent infections of the skin, nails, and oral and genital mucosa caused by *Candida albicans* and sometimes *Staphylococcus*. Previous studies have shown that interleukin 17 (IL-17) receptor-deficient mice were more susceptible to oropharyngeal candidiasis and staphylococcal infections of the skin. The purpose of this study was to assess if findings in the mouse model also applied to humans.

METHODS. Candidate gene sequencing was performed on a child with *C albicans* in the neonatal period and *Staphylococcus aureus* dermatitis at 5 months of age and a family from Argentina with autosomal dominant pattern of CMCD inheritance. Sequences of IL-17–related genes and receptors from affected people were compared with those of family members and controls. Additional experiments were performed by incubating fibroblasts from an affected child with recombinant IL-17A and IL-17F homodimers and heterodimers.

RESULTS. The initial child was found to be homozygous for a mutation in the *IL17RA* gene that was not found in any of the controls. The IL-17RA protein was not detected on the surface of fibroblasts, $CD4^+$ T cells, $CD8^+$ T cells, or monocytes from the patient. The patient's fibroblasts did not respond to any of the 3 IL-17 cytokines. In the family

studied, a heterozygous missense mutation was found in the *IL17F* gene. The mutant allele was found in 2 apparently healthy family members, which suggests incomplete clinical penetrance, and in all of the affected members of the kindred. This mutant protein was tested in a cell line and was nonfunctional.

CONCLUSIONS. Mutations in IL-17–family genes that cause functional deficiency of this pathway are associated with CMCD.

REVIEWER COMMENTS. This is an excellent example of bench-to-bedside medicine and illustrates the utility of murine models of immunity in the search for causes of human disease. These findings provide definitive evidence that IL-17A and IL-17F are essential for protective immunity to *C albicans* and, to a lesser extent, *S aureus* in the nails, skin, and oral and genital mucosa and provide new opportunities for designing novel treatments for this chronic immunologic disorder. It is also important to consider that elevated levels of IL-17 have been associated with various chronic inflammatory conditions, which raises the possibility that anti–IL-17 treatment strategies now under development could lead to increased susceptibility to infections with *C albicans* or *S aureus*.

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Hypomorphic *Rag* Mutations Can Cause Destructive Midline Granulomatous Disease

De Ravin SS, Cowen EW, Zarember KA, et al. *Blood.* 2010;116(8):1263–1271

PURPOSE OF THE STUDY. To describe a new clinical phenotype in patients who inherit mutations in the recombination activation gene (*Rag*) necessary for effective immunoglobulin and T-cell receptor gene rearrangement.

STUDY POPULATION. This was a case report of a 14-year-old patient referred with a 1-year history of extensive granulomatous destruction of the midface structures and a past history of myasthenia gravis treated with thymectomy. The patient had a sister who died at 5 years of age of staphylococcal sepsis; she also had a history of ptosis that the authors suggested might have reflected undiagnosed myasthenia gravis.

RESULTS. The patient underwent extensive immunologic and genetic testing for both autoimmune disease and immunodeficiency disorders that revealed compound heterozygous mutations in *Rag*. These mutations resulted in ~50% loss of Rag enzyme functional activity. The immunologic studies revealed relatively normal T and B cells and normal immunoglobulin levels and T-cell diversity but markedly decreased FoxP3$^+$ T-regulatory cells.

CONCLUSIONS. Immune dysregulation with granulomatous hyperinflammation and autoimmunity can result from hypomorphic mutations in the gene encoding Rag.

REVIEWER COMMENTS. This study adds to the phenotypic range of disease that is now associated with mutations in the *Rag* gene, which now include classical severe combined immunodeficiency, Omenn syndrome, combined immunodeficiency with expansion of γ-δ T cells, granulomatous disease, and autoimmunity. Readers are encouraged to refer to a recent review in which phenotypical variability based on cases with RAG1 deficiency was demonstrated (Valayannopoulos V, de Blic J, Mahlaoui N, et al. *Pediatrics*. 2010;126[5]; available at: www.pediatrics.org/cgi/content/full/126/5/e1242). Recognition of variable phenotypes with mutations in a gene associated with primary immunodeficiency disorders has become a common phenomenon, which clearly suggests that practitioners must be aware that "textbook" descriptions of gene defects associated with primary immunodeficiencies only present part of the full story and that the potential for phenotypic variability is significant.

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Clinical Disease Caused by *Klebsiella* in 2 Unrelated Patients With Interleukin 12 Receptor β1 Deficiency

Pedraza S, Lezana JL, Samarina A, et al. *Pediatrics*. 2010;126(4). Available at: www.pediatrics.org/cgi/content/full/126/4/e971

PURPOSE OF THE STUDY. To describe a new infectious disease phenotype in patients who inherit mutations in the interleukin 12 (IL-12) signaling pathway.

STUDY POPULATION. In this report the authors documented sepsis with *Klebsiella pneumoniae* in 2 unrelated patients with complete defects in the IL-12 receptor β1.

METHODS. This was a chart review with case reports.

RESULTS. The first patient was born to unrelated parents and developed BCGitis after BCG vaccination in infancy followed by nontyphoidal salmonellosis. Both infections were difficult to treat despite multiple appropriate antimicrobial agents administered over 26 months. This was followed by development of disseminated *Mycobacterium bovis* infection, which also responded poorly to multidrug antimicrobial agents along with interferon γ therapy. The patient's condition worsened, and he developed

systemic infection with *Candida albicans* and with *K pneumoniae*, which ultimately proved to be fatal despite aggressive and appropriate antimicrobial therapy. The second patient was born to consanguineous parents and did not receive the BCG vaccine, but at the age of 14 months she developed multiple adenopathies that stained for *Nocardia nova*; she also developed a positive blood culture for *K pneumoniae*. The initiation of appropriate antimicrobial agents and interferon γ resulted in resolution of her infections.

CONCLUSIONS. *Klebsiella* infections should be considered in patients with IL-12 receptor β1 deficiency. In addition, IL-12 receptor β1 should be considered in patients with unexplained klebsiellosis.

REVIEWER COMMENTS. This is another example of the expanding range of microbial pathogens that can be observed in patients with defects that affect the IL-12 pathway. The historical observation that these patients primarily are affected by mycobacterial and salmonella infections needs to be modified to include mucocutaneous disease with *C albicans* seen in up to 25% of these patients and now also *Klebsiella* infection. This again points out that clinicians should be wary of not considering a specific defect caused by an infectious organism that does not fit with the initial or "classical" description of infections associated with a genetic defect. These disorders should be considered a "work in progress" in terms of the clinical phenotype. As with all rare diseases, it is best to consult with an experienced clinical immunologist when a child presents with an unusually severe or persistent infection.

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Clinical Features and Outcome of Patients With IRAK-4 and MyD88 Deficiency

Picard C, von Bernuth H, Ghandil P, et al. *Medicine (Baltimore)*. 2010;89(6):403–425

PURPOSE OF THE STUDY. To describe the clinical features and outcomes of patients with autosomal recessive defects in the interleukin 1 receptor-associated kinase 4 (IRAK-4) and the myeloid differentiation factor 88 (MyD88).

STUDY POPULATION. The authors provided the cumulative data of 48 patients with IRAK-4 deficiency and 12 patients with MyD88 deficiency from 37 kindreds in 15 countries.

METHODS. The data for this report were collected on the basis of a detailed questionnaire filled out by the physician who cared for the enrolled patient.

RESULTS. The leading threat to these patients was invasive pneumococcal disease, which was seen in 41 of the 60 patients (68%) and caused 72 documented invasive infections (52.2%). Invasive infections with *Pseudomonas aeruginosa* and *Staphylococcus aureus* were observed in 13 patients each. Noninvasive infections, typically involving the skin and lungs associated with *Pseudomonas aeruginosa* and *Staphylococcus aureus*, were also seen frequently (52 of 60 patients). Signs of inflammation (fever, elevated C-reactive protein level) are usually weak or delayed. It is important to note that there were no instances of severe viral, fungal, or parasitic infections. The clinical outcome to date has been poor; there have been 24 infection-related deaths (38%), and in 10 cases death was associated with the first invasive episode. Antibiotic prophylaxis, antipneumococcal vaccination, and/or immunoglobulin infusions seem to have a beneficial effect on outcomes. It is also important to note that there were no deaths after the age of 8 years and no invasive infections after the age of 14 years, which indicates that once a child with these defects reaches adolescence, there might be little risk for infection and prophylactic therapy might not be needed at that point.

CONCLUSIONS. The authors concluded that patients and families should be informed of the risk of developing life-threatening infections, and empiric antibacterial treatment and immediate medical consultation were strongly recommended in cases of suspected infection or moderate fever. Prophylactic measures in childhood were considered beneficial until spontaneous improvement occurs in adolescence.

REVIEWER COMMENTS. This is the most complete account to date of the clinical features and outcome of these 2 defects, both of which target critical signaling pathways in the innate immune system involving Toll-like receptors and the interleukin 1 receptor. The authors clearly defined these signaling pathways as playing a critical role in the host defense against invasive bacterial infection earlier in life. This also suggests that the full maturation of adaptive immunity involving T and B cells that occurs during later childhood compensates for the innate defect and prevents susceptibility to invasive bacterial infection after reaching adolescence. The consistent finding that the inflammatory response is somewhat diminished represents a clinical clue in these disorders, and the therapeutic recommendations clearly seem to alter what is otherwise a serious primary immunodeficiency in terms of mortality.

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Stem-Cell Gene Therapy for the Wiskott-Aldrich Syndrome

Boztug K, Schmidt M, Schwarzer A, et al. *N Engl J Med.* 2010;363(20):1918–1927

PURPOSE OF THE STUDY. To examine the efficacy of transfusion of autologous genetically modified hematopoietic stem cells for Wiskott-Aldrich syndrome (WAS). WAS is an X-linked recessive primary immunodeficiency disorder associated with thrombocytopenia, eczema, and autoimmunity.

STUDY POPULATION. Two 3-year-old boys with WAS were included. Inclusion criteria included severe WAS, no evidence of malignancy, and isolation of sufficient numbers of $CD34^+$ cells.

METHODS. Autologous $CD34^+$ cells were collected by leukopheresis. The cells were then transduced with WAS protein (WASP)-expressing retroviral vectors. The subjects were infused with busulfan. The cells were reinfused back into the subjects 4 days after they were transduced.

RESULTS. WASP expression was demonstrated in a variety of subgroups of leukocytes. At the level of hematopoietic stem cells in the bone marrow, stable chimerism of cells expressing WASP was demonstrated in both subjects. An increase in platelet counts was found starting 6 to 9 months after gene therapy. Improvement was also demonstrated in the function of a variety of subgroups of leukocytes, including natural killer cells, monocytes, T lymphocytes, and B lymphocytes. The frequency and severity of infection decreased in both patients. Signs and symptoms of autoimmunity and eczema disappeared. Comprehensive insertion-site analysis showed vector integration that targeted multiple genes controlling growth and immunologic responses in a persistently polyclonal hematopoiesis. These subjects had been followed for 3 years at the time of the report, and no clonal imbalance (indicating possible neoplastic growth) has been detected.

CONCLUSIONS. This study found that gene therapy for WAS is feasible and effective and, during the time of observation, is not associated with treatment-limiting adverse events.

REVIEWER COMMENTS. Add WAS to the list of disorders, including severe combined immunodeficiency, chronic granulomatous disease, and adrenoleukodystrophy, that have been treated with gene therapy. These results are fascinating and exciting.

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Nanofiltered C1 Inhibitor Concentrate for Treatment of Hereditary Angioedema

Zuraw BL, Busse PJ, White M, et al. *N Engl J Med.* 2010;363(6):513–522

PURPOSE OF THE STUDY. To determine the efficacy of nanofiltered C1 inhibitor concentrate in the management of hereditary angioedema (HAE).

STUDY POPULATION. Subjects were from 2 studies; the lowest age was 6 years (median age: 36 years).

METHODS. Both studies compared an intravenous dose of 1000 U of nanofiltered C1 inhibitor concentrate in the management of HAE. The first study end point was the time to unequivocal relief of symptoms during an acute attack of HAE. The second study was a crossover trial that involved 22 subjects; prophylactic twice-weekly infusions of drug (1000 U or placebo) was given during two 12-week periods. The primary end point in the second study was the number of attacks in the 12-week treatment period compared with placebo.

RESULTS. In the first study, the mean time of the onset of unequivocal relief of an attack was 2 hours in treated subjects compared with 4 hours in those given placebo ($P = .02$). In the second study, the number of attacks per 12-week period was 6.2 with active drug compared with 12.73 with placebo ($P < .001$). The treated subjects also had significant reduction in both the severity and duration of the attacks.

CONCLUSIONS. When given as treatment, the nanofiltered C1 inhibitor concentrate shortened the duration of acute attacks. When used for prophylaxis, the treatment reduced the frequency of acute attacks.

REVIEWER COMMENTS. This treatment allows for at least a 50% reduction in the frequency and duration of HAE attacks. In patients with less-severe clinical presentation for whom continuous treatment is not necessary, 2 preparations that are available for as-needed use are reported in the same issue of the journal (Cicardi M, Levy RJ, McNeil DL, et al. *N Engl J Med*. 2010;363[6]:523–531; and Cicardi M, Banerji A, Bracho F, et al. *N Engl J Med*. 2010;363[6]:532–541). Both are subcutaneous preparations given within 8 hours of attack onset. Both preparations showed significant efficacy with a <5-hour onset for relief of acute symptoms. An accompanying editorial provided important perspective regarding the efficacy of these treatments (Morgan BP. *N Engl J Med*. 2010; 363[6]:581–583). These 2 studies allowed for therapy of HAE specific for the burden of the illness for each individual patient in a rare but potentially lethal disease.

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Evidence for the Cure of HIV Infection by CCR5δ32/Δ32 Stem Cell Transplantation

Allers K, Hütter G, Hofmann J, et al. *Blood*. 2011;117(10):2791–2799

PURPOSE OF THE STUDY. HIV uses $CD4^+$ as its primary receptor and chemokine receptors (CCR5 and CXCR4) as co-receptors. The primary receptor used to transmit HIV between people, including in maternal-child transmission, is CCR5. Approximately 1% of northern Europeans have a homozygous deletion (Δ32) in the *CCR5* gene that dramatically increases the resistance to HIV infection in affected people. There has been great speculation as to the "curability" of active HIV infection. The purpose of this study was to describe the apparent cure of a single patient.

STUDY POPULATION. The case of a single person who received a stem cell transplant from a donor with "natural" resistance to HIV was reported.

METHODS. Extensive immunologic, virologic, and genetic tests were performed serially on this person.

RESULTS. The patient received a successful transplant for treatment of relapsed acute myeloid leukemia. Long-term follow-up, 4 years at the time of writing, revealed that the patient's $CD4^+$ T cells recovered efficiently; donor-derived $CD4^+$ T cells repopulated the gut mucosal immune system; in vitro alternative chemokine receptor usage, CXCR4, was not impaired on the new T cells; long-lived HIV target cells of host origin (tissue $CD4^+$ T cells and macrophages) were replaced with donor-derived cells after transplantation; and HIV remains undetectable in peripheral blood and multiple tissue compartments over the 45-month course of observation.

CONCLUSIONS. This patient was cured of HIV infection.

REVIEWER COMMENTS. The now-famous person often referred to as the "German patient," although in reality an American living in Berlin, provides proof of concept that HIV infection is a curable disease. Although the identification of a CCR5Δ32/Δ32 donor is impractical for almost all other people with HIV, the experience with the German patient has led to a dramatic increase in the attempt to cure HIV. Multiple approaches have been proposed, and many would be applicable to the "average" HIV-infected person. This is reflected in a recent article entitled "The Emerging Race to Cure HIV Infections" (*Science*. 2011;332[6031]: 784–789).

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Evaluation of 4 Weeks' Neonatal Antiretroviral Prophylaxis as a Component of a Prevention of Mother-to-Child Transmission Program in a Resource-Rich Setting

Ferguson W, Goode M, Walsh A, Gavin P, Butler K. *Pediatr Infect Dis J*. 2011;30(5):408–412

PURPOSE OF THE STUDY. A 6-week course of neonatal antiretroviral prophylaxis has been standard in most developed countries. In the same settings, a 4-week rather than 6-week intervention might reduce toxicity and reduce cost.

STUDY POPULATION. The study involved a cohort that included all HIV-exposed live births in Ireland from January 1999 through December 2008 with a minimum of 18-months of follow-up.

METHODS. This was a 10-year observational study of the Irish experience in their use of a 4-week rather than 6-week neonatal antiretroviral regimen.

RESULTS. Of the 916 infants with known outcome, 1% were infected. If analysis was limited to the 910 infants whose mothers received at least 4 weeks of antiretroviral therapy, the vertical transmission rate was 0.4%. These numbers are consistent with those found in other areas in which the standard 6-week regimen is followed.

CONCLUSIONS. The current clinical practice of using a 4-week neonatal antiretroviral prevention regimen seems to be as effective as a 6-week regimen.

REVIEWER COMMENTS. Although it is reasonable to surmise that a 4-week regimen is as effective as a 6-week regimen in preventing vertical transmission of HIV, the data presented here are unlikely to convince the public health authorities of other countries to move in this direction. This was not a controlled trial, and the patient population might differ in other countries.

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Cardiac Effects of Antiretroviral Therapy in HIV-Negative Infants Born to HIV-Positive Mothers: NHLBI CHAART-1 (National Heart, Lung, and Blood Institute Cardiovascular Status of HAART Therapy in HIV-Exposed Infants and Children Cohort Study)

Lipshultz SE, Shearer WT, Thompson B, et al. *J Am Coll Cardiol*. 2011;57(1):76–85

PURPOSE OF THE STUDY. HIV is known to cause a cardiomyopathy. In addition, the mitochondrial abnormalities reported in children exposed to antiretroviral therapy but not infected with HIV might also be associated abnormal

heart function. The purpose of this study was to examine the cardiac effects of perinatal exposure to antiretroviral therapy.

STUDY POPULATION. This was a prospective multisite cohort study with 2 groups of HIV-uninfected infants of HIV-infected mothers: 136 infants had been exposed to antiretroviral therapy, and 216 were unexposed.

METHODS. Echocardiograms were obtained between birth and 24 months of age. Data were expressed in mean *z* scores.

RESULTS. Mean left ventricular mass *z* scores were consistently lower in girls exposed to antiretroviral therapy than in those not exposed. These differences persisted to the end of study at 2 years. Similar differences were noted for boys but were smaller. Septal wall thickness and left ventricular dimension were smaller than expected in exposed infants, but left ventricular contractility was higher in exposed infants.

CONCLUSIONS. Exposure to antiretroviral therapy is associated with reduced left ventricular mass and size and septal wall thickness. It is also associated with increased left ventricular fractional shortening and contractility up to 2 years of age. Fetal exposure to antiretroviral drugs seems to impair myocardial growth but improves left ventricular function.

REVIEWER COMMENTS. That exposure to potent nucleoside analogs in utero might have a variety of adverse effects is not surprising. The mechanism of reduced cardiac growth in antiretroviral drug–exposed but HIV-uninfected infants is unknown. However, nucleoside analog–associated suppression of mitochondrial DNA replication might be responsible for this effect. That organogenesis is not more severely affected with long-term exposure to such agents is reasonably comforting. However, only long-term follow-up of antiretroviral drug–exposed infants will address this concern.

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An Interferon-Inducible Neutrophil-Driven Blood Transcriptional Signature in Human Tuberculosis

Berry MPR, Graham CM, McNab FW, et al. *Nature*. 2010;466(7309):973–977

PURPOSE OF THE STUDY. Most people infected with *Mycobacterium tuberculosis* (TB) develop a latent form of the disease and remain asymptomatic; however, approximately 10% of these people are at risk of developing active, transmissible disease in their lifetime. An inability to accurately identify these at-risk patients with conventional tests has limited efforts to control TB. The purpose of this study was to identify novel biomarkers of active disease by using genomic techniques.

STUDY POPULATION. The investigators generated genome-wide transcriptional profiles from the blood of patients with active TB (before treatment), patients with latent TB, and healthy controls. This study was conducted at St Mary's Hospital in London, United Kingdom, and the University of Cape Town in South Africa.

METHODS. Whole blood was obtained from healthy volunteers and patients with TB before starting antimicrobial therapy. A subset of patients diagnosed with active TB were also sampled 2 and 12 months after starting therapy. RNA was extracted from the whole blood of these subjects and used in a genome-wide microarray analysis. Extent of disease was assessed by plain chest radiographs.

RESULTS. The authors identified a distinct 393-transcript signature that defined patients with active disease. In addition, this transcript signature strongly correlated with extent of disease in patients with active TB. It is interesting to note that between 10% and 25% of patients with latent TB had similar transcript profiles to those patients with active disease, which suggests that this profile might identify those at risk for developing active disease. After 2 months of therapy, the transcriptional signature in patients with active TB reverted back to that of healthy controls, which suggests that this signature could be used to monitor the course of the disease. Using data-mining strategies, the authors found that the largest set of transcripts that changed in active TB were those induced by type I interferon (IFN) or IFN-γ in cells that were likely of neutrophil and monocyte origin.

CONCLUSIONS. A unique, treatment-sensitive, genome-wide transcriptional signature predominantly in phagocytes is associated with active TB and might predict those patients at risk of developing active disease. Type I IFN might play a larger role in the pathogenesis of TB than was previously appreciated.

REVIEWER COMMENTS. Development of an accurate biomarker for disease progression and treatment response would be a quantum leap forward in the global fight against TB and would potentially be useful for other similar diseases. This study is the first to associate active TB with a specific gene-expression signature that could be used to monitor those patients on therapy and identify those at risk of treatment failure. More research is needed to determine whether this signature could be used as a marker to identify those with latent TB and at risk of going on to develop active disease. This signature could be extremely valuable in aiding the diagnosis and

treatment of TB, which remains a major cause of morbidity and mortality worldwide.

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Burden of Seasonal Influenza Hospitalization in Children, United States, 2003 to 2008

Dawood FS, Fiore A, Kamimoto L, et al; Emerging Infections Program Network. *J Pediatr.* 2010;157(5): 808–814

PURPOSE OF THE STUDY. To estimate the rates of hospitalization with seasonal influenza in children younger than 18 years from a large, diverse surveillance area during 2003–2008.

STUDY POPULATION. A case-subject was defined as a child younger than 18 years residing in the surveillance area who was hospitalized with laboratory-confirmed influenza virus infection from the 2003–2004 and 2007–2008 influenza seasons. Surveillance was conducted through the Centers for Disease Control and Prevention Emerging Infections Program Network, which included up to 10 different states and 5.3 million children.

METHODS. Hospitalized children were identified retrospectively; clinicians made influenza-testing decisions. Data collected from the hospital record included demographics, medical history, and clinical course. Incidence rates were calculated with census data.

RESULTS. The highest hospitalization rates occurred in children younger than 6 months (seasonal range: 9–30 per 10 000 children), and the lowest rates occurred in children aged 5 to 17 years (0.3–0.8 per 10 000). Overall, 4015 children were hospitalized, 58% of whom were identified with rapid diagnostic tests alone. Forty percent of the children who were hospitalized had underlying medical conditions; asthma (18%), prematurity (15% of children younger than 2 years), and developmental delay (7%) were the most common. Severe outcomes included ICU admission (12%), respiratory failure (5%), bacterial coinfection (2%), and death (0.5%).

CONCLUSIONS. Influenza-associated hospitalization rates varied according to season and age and likely underestimated true rates, because many hospitalized children are not tested for influenza. The proportion of children with severe outcomes was substantial across seasons. Quantifying the incidence of influenza hospitalization and severe outcomes is critical to defining disease burden.

REVIEWER COMMENTS. Children younger than 6 months had the highest rates of hospitalization across all seasons. Because these children cannot receive the influenza vaccine, immunization of household contacts, out-of-home caregivers of children in this age group, and pregnant women and women who are or will become pregnant during influenza season remains the primary way to reduce the risk of influenza in infants younger than 6 months. The data from this investigation should provide an even stronger argument for recommending the influenza vaccine for appropriate patients.

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A Placebo-Controlled Trial of Antimicrobial Treatment for Acute Otitis Media

Tähtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. *N Engl J Med.* 2011;364(2): 116–126

PURPOSE OF THE STUDY. To examine the efficacy of treatment of acute otitis media (AOM) with amoxicillin-clavulanate.

STUDY POPULATION. The study included a total of 319 children aged 6 to 35 months with AOM.

METHODS. The diagnosis of AOM was made with strict criteria, including signs on physical examination and typical symptoms. The subjects were randomly assigned to receive amoxicillin-clavulanate or placebo for 7 days. The primary outcome was the time to treatment failure from the first dose until the end of treatment on visit day 8. Treatment failure was based on the overall condition of the subjects (including adverse events) and otoscopic examination.

RESULTS. Among the subjects who received amoxicillin-clavulanate, treatment failure occurred 18.6% of the time compared with a rate of 44.9% for the subjects who received placebo ($P < .001$). This difference was already apparent at the first scheduled visit at day 3, at which time 13.7% of the subjects who received amoxicillin-clavulanate, compared with 25.3% of subjects who received placebo, had treatment failure. Amoxicillin-clavulanate reduced the progression to treatment failure by 62% ($P < .001$) and the need for rescue treatment by 81% ($P < .001$). Adverse events (primarily diarrhea) were significantly more common in the amoxicillin-clavulanate group than in the placebo group.

CONCLUSIONS. Children with AOM (aged 6–35 months) treated for 7 days with amoxicillin-clavulanate had a much lower rate of treatment failure and much lower need for rescue treatment than children treated with placebo. However, the children treated with amoxicillin-clavulanate had more adverse effects.

REVIEWER COMMENTS. This article challenges us to rethink an approach to therapy. Some of the reasons for the differences between these results and other studies that have been performed in past years (which have not shown as pronounced an effect of treatment versus placebo) might include the strict criteria for diagnosing AOM, the decision to include all subjects in the trial with AOM irrespective of the severity, and the use of a potent antibiotic. The authors pointed out that, because the treatment group showed improvement as early as day 3, additional investigation might be needed to examine the practice of "watchful waiting." Another article in the same issue of the journal (Hoberman A, Paradise JL, Rockette HE, et al. *N Engl J Med.* 2011;364[2]:105–115) reported that among children younger than 2 years with AOM, treatment with amoxicillin-clavulanate for 10 days, relative to placebo, tended to reduce the time to resolution of symptoms and reduced both the overall burden of symptoms and the rate of clinical failure of treatment.

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