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’s Speakers Bureau and Visiting Professor Program offer the public, pediatricians, and other health care professionals pediatric allergist and immunologists to speak on various topics. The Section’s annual asthma poster contest encourages young children to illustrate how well they have managed their asthma.

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 2007 synopsis were written by Fellows of the AAP Section on Allergy and Immunology, guest reviewers, and fellows in allergy and immunology training programs who contributed reviews with their mentors.

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

The editor and the Section on Allergy and Immunology gratefully acknowledge the work of the reviewers and their trainees who assisted. The reviewers were: Allen Adinoff, MD, Denver, CO; James R. Banks, MD, Arnold, MD; Sally Joo Bailey, MD, Washington, DC; Mary E. Bollinger, DO, Baltimore, MD; Francisco A. Bonilla, MD, PhD, Boston, MA; Bradley E. Chipp, MD, Sacramento, CA; Joseph A. Church, MD, Los Angeles, CA; John E. Duplantier, MD, Indianapolis, IN; Casey Geaney, MD, Salem, OR; James E. Gern, MD, Madison, WI; Alan B. Goldsoebel, MD, San Jose, CA; John M. James, MD, Fort Collins, CO; Stacie M. Jones, MD, Little Rock, AR; Michael S. Kaplan, MD, Los Angeles, CA; John M. Kelso, MD, San Diego, CA; Mitchell R. Lester, MD, Norwalk, CT; Andrew H. Liu, Denver, CO; Harvey L. Leo, MD, Ann Arbor, MI; Todd A. Mahr, MD, La Crosse, WI; Jennifer M. Maloney, MD, New York, NY; Elizabeth C. Matsui, MD, MHS, Baltimore, MD; Cecilia P. Mikita, MD, Washington, DC; Mark H. Moss, MD, Madison, WI; Anna Nowak-Wegrzyn, MD, New York, NY; Tamara T. Perry, MD, Little Rock, AR; Wanda Phipatanakul, MD, MS, Boston, MA; Christopher Randolph, MD, Waterbury, CT; Wayne G. Shreffler, MD, PhD, New York, NY; Scott H. Sicherer, MD, New York, NY; Elinor Simons, MD, Albany, NY; Helen Skolnick, MD, Princeton, NJ; Brian A. Smart, MD, Glen Ellyn, IL; Jonathan M. Spergel, MD, PhD, Philadelphia, PA; David E. Tunkel, MD, Baltimore, MD; Julia Wang, MD, New York, NY; Larry W. Williams, MD, Durham, NC; and Robert A. Wood, MD, Baltimore, MD.

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In these pages you will find reports of advances and key observations that will affect the care of children with allergic and immunologic diseases now and in the near future. The pediatrician is poised to identify infants and children at risk for disease and to intervene. Along the themes of preventing and predicting allergy, several articles present clinical and laboratory evidence that respiratory allergy, asthma, and allergic diseases may be predicted on the grounds of early lung mechanics, atopic disposition, and exposure to allergen. Potential interventions such as the use of probiotics and allergen avoidance are highlighted by several articles, but the area is complex, and additional articles emphasize the role of exposure to tobacco, pollutants, and respiratory infections in determining outcomes. Avoiding a progression of allergic disease and preventing allergies remain a key focus of research; however, as indicated by several articles, a perplexing controversy remains regarding the impact of reduced infection (the so-called hygiene hypothesis) on increasing rates of allergic disease. Notions about allergen avoidance are being refined; for example, the role of food avoidance in prevention of atopic dermatitis and food allergy is becoming less clear as studies reviewed herein show that delayed introduction of certain allergenic solids may not prevent allergy and may increase risks. Several selected articles focus on the importance of, and methods for, reducing exposure to environmental tobacco smoke, focusing on genetic risks, and identifying tobacco-smoke–related inflammation and modalities to improve intervention. Key observations in the area of food allergy present a potential for improved diagnosis and management. In particular, several articles present practical lessons regarding instructing patients on self-injection of epinephrine and pitfalls in avoiding allergens (eg, exposure during kissing). Major advances in atopic dermatitis include the clinical relevance of skin infection and the identification of loss-of-function mutations in the filaggrin gene, which result in skin-barrier dysfunction. Several articles paint a story of a disrupted skin barrier that may predispose to allergen sensitization, which in turn leads to further allergic disease. A variety of articles on asthma diagnosis and management were published just before the new National Heart, Lung, and Blood Institute Expert Panel 3 guidelines for the diagnosis and management of asthma and address evolving paradigms. For example, studies included here address issues of asthma classification, monitoring, and treatment. Practical implications to improve monitoring (eg, the use of spirometry), treatment (eg, practical tips for the use of metered-dose inhalers), and prevention are highlighted. Articles about the use of inhaled steroids continue to address chronic compared with intermittent use, impact on adrenal function, and whether these medications alter the course of asthma (an area of continued controversy). There is increasing interest in, and evidence for efficacy of, immunotherapy and immunomodulators. Reviewers selected a dozen articles on these themes that reveal the promise of allergen immunotherapy to prevent and effectively treat allergic disease; modalities of treatment that may be more child-friendly (eg, oral administration rather than injection); modifications of allergens that may allow fewer adverse effects, better efficacy, and faster onset; and the mechanism of these therapies. Several articles on primary and secondary immunodeficiency provide insights into disease pathogenesis, diagnosis, and emerging therapies. Our reviewers were asked to identify original research articles of interest, but several of them felt obliged to point out that the pediatrician should be aware of a number of superb review articles, practice articles, and guidelines on various aspects of pediatric allergy, asthma, and immunology. In the coming year, we will post such identified articles on the Section on Allergy and Immunology Web site (www.aap.org/sections/allergy).

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Early sensitization and exposure to perennial allergens in the first 3 years of life in atopic wheezers predicts chronic asthma characterized by more frequent symptoms and lower lung function by 7 years of age.

CONCLUSIONS. Early sensitization and exposure to perennial allergens in the first 3 years of life in atopic wheezers predicts chronic asthma characterized by more frequent symptoms and lower lung function by 7 years of age.

REVIEWER COMMENTS. Halting the progression toward development of chronic asthma symptoms has been a major goal of pediatric asthma research. Recent studies on daily inhaled corticosteroid therapy in wheezy infants have shown an improvement in symptom-free days while the infants were taking the inhaled corticosteroid but no sustained difference in preservation of lung function or ultimate progression to chronic asthma symptoms after cessation of daily steroid therapy. Thus, the mechanisms that cause asthma disease progression and loss of lung function may be different from those that determine acute symptoms and the frequency of asthma exacerbations. Because none of the previous studies have stratified patients into atopic and nonatopic wheezers, future studies aimed at preventing airway remodeling and the development of chronic asthma in children may need to focus more closely on the early wheezers with perennial allergen sensitization and exposure. It may be that early atopy control may affect the subsequent clinical expression of asthma in children.

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Long-term Follow-up of Atopic Dermatitis: Retrospective Analysis of Related Risk Factors and Association With Concomitant Allergic Diseases


PURPOSE OF THE STUDY. To examine the natural course of atopic dermatitis (AD), the factors influencing its persistence, and the appearance of other allergic diseases with particular focus on asthma and the presence of specific immunoglobulin E (IgE) at first observation.

STUDY POPULATION. The prospective study included 252 children between 6 and 36 months of age with AD noted on first clinical visit to a pediatric or dermatology department in Bologna, Italy.

METHODS. Patients were followed for 13 to 22 years. AD diagnosis was based on the criteria of Hanifin and Rajka. Allergic rhinitis and asthma were determined by physician diagnosis. AD severity was based on validated clinical score. Total IgE and specific IgE to various allergens (cow’s milk, egg white, soybean, wheat, peanut, nut, codfish, tomato, grass pollens, house dust mites, cat dander, horse dander, dog dander, and Alternaria) were determined at baseline. For radioallergosorbent test (RAST) testing, ≥1 was considered positive for inhalant allergen and ≥2 was considered positive for food allergies.

RESULTS. AD had completely resolved in 124 cases (60.5%). Other allergic manifestations that appeared included asthma in 70 cases (34.1%) and rhinoconjunctivitis in 118 cases (57.6%). Generally, the average age of patients who recovered from AD was higher in severe
AD (6.0 ± 3.5 years) than in its moderate or mild forms (5.8 ± 4.5 and 5.5 ± 3.9 years, respectively). This phenomenon was particularly evident in children with egg sensitization, who showed a longer persistence of the condition (P < .02). The initial severity score of AD (P < .001) or egg sensitization (P < .007) was significantly related to the later development of asthma. Egg sensitization also predicted rhinitis (P < .05). A retrospective analysis of related risks factors and their association with concomitant allergic diseases showed that the egg sensitization, severity of AD, and onset of allergic rhinitis were positively related to the occurrence of asthma.

CONCLUSIONS. AD severity and the course of AD are significantly related to egg sensitivity. AD severity and egg allergy are risk factors for asthma.

REVIEWER COMMENTS. This article provides further evidence of the “atopic march” of AD to asthma. However, it is important to realize that a positive IgE test is simply evidence for sensitization, not confirmed clinical allergy. Also, the diagnosis of asthma and allergic rhinitis was not clearly defined. Nevertheless, patients with severe AD, egg sensitization, and allergic rhinitis are at higher risk for progressing in the atopic march to asthma and allergic rhinitis.

ImmunoCAP Phadiatop Infant: A New Blood Test for Detecting IgE Sensitisation in Children at 2 Years of Age

PURPOSE OF THE STUDY. To evaluate the efficacy of a blood test, Phadiatop Infant (PI), in determining immunoglobulin E (IgE) sensitization to food and aeroallergens in children at 2 years of age.

STUDY POPULATION. Prospective study of 239 children followed from birth. Families were recruited during pregnancy. For 75% of the participants, 1 or both parents had a history of atopic disease.

METHODS. Clinical evaluation occurred every 6 months through 2 years of age. At 2 years of age, all children underwent skin-prick testing (SPT), allergen-specific IgE testing to a panel of common food and aeroallergens, and the PI blood test. Subjects with ≥1 positive SPT and allergen-specific IgE test were as categorized IgE sensitized. Those with either ≥1 positive SPT or ≥1 positive allergen-specific IgE were labeled as inconclusive. Those with all negative tests were considered non–IgE sensitized. Cutoff for a positive PI test result was >0.35 kU/L.

RESULTS. On the basis of SPT and allergen-specific IgE tests, 26 (11%) of the 239 children were considered IgE sensitized, 182 (76%) were non–IgE sensitized, and 31 (13%) were labeled inconclusive. Using SPT and allergen-specific IgE tests as a reference, in the IgE-sensitized and non–IgE-sensitized groups, the sensitivity of the PI test was 96%, specificity was 98%, positive predictive value (PPV) was 89%, and negative predictive value (NPV) was 99%. When children with any positive SPT or allergen-specific IgE test (ie, the inconclusive group) were included, sensitivity was 82%, specificity was 98%, PPV was 94%, and NPV was 95%. There was a statistically significant association between any clinical symptom of atopic disease and a positive PI test result (odds ratio: 2.7; 95% confidence interval: 1.3–5.5).

CONCLUSIONS. The ability of PI used as an independent test to detect IgE sensitization in young children seems to be a reliable alternative to SPT or allergen-specific IgE antibody testing.

REVIEWER COMMENTS. As the prevalence of atopic diseases in the population increases, early identification of IgE-sensitized, atopic children is desirable. The PI test seems to be a reasonable alternative that does not require the placement of SPT or the selection of specific antigens for SPT or blood tests. In this study, the correlation of the PI test with SPT or blood-test results was good. The correlation with clinical symptoms was not quite as convincing. In terms of individual allergic symptoms, a positive PI test result only correlated significantly with eczema. This was probably limited by the fact that children were only followed up to age 2, when asthma and rhinoconjunctivitis are more frequently infection related than allergic.

Environmental and Dietary Risk Factors for Infantile Atopic Eczema Among a Slovak Birth Cohort

PURPOSE OF THE STUDY. To evaluate and quantify how various modifiable environmental and dietary exposures contribute to the development of infantile atopic eczema (AE).

STUDY POPULATION. Birth cohort of 1990 infants followed and evaluated at 12 months of age.

METHODS. Parents completed 2 questionnaires: 1 during the mother’s admission for delivery and 1 at the 12-month follow-up appointment. At the follow-up visit, children were examined by an allergist who performed
an assessment of AE on the basis of the scoring atopic dermatitis (SCORAD) index. Data analysis (univariate and multivariate) was performed to evaluate the effects of “modifiable” and “nonmodifiable” exposures on development of AE.

RESULTS. At the 12-month follow-up, 1326 (67%) of the children remained in the cohort, of which 207 (15.6%) were determined to have AE. There were several modifiable factors found to be significant in univariate and/or multivariate analysis. Ownership of livestock and exclusive breastfeeding for at least 4 months were protective. Exposure to any infant formula (cow’s milk formula specifically), eggs, or fish in the first year of life, parental smoking, and cat ownership were associated with increased AE. There were also several significant nonmodifiable exposures. Residing in an agricultural region and birth in the spring as compared with the winter were protective. Maternal or paternal history of atopy, high paternal education, and residence in a rural region or in a “town” as compared with a “village” were associated with increased AE. The impact of modifiable versus nonmodifiable exposures on outcome was evaluated by calculating a percent total regression score. Using this method, modifiable exposures were found to contribute just over one third (38%) to the total regression score, whereas nonmodifiable exposures contributed just under two thirds (62%).

CONCLUSIONS. Although nonmodifiable exposures seem to have greater overall impact on development of AE, modifiable exposures seem to contribute significantly as well. Among these, infant feeding practices (including breastfeeding exposure to cow’s milk, egg, and fish) in the first year of life are the biggest factors.

REVIEWER COMMENTS. The finding that breastfeeding is protective against developing AE is consistent with multiple previous studies, although there are also quite a few studies that have found no effect. This effect is seen primarily in children with a family history of atopy. There are also other data that support the concept of early sensitization to certain foods, including cow’s milk, eggs, and fish, increasing the risk for AE. Cat ownership has frequently been noted to be a risk factor, whereas living environments that result in exposure to livestock have been protective. This study adds to the data suggesting that among infants at high risk of developing AE, there are some exposure factors that may be modified to lessen the likelihood of developing AE. Because infantile AE is associated with the development of asthma later, one may presume that preventing AE could decrease the odds of developing asthma as well.

Does Antibiotic Exposure During Infancy Lead to Development of Asthma? A Systemic Review and Metaanalysis


PURPOSE OF THE STUDY. To determine the association between antibiotic exposure in the first year of life and the development of childhood asthma by conducting a meta-analysis.

METHODS. A search of all available electronic databases (Medline, Embase, EBM databases, Web of Science, PapersFirst, ProceedingsFirst, and the Cochrane database) for the period between January 1966 and September 2004 was performed. Studies included populations receiving at least 1 prescription for an antibiotic during the first year of life. The primary outcome was the development of physician-diagnosed asthma between the ages of 1 and 18 years. Only studies published in English and those that reported odds ratios (ORs) were included.

RESULTS. Review of 2042 references yielded 8 studies that met criteria; 4 were retrospective, and 4 were prospective. The studies were reported between 1999 and 2004 and included sample sizes between 263 and 21 129 children. All retrospective studies used questions from the International Study of Asthma and Allergies in Childhood survey. Five studies were used to determine if there was a dose-response relationship between the number of antibiotic courses received and the risk of childhood asthma. These 5 studies included 27 167 children and 3392 asthma cases. The pooled OR for the 8 studies was 2.05 (95% confidence interval [CI]: 1.41–2.99). The association between antibiotic use in the first year of life and asthma was significantly higher in the retrospective studies (OR: 2.82; 95% CI: 2.07–3.85) than in the prospective studies (OR: 1.12; 95% CI: 0.88–1.42). The overall OR for the dose-response association of antibiotic use in the first year of life and asthma was 1.16 (95% CI: 1.05–1.28), but there was a trend toward a stronger association in the retrospective studies than in the prospective studies.

CONCLUSIONS. Meta-analysis of the impact of antibiotics in the first year of life revealed a possible increase in later development of asthma in childhood on the basis of only the retrospective study results. Additional study is needed to determine a causal relationship.

REVIEWER COMMENTS. This meta-analysis was the first to address the question of whether antibiotic use in the first year of life is associated with subsequent development of asthma. On the basis of the analysis, exposure to at least 1 antibiotic in the first year of life seems to be a risk factor for the development of childhood asthma; however, when the analysis was stratified by the subtypes of studies (prospective versus retrospective), only the
pooled results from the retrospective studies yielded a positive association. All of the 95% CIs for the prospective studies crossed 1.00, which brings into question the association between exposure to antibiotics in the first year of life and the subsequent development of childhood asthma. Additional large-scale, prospective studies will be needed to confirm or refute the association.

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Effect of Albendazole Treatments on the Prevalence of Atopy in Children Living in Communities Endemic for Geohelminth Parasites: A Cluster-Randomized Trial

PURPOSE OF THE STUDY. To determine if repeated antihelminthic treatments with albendazole affect the prevalence of atopy and clinical indices of allergy among children who live in parasite-endemic communities.

STUDY POPULATION. Children (N = 2373) attending the second to seventh year of primary education at 1 of 68 rural schools in a tropical and subtropical region of Ecuador.

METHODS. Children were cluster randomized by school to receive albendazole treatment every 2 months for 12 months or no treatment. The primary outcome was the proportion of children with at least 1 positive skin-test result to an environmental allergen after 12 months; secondary outcomes included the proportion of children with reported allergy symptoms, flexural dermatitis, and exercise-induced bronchospasm. No placebo was used, but the investigators who evaluated the children were blinded to their treatment-group assignment.

RESULTS. At baseline, there was an inverse association between geohelminth infection and skin-test reactivity (odds ratio: 0.78; 95% confidence interval: 0.65–0.95). Of children who attended albendazole-allocated schools, 91.5% received all 7 albendazole doses; albendazole treatment by parents was reported for 29.4% of the children allocated to no-treatment schools. After 12 months, the prevalence of geohelminth infection declined from 69.3% to 20.5% in the treatment group and from 74.6% to 65.7% in the no-treatment group. There was no evidence of an increase in the prevalence of atopy among children who received albendazole (17%) compared with those in the no-treatment group (17%; age- and gender-adjusted odds ratio: 0.97; 95% CI: 0.68–1.39). Both groups had similar reported allergy symptoms, flexural dermatitis, and exercise-induced bronchospasm after 12 months.

CONCLUSIONS. After 12 months, the prevalence of atopy did not increase among school-aged children who were treated with albendazole, compared with children who were not treated.

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Effect of Probiotic Supplementation for the First 6 Months of Life on Allergen- and Vaccine-Specific Immune Responses

PURPOSE OF THE STUDY. To determine if probiotic dietary supplementation in the first 6 months of life could modify allergen- and vaccine-specific immune responses.

STUDY POPULATION. One hundred seventy-eight term infants born to women with a history of allergic disease and a positive prick-skin test result were enrolled in Australia between July 2002 and March 2005.

METHODS. In a randomized double-blind, placebo-controlled design, 3 × 10⁹ colony-forming units of Lactobacillus acidophilus (LARVI-A1; Probiomics, Eveleigh, New South Wales, Australia) was administered daily to term infants for the first 6 months of life. Peripheral blood mononuclear cell cytokine responses to tetanus toxoid (TT), house dust mite (HDM), ovalbumin, β-lactoglobulin, Staphylococcus enterotoxin B, and phytohemagglutinin were measured at 6 months of age.

RESULTS. Of the 178 infants who completed the study, blood samples were available from 118 children (60 placebo treated, 58 probiotic treated). Infants treated with probiotics had significantly lower interleukin 10 (IL-10) production to TT vaccine antigen than those in the placebo group (P = .03). Infants treated with probiotics had no significant differences in the levels of T-helper 1 and T-helper 2 cell responses to foods (ovalbu-
Role of Breast Milk in a Mouse Model of Maternal Transmission of Asthma Susceptibility

PURPOSE OF THE STUDY. There is some epidemiologic evidence that the risk of asthma in children born to asthmatic mothers increases with breastfeeding; however, this association remains controversial. This study used a mouse model of maternal transmission of asthma risk to investigate the effect of adoptive nursing on asthma susceptibility in offspring.

METHODS. Future maternal mice were sensitized as neonates by intraperitoneal ovalbumin injections followed by repeated exposure to aerosolized ovalbumin at 4, 8, and 12 weeks of age. The mice then mated, and some litters from asthmatic mothers were nursed by normal mothers; similarly, some litters from normal mothers were nursed by asthmatic mothers. The offspring received a single intraperitoneal ovalbumin injection on day 4 (intentional suboptimal sensitization, which did not provoke any allergic response in infants born to normal mothers) followed by aerosolized ovalbumin exposure on days 13 to 15. A similar protocol was applied for studies of a second allergen, casein. Pulmonary-function testing was performed on day 16, followed by pathologic analyses on day 17. Cytokines were also analyzed in expressed breast milk from mothers, as well as breast milk retrieved from infant stomachs.

RESULTS. Infant mice born to asthmatic mothers, but not those born to normal mothers, exhibited airway hyperresponsiveness to methacholine and allergic airway inflammation, specifically increased eosinophils on bronchoalveolar lavage and eosinophilic and mononuclear cell infiltration around airways and vessels on lung pathology. After adoptive nursing, both groups (normal infant mice nursed by asthmatic mothers and infants of asthmatic mothers nursed by normal mice) showed airway hyperresponsiveness to methacholine and airway inflammation, exhibited as eosinophilia on bronchoalveolar lavage and histology. Similar results were observed when infant mice born to ovalbumin-allergic and -exposed mothers were suboptimally sensitized to an unrelated allergen, casein, suggesting that allergens and/or specific antibodies are not responsible for the transmission of susceptibility through breast milk. Assays for cytokines (interferon-γ, interleukin 2, interleukin 4, interleukin 5, tumor necrosis factor α, and interleukin 13) were negative in both expressed breast milk and milk-rich stomach contents.

CONCLUSIONS. These findings suggest that breast milk contains factors that are sufficient, but not necessary, to mediate allergen-independent transmission of asthma susceptibility from mothers to offspring mice.

REVIEWER COMMENTS. The results of this study in a mouse model of maternal asthma support some of the epidemiologic data showing that the risk of asthma may increase with breastfeeding. In this study, the increased asthma susceptibility observed in infant mice born to normal mothers and nursed by asthmatic mothers suggests that breastfeeding may be one mechanism for transmission of asthma risk. Given the absence of significant cytokine levels in breast milk in this study, future investigation is needed to identify the mediator(s) in breast milk that is responsible for increasing asthma risk.
Timing of Initial Exposure to Cereal Grains and the Risk of Wheat Allergy

Purpose of the Study. To ascertain the relationship between cereal-grain exposure, wheat, barley, rye, and oats in the infant diet and the subsequent development of wheat allergy.

Study Population. A birth cohort of 1612 children followed to a mean age of 4.7 years.

Methods. A total of 1612 children were enrolled in a birth cohort with questionnaire data, and dietary exposures were determined at 3, 6, 9, 15, and 24 months and annually thereafter. The primary outcome measure was apparent report of wheat allergy. Wheat-specific immunoglobulin E (IgE) levels in children reported to have wheat allergy were obtained. Children with celiac disease or autoimmune were excluded.

Results. Sixteen children (1%) noted wheat allergy. Children who were first exposed to cereal after 6 months of age had a 4.5 times prevalence of wheat allergy when compared with children who were first exposed to cereals before 6 months of age, after controlling for family history and allergic disorder and history of food allergy before 6 months of age. All 4 children with detectable wheat-specific IgE were initially given cereal grains after 6 months. Having a first-degree relative with a history of atopy (ie, asthma, eczema, or hives) was also independently associated with an enhanced risk of subsequent development of wheat allergy.

Conclusions. Delaying first exposure to cereal grains until after 6 months enhanced the risk of subsequent development of wheat allergy. These results do not support delaying introduction of cereal grains for protection against food allergy.

Reviewer Comments. This study was limited by its dependence of parental report of wheat allergy, although IgE was obtained as well. No formal diagnostic oral food challenges were performed. The possibility of reverse causality was addressed by eliminating confounding factors related to history of food allergy but could still be a potential explanation. The birth cohort also was selected on the basis of HLA-genotype screening and family history of diabetes, which may limit its generalizability. However, the results, that delaying exposure to cereal grains until after 6 months is associated with increased risk of wheat allergy, not a protective outcome, are still provocative. Additional large prospective studies using double-blind, placebo-controlled food challenge to confirm these findings are needed.

Fish Consumption During the First Year of Life and Development of Allergic Diseases During Childhood

Purpose of the Study. To assess the association of fish consumption during the first year of life with development of allergic diseases by age 4.


Methods. Parental questionnaires at child ages 2 months and 1, 2, and 4 years were administered to collect information on atopic heredity, diet, exposures, and allergic symptoms. When the children were 4 years old, a clinical investigation, including blood sampling for analysis of specific immunoglobulin E (IgE) to common inhalant and food allergens, was performed.

Results. The mean age of introduction of fish in the child’s diet was 8.3 months. History of parental allergic disease and onset of eczema or wheeze during the first year of life was associated with delayed introduction of fish in the child’s diet. Regular fish consumption during the first year of life was associated with a reduced risk for allergic disease by age 4 (adjusted odds ratio: 0.76; 95% confidence interval: 0.61–0.94) and sensitization (adjusted odds ratio: 0.76; 95% confidence interval: 0.58–1.0) after exclusion of children with onset of eczema or wheeze during the first year of life to avoid disease-related modification of exposure. A dose-dependent reduced risk was observed for all outcomes (asthma, eczema, allergic rhinitis, and sensitization). IgE sensitization to fish was present in 18 of the 2614 children.

Conclusions. Regular fish consumption before the age of 1 seems to be associated with a reduced risk of allergic disease and sensitization to food and inhalant allergens during the first 4 years of life.

Reviewer Comments. In recent decades, a decrease in consumption of omega-3 polyunsaturated fatty acids, prevalent especially in oily fish, has been proposed to contribute to the increased prevalence of allergic diseases. The authors postulated that dietary polyunsaturated fatty acids might influence the development of allergic sensitization by increasing the formation of prostaglandin E2, which in turn promotes the formation of a T-helper 2 response and stimulates the formation of IgE. The authors attempted to control for the disease-related modification of exposure by excluding children with very early symptoms of eczema or recurrent wheeze. However, this attempt to control for “reverse causation” added limitation, because the most atopic infants were excluded. As the authors admitted, fish consumption in early life may be associated with a lifestyle that reduces
the risk of allergic disease in nondietary ways. Nonetheless, the study presented an interesting observation given concerns about inducing allergy by introducing allergenic foods to infants.

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ALLERGENS AND ENVIRONMENTAL EXPOSURES

Home Environmental Intervention in Inner-City Asthma: A Randomized Controlled Clinical Trial

PURPOSE OF THE STUDY. To conduct a randomized, controlled clinical trial to test the efficacy of home-based methods to reduce environmental pollutants and allergen exposure in the homes of asthmatic children living in an inner city.

STUDY POPULATION. One hundred asthmatic children, ranging in age from 6 to 12 years, with physician-diagnosed asthma, current asthma symptoms, and no other chronic lung disease.

METHODS. The families were randomly assigned to a treatment group that received intervention immediately (home-based education, cockroach and rodent extermination, mattress and pillow encasings, and a high-efficiency particulate air cleaner) or to a control group that received intervention at the end of the 1-year trial. In the treatment group, 84% received cockroach extermination, 70% received mouse extermination, and 75% used the air cleaner. Outcomes were evaluated against baseline by home evaluation at 6 and 12 months, clinical evaluation at 12 months, and multiple telephone interviews.

RESULTS. Home particulate concentrations were lower at both 6 and 12 months in the treatment group. Home levels of particulate matter ≤10 µm declined by up to 39% in the treatment group as compared with an increase in the control group (P < .001), and cockroach allergen levels decreased by 51% in the treatment group (P = .04). The proportion of symptomatic children increased in the control group and decreased in the treatment group, with significant differences seen at 6 months and later. In addition, children in the treatment group were significantly less likely to report daytime symptoms during the first 9 months compared with those in the control group. However, the mean difference in daytime symptoms over 12 months was only marginally significant (P = .07). Other measures of participant morbidity, such as nighttime symptoms, emergency department use, and spirometry findings, were not significantly changed during the study period.

CONCLUSIONS. A tailored program of environmental and behavioral interventions to reduce indoor particulate matter and other relevant allergen levels in low-income, inner-city homes had a modest effect on asthma morbidity.

REVIEWER COMMENTS. It is interesting to note that few of the 69% of the households with smokers in them changed smoking habits. Most likely, the environmental-control measures outlined in this article, implemented as part of a more comprehensive treatment plan including smoking cessation, could contribute more significantly to symptom reduction.

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Environmental Risk Factors of Rhinitis in Early Infancy

PURPOSE OF THE STUDY. To examine the impact of environmental tobacco smoke (ETS) and visible mold exposure on the development of allergic rhinitis, rhinitis, and upper respiratory infection (URI) in early infancy.

STUDY POPULATION. Six hundred thirty-three infants ≥35 weeks’ gestation with at least 1 parent who had 1 of 12 selected allergy symptoms and a positive skin-prick–test result to at least 1 of 15 Aeroallergens.

METHODS. The child’s birth certificate and a questionnaire format were used to collect demographic data and information on family smoking habits, family health history, pet ownership, day care attendance, breastfeeding, and the infants’ respiratory health history from birth to the time of enrollment. Parents were asked to complete monthly diaries to collect information on their child’s upper respiratory symptoms. They must have completed 1 diary before the child’s 12-month clinical examination. Allergic rhinitis was defined as having rhinitis symptoms not associated with a cold or chest infection at least once on any diary and a positive skin-prick–test result to ≥1 Aeroallergen at the 12-month visit. Study personnel examined the home for mold exposure within 3 weeks of study enrollment.

RESULTS. Infants were nearly 3 times more likely to have allergic rhinitis at 12 months of age (odds ratio [OR]: 2.7; 95% confidence interval [CI]: 1.04–6.8) and twice as likely to have rhinitis (OR: 1.9; 95% CI: 1.1–3.2) when exposed to ≥20 cigarettes per day. Infants were 5 times more likely (OR: 5.1; 95% CI: 2.2–12) to have frequent URIs when exposed to high mold levels. Having older
siblings was protective for development of rhinitis and allergic rhinitis at age 1.

CONCLUSIONS. ETS exposure is associated with rhinitis and allergic rhinitis in infants. Mold may be a stronger risk factor for URI than ETS.

REVIEWER COMMENTS. This is one of very few studies to have examined the relevance of home exposures in the first year of life and demonstrated that early environmental exposures likely play a significant role in respiratory health outcomes in infancy. One weakness of the study was the fact that ETS exposure and URI and rhinitis symptoms were collected by parental report and may be subject to significant recall bias or erroneous reporting. Nevertheless, these findings support the need for further research in the areas of early environmental-exposure interventions and the role of gene-environment interactions that affect respiratory health outcomes.

TOBACCO AND AIR POLLUTION

Parental Smoking Increases Exhaled Nitric Oxide in Children

PURPOSE OF THE STUDY. Fraction of exhaled nitric oxide (FeNO) seems to reflect allergic airway inflammation. The authors sought to investigate the association between reported parental smoking and FeNO in young children.

STUDY POPULATION. The study included 78 children (mean age: 51.3 weeks; range: 13–106 weeks) who had FeNO data and had been well for at least 2 weeks before testing. Fifty-six children lived in nonsmoking households, 14 lived with 1 smoking parent, and 8 lived with 2 smoking parents.

METHODS. Children underwent pulmonary-function testing that included measures of lung volumes (forced expiratory volume [FEV] in 0.5 second) and FeNO. The effect of parental smoking on FeNO and FEV was analyzed by using unpaired t tests and analysis of variance. Dose-response relationships between the number of smoking parents and FeNO and FEV were determined by using the χ² test. There were no significant anthropometric differences between children in smoking and nonsmoking households.

RESULTS. Children who had at least 1 smoking parent had a higher FeNO compared with children who lived in nonsmoking households (41.9 vs 33.0 ppb, respectively). Within the smoking group, children who lived with 2 smoking parents had a higher FeNO compared with children who lived with 1 smoking parent (48.3 vs 38.0 ppb, respectively). The difference between these 3 groups was not significant. However, there was a significant dose-response relationship across the 3 groups. Moreover, after controlling for other factors, it was found that parental smoking significantly increased the FeNO. Age, gender, maternal atopy, and doctor-diagnosed eczema and FEV were not associated with FeNO.

CONCLUSIONS. Exposure to environmental tobacco smoke was associated with increased FeNO in young children. There also was evidence of a dose-response relationship between childhood FeNO and the number of smoking parents.

REVIEWER COMMENTS. The role of FeNO as a marker for airway inflammation after exposure to tobacco smoke seems ambiguous. The authors mentioned that although some studies have shown that tobacco smoke has been associated with lower FeNO in smokers, other studies have found a short-term increase in FeNO directly after smoking a cigarette. Moreover, most epidemiologic studies have not found an effect of parental smoking on FeNO in older children. The authors argued that reported parental smoking alone may not be a good indicator for exposure in older children, because they are able to remove themselves from the source, compared with younger children who are unable to move from the offending environment. Whether FeNO can prove to be a useful biomarker of allergic sensitization or airway inflammation still remains in question. In addition, even if the association between cigarette-smoke exposure and high FeNO remain after better-powered studies, further investigations are warranted to elucidate what the potential clinical ramifications are for children with high levels of exhaled nitric oxide.

TNF-308 Modifies the Effect of Second-hand Smoke on Respiratory Illness-Related School Absences

PURPOSE OF THE STUDY. To investigate the role of tumor necrosis factor (TNF) G→308A, a variant in the promoter region of TNF, that has been associated with inflammatory diseases including asthma in the susceptibility of secondhand-smoke–exposed children to respiratory illness.

STUDY POPULATION. A prospective cohort of fourth-grade students (N = 1935) from 27 elementary schools in
southern California from whom school-absence data were collected from January to June of 1996. Approximately 70% of the children (n = 1351) provided a buccal cell sample.

METHODS. Schools provided daily absence summary information for the study subjects, and each absence was recorded as illness or nonillness. Telephone interviews regarding each illness-related absence were conducted with parents. School absences were classified as lower respiratory illnesses if wet cough, wheeze, or asthma was present. Secondhand-smoke exposure was determined by parent/guardian written responses on self-administered questionnaires and categorized as none, 1 to 29, or \( \geq 30 \) cigarettes smoked per day inside the home. Asthma status was determined by parental response to the question, “Has a doctor ever diagnosed this child as having asthma?” Buccal cell samples were collected, and the genomic DNA was analyzed for the G-to-A transition polymorphism at position 308 in TNF by polymerase chain reaction and allelic discrimination assays.

RESULTS. There was a 51% greater risk of lower respiratory illness–related school absences among children with secondhand-smoke exposure compared with those who were unexposed. Children with the TNF GG genotype exhibited similar absence rates regardless of whether they were exposed or unexposed to secondhand smoke. Unexposed children with at least 1 copy of the TNF G→308A allele had similar absence rates for lower respiratory illnesses compared with children with the TNF G→308GG genotype. However, absence rates in children with the variant A allele and secondhand-smoke exposure were markedly increased. Children with the variant A allele and secondhand-smoke exposure had a 75% increase in risk for illness-related absences compared with unexposed children with the GG genotype. In children with the variant A allele, illness-related absence risk increased as the number of smokers in the home increased. In addition, children with 1 variant A allele who were exposed to \( \geq 30 \) cigarettes per day had a relative risk of 2.75 for respiratory illness–related school absence compared with unexposed children with the GG genotype. Restricting analysis to children without asthma did not substantially alter the findings.

CONCLUSIONS. Secondhand-smoke–exposed children who carried a TNF G→308A variant allele were at highest risk for respiratory illness–related school absences. A strong dose-response relationship in this group of patients was found for respiratory illness–related absence risk in relation to the number of household smokers and number of cigarettes smoked. The genetic susceptibility associated with the TNF G→308A allele is likely mediated by variation in inflammatory responses to secondhand smoke.

Patterns of Global Tobacco Use in Young People and Implications for Future Chronic Disease Burden in Adults


PURPOSE OF THE STUDY. The Global Youth Tobacco Survey assessed current tobacco use and exposure among young teenagers and evaluated susceptibility to starting smoking among nonsmokers.

STUDY POPULATION. Students aged 13 to 15 years (N = 747 603) at 395 sites in 131 countries and the Gaza Strip and West Bank.

METHODS. Students completed questionnaires to assess current tobacco use, cigarette smoking, susceptibility to smoking among nonsmokers, and exposure to secondhand smoke in homes and public places. Susceptibility to smoking was defined as an answer other than “definitely not” when asked if they would smoke a cigarette offered by a best friend or if they thought they would smoke at any time in the next 12 months.

RESULTS. Among all students, 17.3% currently used tobacco products and 8.9% currently smoked cigarettes. Current tobacco-product use was highest in the region of the Americas (22.2%), and current cigarette smoking was highest in the European region (17.9%) and region of the Americas (17.5%). Among students who had never smoked cigarettes, 18.3% reported susceptibility to smoking during the coming year. Susceptibility was highest in the European region (30.5%) and the region of the Americas (24.8%). Measures of use, susceptibility, and exposure were similar for boys and girls. Worldwide, never-smokers were less likely than current smokers to report exposure to secondhand smoke at home (prevalence: 39.1% [95% confidence interval (CI): 36.6–41.6] vs 72.8% [95% CI: 64.0–81.6]) and in public places (prevalence: 49.5% [95% CI: 46.7–52.3] vs 81.2% [95% CI: 74.2–88.2]).

REVIEWER COMMENTS. Secondhand-smoke exposure is common among children and causes substantial morbidity. However, there is variation in susceptibility to the effects of secondhand smoke. This study demonstrated that differences in genotype of mediators of inflammation may explain variation in susceptibility to secondhand smoke. Additional studies are needed to elucidate differences in genotypes of other inflammatory mediators, which may produce a similar effect. This may provide one more weapon in our arsenal to convince parents to quit smoking or devise protective agents for the exposed.
CONCLUSIONS. Although tobacco exposure and susceptibility remain high among young teenagers, this study demonstrated a significant association between lower secondhand cigarette-smoke exposure and never smoking.

REVIEWER COMMENTS. Cigarette smoke is a common respiratory irritant that contributes to exacerbations of childhood asthma and rhinitis. This study provided evidence supporting the association between lower secondhand cigarette-smoke exposure and never smoking among young teenagers, which suggests an additional reason to counsel patients and their families regarding the immediate and long-term risks of exposure to secondhand cigarette smoke and cigarette smoking.

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Enabling Parents Who Smoke to Prevent Their Children From Initiating Smoking: Results From a 3-Year Intervention Evaluation


PURPOSE OF THE STUDY. To evaluate effects of a home-based antismoking socialization program on the initiation of smoking among children whose parents smoke.

STUDY POPULATION. Parents who were current smokers and had a third-grader who had not tried smoking were eligible. The study included 776 children who completed an interview 3 years after initial randomization of 873 parent-child pairs; 371 were in the intervention group, and 405 were in the control group.

METHODS. This was a 3-year randomized, controlled trial. During 3 months, the intervention group received 5 printed activity guides, parenting tip sheets, child newsletters, and incentives. One year later, this group also received a booster activity guide. The control group only received fact sheets about smoking.

RESULTS. Initiation of smoking was reported by 19% of children in the control group versus 12% of those in the intervention group (adjusted odds ratio: 2.16; P < .001).

CONCLUSIONS. Children in the preinitiation phase of smoking who receive antismoking socialization from their parents are less likely to initiate smoking, even if their parents smoke. The authors defined antismoking socialization as internalization of attitudinal and behavioral norms against initiation of smoking, acceptance of parental monitoring of access to cigarettes and affiliation with peers who have tried smoking, expectations of negative consequences for trying smoking, and expectations of positive consequences for not smoking, which is much more than simply telling children that they should not smoke.

Association of Indoor Nitrogen Dioxide Exposure With Respiratory Symptoms in Children With Asthma


PURPOSE OF THE STUDY. Chronic exposure to indoor nitrogen dioxide (NO₂) may be a public health concern. The primary source of residential NO₂ is gas-fueled cooking appliances. The authors’ objective was to examine associations of indoor NO₂ exposure with respiratory symptoms among children with known asthma.

STUDY POPULATION. Subjects were 728 children younger than 12 years with physician-diagnosed asthma living in Connecticut and southwest Massachusetts. All children had active asthma and had lived at the same address for at least 2 months before NO₂ sampling.

METHODS. At enrollment, a research assistant visited the home and recorded family ethnicity, housing characteristics (multifamily versus single family, number of rooms, water leaks, visible mold), presence of smoking in the home, and the use of household appliances fueled by natural gas. Mothers were also asked about number of days of respiratory symptoms experienced by the child and medications used for each month of the previous year. NO₂ was measured in each home by using a Palmes tube placed in the main living area for 10 to 14 days after the enrollment visit.

RESULTS. The mean concentration of indoor NO₂ was 8.6 ppb in homes with electric ranges and 25.9 ppb in homes with gas stoves. The mean NO₂ level measured in multifamily homes was 22.9 ppb, and the mean NO₂ level in single-family homes was 10.2 ppb. Measured NO₂ (>20 ppb) was associated with ethnicity: white families were least likely to have high exposures, and Hispanic families were the most likely. Among children living in multifamily housing, exposure to gas stoves and high levels of NO₂ were associated with wheezing, shortness of breath, and chest tightness. For children in single-family homes, neither exposure to gas stoves nor measured NO₂ was associated with any respiratory symptom.
CONCLUSIONS. The authors concluded that there is an association between exposure to high levels of indoor NO₂ and respiratory symptoms in children with physician-diagnosed asthma. This association, however, was limited to children who lived in multifamily homes, probably because of the smaller size (and air volume) of the apartments. The authors also suggested a strong association of NO₂ exposure with housing characteristics, lower socioeconomic status, and ethnicity.

REVIEWER COMMENTS. This study demonstrated an association between increased NO₂ levels and asthma symptoms of children in multifamily homes. The important potential confounders in the analysis should have been adequately dealt with in the logistic regression analysis used. The biological basis of the association is poorly understood, and the value of intervention to reduce exposure is speculative. Additional studies will be needed to clarify and confirm the association.

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Carbon in Airway Macrophages and Lung Function in Children

PURPOSE OF THE STUDY. To define the extent of pulmonary-function abnormalities that may be attributed to exposures to particulate matter with a median aerodynamic diameter of <10 μm (PM₁₀) as a result of fossil fuel combustion.

STUDY POPULATION. The study included 114 children (aged 8 to 15 years) without any chronic respiratory condition who were living in the same residence for 1 year. All children had a forced expiratory volume in 1 second (FEV₁) of >80% predicted.

METHODS. Pulmonary-function testing and induced sputum were obtained on the same day. PM₁₀ values from all sources were collected for 1 year. The results were controlled for passive tobacco-smoke exposure.

RESULTS. A total of 62 (56%) of the 114 subjects were able to produce sputum. An increase of 1 μg/m³ in PM₁₀ was associated with an increase of 0.10 μm² in the carbon content of airway macrophages. Each 1.0 μm² increase in carbon content was associated with a significant decrease in pulmonary function (decrease of 17% in FEV₁, 12.9% in forced vital capacity, and 34.7% in forced expiratory flow, midexpiratory phase).

CONCLUSIONS. A significant reduction in pulmonary function resulted from increased exposure to products of fossil fuel combustion.

Reviewer comments. The reduction in pulmonary function in this cohort of children who did not have current lower airway symptoms is in the same order of magnitude as patients with moderate persistent asthma, which underscores the need for less toxic energy sources.

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Particulate Levels Are Associated With Early Asthma Worsening in Children With Persistent Disease
Rabinovitch N, Strand M, Gelland EW. Am J Respir Crit Care Med. 2006;173:1098–1105

PURPOSE OF THE STUDY. To determine if exposure to particulate matter has immediate effects on asthma control in children with persistent disease.

STUDY POPULATION. Seventy-three schoolchildren (aged 6–13 years) with physician-diagnosed asthma in Denver, Colorado, were studied.

METHODS. Over 2 consecutive winters, the subjects were followed daily. The association among ambient fine-particulate levels, bronchodilator use, and urinary leukotriene E₄ levels was assessed.

RESULTS. Fine-particulate concentrations peaked in the morning hours during hours when children were commuting to school. Children with severe asthma had a stronger association (+8.1%) than those with mild-to-moderate disease (+1.6%), with increased bronchodilator usage at school on days with an increase of 1 interquartile range in morning maximum fine-particulate levels. Morning maximum fine-particulate levels were also associated with urinary leukotriene E₄ measured during school hours (average increase of 6.2% per interquartile-range increase).

CONCLUSIONS. Peak concentrations of ambient fine particulate are associated with early increases in bronchodilator use and urinary leukotriene E₄ levels among children with persistent asthma, despite the use of controller medications.

REVIEWER COMMENTS. Managing patients with asthma requires knowing possible triggers. This study examined the timing of particulate associations with disease control in children with moderate or severe asthma who were taking controller medications. The interval between exposure and initiation of health effects was seen to occur within the first few minutes or hours after exposure. The effects were strongest in children with more severe asthma. This effect plus the increase in urinary leukotriene E₄ levels suggest that in children with persistent asthma, particulate exposure may lead to early release of mediators related to asthma worsening.
This study suggests that in children with poorly-controlled asthma, air-pollution effects (well below National Ambient Air Quality standards) may be observed despite the use of daily controller medications.

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FOOD ALLERGY

Skin Prick Test to Egg White Provides Additional Diagnostic Utility to Serum Egg White-Specific IgE Antibody Concentration in Children

PURPOSE OF THE STUDY. To determine if skin-prick tests (SPTs) can differentiate children with low egg white–specific immunoglobulin E (IgE) levels who pass an oral egg challenge from those who fail.

STUDY POPULATION. The study was a retrospective analysis of oral egg challenges (N = 74) in children with egg allergy and low egg white–specific IgE antibody levels (<2.5 kIU/L).

METHODS. A retrospective analysis of serum egg white–specific IgE levels, SPT results, and egg oral food challenge (OFC) outcomes and clinical history in children with egg allergy were performed. Children were typically selected for OFC on the basis of low egg white–specific IgE levels (<2.5 kIU/L). Sixty eight of the challenges were double-blind, placebo-controlled OFCs conducted in the Mount Sinai General Clinical Research Center (New York, NY), and 12 OFCs were open challenges conducted in outpatient clinics between April 2001 and April 2005. Children who passed their OFC were compared with those who failed for differences in age, gender, history of egg reaction, asthma, eczema, allergic rhinitis, oral allergy syndrome, family history of food allergy, and family history of any allergy.

RESULTS. Children who passed the egg OFC (n = 29) had a median wheal size of 3 mm (range: 0–9 mm) and a median egg/histamine index of 0.71 (range: 0.00–2.30), whereas those who failed (n = 45) had a median wheal size of 5 mm (range: 0–8 mm) and a mean egg/histamine index of 1.0 (range: 0.0–2.7), which demonstrated significance of \( P = .003 \) for SPT and \( P = .0009 \) for index. In patients with egg white–specific IgE levels of <2.5 kIU/L, an SPT wheal of 3 mm or an egg/histamine wheal-size index of 0.65 was associated with a 50% chance of passing an egg OFC. Children who passed their OFC did not differ from those who failed with regard to egg white–specific IgE levels, age, gender, or clinical history, except for allergic rhinitis, which was found in 82% of those who failed versus 55% of those who passed (\( P = .02 \)).

CONCLUSIONS. In egg-allergic children, those with low egg white–specific IgE levels, a small SPT response, and a low egg/histamine index are more likely to pass egg OFCs. The size of the egg SPT wheal response may be used to predict the outcome of the egg OFC, thus aiding clinicians in timing of OFCs in egg-allergic patients.

REVIEWER COMMENTS. With the increasing prevalence of food allergy in young children, diet restriction is becoming an increasing burden for families of food-allergic children, which makes it important to test for tolerance as early as possible. The current study population represented more severely affected patients with comorbidities and demonstrated a high OFC failure rate of 62%. Although these findings provide new and useful information for clinicians who treat children with egg allergy, additional studies are needed to validate these findings prospectively and in different populations.

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The Atopy Patch Test in the Diagnostic Workup of Suspected Food-Related Symptoms in Children

PURPOSE OF THE STUDY. To determine the utility of atopy patch tests (APTs) in the diagnostic evaluation of food allergy.

STUDY POPULATION. A cohort of 437 children (median age: 13 months; 90% with atopic dermatitis) who were referred for evaluation of suspected food allergy.

METHODS. Specific serum immunoglobulin E (sIgE) measurements, skin-prick tests (SPTs), APTs, and controlled oral food challenges were performed.

RESULTS. The outcomes of 873 oral challenges with cow’s milk, hen’s egg, wheat, and/or soy were analyzed. One thousand seven hundred single APTs were performed. As a single parameter, the APTs showed the best specificity compared with sIgE measurements, SPTs, or both. Combining the APT with either the SPT or sIgE measurement resulted in improved sensitivity and specificity. Decision points for sIgE measurement and for the SPT showed lower values when combined with a positive APT result. By including the APT in the evaluation, only between 0.5% and 7.0% (99% predicted probability) and between 6% and 14% (using 95% predicted probability) of children would fulfill the criteria for avoiding an oral food challenge.
Although the predictive capacity of the APT is improved when combined with sIgE measurement or the SPT, oral food challenges become superfluous in only 0.5% to 14.0% of study patients. In addition, the APT is time-consuming and demands a highly experienced test evaluator. For daily clinical practice, the APT adds only a small predictive value to the standard SPT and sIgE measurement in the diagnostic workup of suspected food-related symptoms in children with atopic dermatitis.

REVIEWER COMMENTS. The APT is presumed to reflect late-phase clinical reactions. However, even with late onset of symptoms (>2 hours after food ingestion), the performance of the APT was not consistent in the children with atopic dermatitis. The question that remains unanswered is whether the APT could be used to diagnose non–IgE-mediated gastrointestinal reactions to foods, such as allergic eosinophilic esophagitis/gastroenteritis or food protein–induced enterocolitis syndrome.

**Atopy Patch Test for the Diagnosis of Food Protein-Induced Enterocolitis Syndrome**


**PURPOSE OF THE STUDY.** This prospective study was undertaken to determine if the atopy patch test (APT) is able to predict the results of the oral food challenge (OFC) for food protein–induced enterocolitis syndrome (FPIES). The APT involves placement of food in a Finn chamber (metal cap) left on the skin for 48 hours and evaluated for rash in the subsequent days after removal.

**STUDY POPULATION.** Nineteen patients aged 5 to 30 months who had suspected FPIES on the basis of clinical history.

**METHODS.** The infants underwent APT to the suspected foods. After APT was performed, the subjects underwent OFC to determine if FPIES was present. The results of APT and OFC were compared and used to calculate sensitivity and specificity of the APT.

**RESULTS.** APT predicted the results of OFCs in 28 of 33 instances. There were 16 cases of FPIES confirmed by OFCs. In all 16 cases of FPIES, the APT result was positive to the suspected food. However, the APT was positive in 5 instances in which the OFC result was negative. All 12 patients with a negative APT result had a negative OFC result to the suspected food.

**CONCLUSIONS.** APT seems to be a promising diagnostic tool for the diagnosis of FPIES.

**REVIEWER COMMENTS.** FPIES is a non–immunoglobulin E (IgE)-mediated food allergy in which affected infants develop gastrointestinal symptoms hours after ingestion of the offending food. Current allergy skin and serum tests are not useful for diagnosing this disorder, because they test for food-specific IgE levels that are often negative in FPIES. A diagnostic OFC is the gold standard. The role for APT in diagnosing other non–IgE-mediated food hypersensitivities has been investigated. The results of this study suggest that APT may have some utility in guiding the diagnosis and management of FPIES.

**Allergic Eosinophilic Gastroenteritis With Protein-Losing Enteropathy: Intestinal Pathology, Clinical Course, and Long-term Follow-up**


**PURPOSE OF THE STUDY.** To identify gross and/or histologic distinguishing features of antral and duodenal biopsy specimens as well as clinical response to various treatment regimens in the subset of patients with eosinophilic gastroenteritis (AEG) with protein-losing enteropathy (PLE).

**STUDY POPULATION.** The experimental group consisted of 6 children with anemia and hypoalbuminemia and biopsy-proven AEG identified retrospectively from a series of 93 patients with AEG who were evaluated at Mount Sinai Medical Center (New York, NY) over a 7.5-year period.

**METHODS.** Two comparison groups were used in addition to the experimental group. The first included 6 randomly selected patients from the series of 93 patients with AEG without anemia and/or hypoalbuminemia. The second comparison group included 5 patients who presented with symptoms consistent with possible AEG yet normal gross findings and histology after endoscopy. Causes of eosinophilia other than AEG were ruled out. The diagnoses of AEG required the presence of >20 eosinophils per high-power field in antral biopsy specimens and >50 in the duodenum. Hematoxylin/eosin staining and immunohistochemical staining of tryptase were used for identification of eosinophils and mast cells, respectively. The cell count was taken from the high-power field with maximum infiltration.

**RESULTS.** Various therapies were attempted in the experimental group including oral corticosteroids, cromolyn sodium, 6-mercaptopurine, food-elimination diets, and montelukast. They were, at best, partially or temporarily beneficial. All experimental patients received an exclusive amino acid–based formula diet at some point in their care; this formula was associated with rapid im-

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proof of anemia and hypoalbuminemia as well as clinical symptoms. These patients eventually tolerated the addition of various foods to their diet. In duodenal biopsy specimens, mast cells were significantly increased in patients with AEG and PLE compared with those with AEG only, whereas eosinophil numbers were comparable. This was not seen in the antral samples. Eosinophilia was more prominent in the antrum of patients with AEG and PLE compared with those with AEG only. Patchy duodenal villous blunting was seen in 1 patient with AEG and PLE and 1 with AEG.

CONCLUSIONS. As in the treatment of eosinophilic esophagitis, amino acid–based formulas seem to be the most effective form of therapy. After improvement on an amino acid–based formula diet, many patients eventually tolerate expanded diets. Malabsorption and villous blunting do not seem to be the cause of hypoalbuminemia and anemia in those patients with AEG and PLE. Increased intestinal mast cells seen in the patients with AEG with PLE may be the source of the intestinal protein loss.

REVIEWER COMMENTS. Although the sample size in this study was small, these data provide additional insight into the specific role of mast cells in patients with AEG and PLE.

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Mixed-up Nuts: Identification of Peanuts and Tree Nuts by Children
Ferdman RM, Church JA. Ann Allergy Asthma Immunol. 2006;97:73–77

PURPOSE OF THE STUDY. To determine the age at which nut-allergic and nonallergic children can accurately identify various nuts.

STUDY POPULATION. Thirty-seven children who were allergic to peanut or tree nuts (TNs) and 63 nonallergic children.

METHODS. A “nut box” was constructed with peanuts (shelled and unshelled) and 9 different TNs fastened to its base in separate compartments. The box was covered with a clear top for easy viewing and to prevent accidental exposure. Children were asked to identify any peanuts they saw in the box. They then were asked to identify each TN in the box. Children were asked to identify which nuts they could not eat.

RESULTS. Twenty-three children were allergic only to peanut, 5 were allergic to peanut and at least 1 TN, 5 were allergic to all TNs and peanut, 3 were allergic to ≥2 TNs, and 1 was allergic to ≥3 TNs. On average, children identified 2.7 nuts, with no difference between allergic and nonallergic children. Among allergic and nonallergic children, older children identified more nuts correctly. There was a better correlation of age with number of nuts identified correctly in the allergic ($r = 0.82$) than in the nonallergic ($r = 0.52$) group ($P < .001$ for each group). Ten children (9 <5 years old) did not identify any nuts correctly. Twenty-eight children identified only peanut in the shell. An additional 21 children identified only 2 nuts correctly, 13 of whom only identified shelled and unshelled peanut. Eighty-nine percent of those who correctly identified a nut recognized peanut in the shell, and 52% recognized shelled peanut. Although there were few differences between allergic and nonallergic children, the allergic children were less likely to recognize peanut either in the shell (81.1% vs 93.7%; $P = .052$) or shelled (29.7% vs 65.1%; $P < .001$). Of the 37 allergic children, 12 (32%) correctly identified the nut(s) to which they were allergic. Another 15 children (41%) said they would eat none of the nuts, and 10 (27%) indicated that they would eat ≥1 nut to which they were allergic.

CONCLUSIONS. Peanut- and TN-allergic children can identify few nuts, which places them at increased risk of accidental ingestion of a food to which they are allergic. Avoidance and correct identification of the nuts to which a child is allergic should be part of an overall educational plan.

REVIEWER COMMENTS. Most allergists instruct strict avoidance of all TNs to their sensitive patients to decrease the risk of accidental ingestion of the offending nuts(s). Because of the high rate of TN sensitization in peanut-allergic patients and vice versa, many also recommend avoidance of TNs and peanut in both groups. Considering the high rate of misidentification of peanut and TNs in this study, that advice seems prudent. Furthermore, nuts are frequently present in small pieces in baked products, etc, and cannot easily be identified. Most patients are satisfied with the safety of complete avoidance. If a patient is intent on eating TNs to which he or she is not known to be sensitive, I recommend waiting until he or she is mature enough to correctly identify TNs proven to be safe by a thorough allergy evaluation. Even then, I recommend eating the “safe” TN from the shell.

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Accidental Ingestions in Children With Peanut Allergy

PURPOSE OF THE STUDY. To determine the current frequency of accidental exposures occurring in peanut-allergic children and identify factors associated with exposure.

STUDY POPULATION. Children 4 years of age and older, who were diagnosed with peanut allergy at the Montreal...
Children’s Hospital Allergy Clinic (Quebec, Canada) between January 2000 and February 2005.

METHODS. Parents of children with peanut allergy completed questionnaires about accidental exposure to peanut occurring over the preceding year. Details of the accidental exposure requested included age of the child, quantity and type of food ingested, location of ingestion, allergic symptoms, onset and duration of reaction, and treatment administered. Medical charts were reviewed to confirm eligibility criteria, demographic information, atopic history, family history, details of the initial and most severe accidental reaction, number of previous accidental reactions, and previous use of epinephrine.

RESULTS. A total of 252 (57.7%) of 437 parents of children with peanut allergy completed a questionnaire. Chart review allowed comparison between participants and nonparticipants. Of participants, 62% were boys and the mean age was 8.1 years. The mean age at diagnosis was 2 years. There were 35 accidental exposures among 29 children over a period of 244 patient-years (annual incidence rate: 14.3%). Reactions were mild (15), moderate (16), and severe (4). Of the 20 children with reactions that were moderate to severe, only 4 received epinephrine. Eighty percent of children attended schools that prohibit peanut; only 1 accidental exposure occurred at school. Neither univariate nor multivariate logistic regression analyses identified any clinically important associations with inadvertent exposure to peanut.

CONCLUSIONS. Children with peanut allergy residing in Quebec had an annual incidence rate of accidental exposure to peanut of 14.3%. This finding is substantially lower than previously reported incidence rates. Predictors of accidental exposure could not be identified.

REVIEWER COMMENTS. In this study, only 1 of 35 accidental exposures occurred in school. Coupled with the lower incidence of accidental exposures reported in this study, these data may suggest that enhanced education about and awareness of peanut allergy in the public sector have been effective. The majority of accidental exposures occurred at the patient’s home (14) or the home of a friend or relative (12), which underscores the critical importance of education of the family, friends, and caregivers of children with peanut allergy.

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Peanut Allergen Exposure Through Saliva: Assessment and Interventions to Reduce Exposure

PURPOSE OF THE STUDY. To determine the impact of food allergy on the daily life and activities of food-allergic children and their families.

The Impact of Food Allergy on the Daily Activities of Children and Their Families
STUDY POPULATION. The study included 87 families with food-allergic children who ranged in age from birth to 18 years and attended a regularly scheduled clinic visit at the University of Maryland allergy practice (Baltimore, MD).

METHODS. A 32-item questionnaire was completed by the caregiver of the food-allergic child. The questionnaire evaluated the caregiver’s perception of the impact of the child’s food allergy on 8 aspects of daily family activities: meal preparation, family social activities, caregiver-supervised child social activities, autonomous child social activities, school activities, family relations, caregiver stress and free time, and employment and finances. The caregiver rated each item as to its affect on a 7-point scale (1 indicating not at all and 7 indicating very much).

RESULTS. More than 60% of the families reported that food allergy affected meal preparation, and approximately ≥50% families indicated that food allergy significantly affected their family social activities. Greater than 50% of the caregivers felt that food allergy affected their child’s “playing at friend’s house” as well as autonomous social activities such as birthday parties and sleepovers. Forty-one percent of caregivers reported significant impact on their stress levels secondary to their child’s food allergy. Food allergy seemed to have a smaller impact on school attendance; only 34% of the families reported a significant affect, and 10% reported choosing to homeschool their children because of the food allergy. Parental employment, finances, and family relations were not significantly affected. The total number of food allergies for each child was significantly associated with the impact of food allergy on activity scores; however, neither the specific food to which the child was allergic nor the history of a previous anaphylactic reaction was related. Having a comorbid condition such as asthma and/or atopic dermatitis did not significantly affect the results.

CONCLUSIONS. Food allergy has a significant effect on the activities of daily living. Additional studies are needed to determine more detailed effects of food allergy on parent-child interactions, family relationships, and child development.

REVIEWER COMMENTS. It is important that the medical community recognize not only the medical significance of a food-allergy diagnosis but the emotional significance as well. Often, parents are unsure of where to turn for help. The Food Allergy & Anaphylaxis Network (www.foodallergy.org) is a helpful resource for the nuts and bolts of avoidance and strategies for day-to-day living. Children with food allergies may be at risk for difficulties with their social and emotional development. Thus, it is important that pediatric health practitioners address these issues with children and their families and, if needed, refer to mental health services.

Use of Complementary and Alternative Medicine by Food-Allergic Patients

PURPOSE OF THE STUDY. To determine the prevalence of complementary and alternative medicine (CAM) use, the types of CAM modalities used, and opinions regarding CAM in food-allergic patients.

STUDY POPULATION. A total of 442 individuals were polled, 95% of whom were parents of food-allergic children. Two groups were evaluated by using an anonymous questionnaire: attendees at a Food Allergy & Anaphylaxis Network conference in 2002 and a convenience sample from the Pediatric Allergy and Immunology practice of Mount Sinai Medical Center (New York, NY). Three hundred eighty individuals filled out questionnaires, equal numbers from both groups.

METHODS. A 19-item questionnaire was constructed to collect data on types, frequency, and opinions of CAM use, severity of food allergy, and demographic information.

RESULTS. Diagnostic modalities considered unproven or disproven (including immunoglobulin G4 testing, kinesiology, electrodermal skin testing, and provocation testing) were used by 22% of the respondents. Chiropractors (10%) were the most common CAM providers, followed by homeopaths (5%), acupuncturists (4%), and herbologists (4%). Of food-allergic CAM users, 33% reported using chiropractic, 33% homeopathy, 17% Nambudripad’s allergy-elimination technique, 12% acupuncture, 9% massage, 6% acupuncture, and 3% reflexology. Sources of information about CAM included friends (39%), family (28%), the Internet (8%), and television (6%). Only 49% of the participants reported CAM use to their regular physicians. On a scale from 0 (not effective) to 5 (very effective), patients found that CAM therapies were not particularly effective (mean score: 2.08). If available, an herbal therapy of equal efficacy, safety, and cost was preferred as compared with a pharmaceutical drug (37% vs 12%; \( P = .001 \)).

CONCLUSIONS. Unproven or disproven diagnostic methods and CAM treatments were used by ~20% of the respondents (most of whom were parents of food-allergic patients). Most of those who used CAM noted poor efficacy, but if given a choice, many would prefer herbal therapies to pharmaceutical drugs.
ANAPHYLAXIS

Administration of Epinephrine for Life-Threatening Allergic Reactions in School Settings

PURPOSE OF THE STUDY. To ascertain the incidence of anaphylaxis in schools, characterize the circumstances surrounding anaphylactic episodes, and evaluate practices that are used to manage students with life-threatening allergies.

STUDY POPULATION AND METHODS. School districts in Massachusetts (N = 109) that completed an epinephrine-administration form whenever epinephrine was injected at school. Data were obtained from September 2001 to August of 2003.

RESULTS. Forty-eight school districts noted a total of 159 administrations of epinephrine during the 2-year period of reporting. The individual was not known to have a life-threatening allergy in 24% of the cases. Thirty-one percent of the students who received epinephrine had allergy to multiple antigens, and 25% had allergy to tree nuts or peanuts only. Nineteen percent of the cases occurred outside the school building on a playground or when transporting them to or from school or on field trips. The registered school nurse in the health office administered the epinephrine in most cases. The average time from development of symptoms until epinephrine was delivered was 10 minutes. In 92% of the cases, the student involved was taken to a medical facility using the emergency medical system.

CONCLUSIONS. Anaphylactic reactions in schools, although not frequent, are not uncommon events. A systematic review of anaphylactic events that required epinephrine administration identified opportunities for improvement in the treatment of students with life-threatening allergies.

REVIEWER COMMENTS. The limitation of this study is that it was based on voluntary reporting. There are variations in reporting among regions in the state, but it is not possible to determine if the differences are attributable to reporting practices or actual difference in epinephrine administration. Because there were no unique identifiers for subjects in the study, there is no assurance that allergy events are not recurring repeatedly in the same student. In summary, a thorough program should be in place in the schools to evaluate, treat, and manage students with life-threatening anaphylaxis to foods.

Parental Knowledge and Use of Epinephrine Auto-injector for Children With Food Allergy

PURPOSE OF THE STUDY. To assess parental use and knowledge of an epinephrine autoinjector (EAI), Anapen, prescribed for their food-allergic child(ren), and to examine the availability of emergency kits and personalized care plans.

STUDY POPULATION. The parents of 152 food-allergic children prescribed an EAI between June 2000 and March 2003 at 1 of 5 children’s hospitals in northern France.

METHODS. An anonymous-questionnaire format was used to collect details on the child’s clinical manifestations of allergies, EAI education by a health care provider, verification of proper EAI use at each follow-up visit, availability of a personalized care plan at school, physician instructions in case of allergic reaction, and medications available at home or outside the home. Parents were also asked to list symptoms that required epinephrine (open-ended item).

RESULTS. One hundred nine families representing 111 children completed and returned the survey. The majority (90%) of families had the use of Anapen demonstrated (76% with a trainer device), and 83% had received written instructions. Nineteen percent had a repeat demonstration at follow-up visits, and 10% never received a demonstration; yet, 88% of parents felt that they could use an EAI in an emergency. Only 54% of school-aged children had a personalized care plan, and 11% had an EAI at school with no personalized care plan. Only 48% of the parents could list >1 symptom that required an EAI. There was no difference in the quality of instructions between pediatricians and allergists and no difference in knowledge between parental socioeconomic groups.

CONCLUSIONS. EAs and personal care plans were insufficiently available at schools and in daily life. Proper EAI use and education were unsatisfactory.

REVIEWER COMMENTS. This study emphasized the importance of extensive and repeated education about food-allergy risks and measures that need to be in place in case of an emergency. Although a majority of parents felt that they knew how to use an EAI, many could not recognize >1 symptom that would require the use of an EAI, and
nearly half of the patients did not have an EAI or emergency plan available at school. A disturbing number (10%) of parents never received EAI education, and for those who received education, only a few (19%) had a review of instructions at follow-up. Repeated EAI education is important, because skills acquired at the initial visit are likely to be lost if they are not practiced, and failure to reiterate the importance of knowing how or when to use an EAI may contribute to parents’ indifferent attitude about carrying an EAI or submitting an appropriate personal care plan to the child’s school.

Pediatric Emergency Department Anaphylaxis: Different Patterns From Adults

PURPOSE OF THE STUDY. Data on acute pediatric anaphylaxis presentations to the emergency department (ED) are limited.

STUDY POPULATION. Patients under 16 years of age who presented to a metropolitan, pediatric teaching hospital ED in Australia over a 3-year period with generalized allergic reactions (skin and/or gastrointestinal symptoms) and anaphylaxis (respiratory, cardiovascular, or hypotensive symptoms) that satisfied relevant International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic codes.

METHODS. Medical charts were reviewed for incidence, comorbidities, likely etiology, clinical features, management, and disposal.

RESULTS. There were 526 children with generalized allergic reactions (9.3 per 1000 ED presentations) and 57 with anaphylaxis (1 per 1000 ED presentations) included. There were no fatalities. For anaphylaxis cases, a cause was recognized in 68% (food: 56% of total; drug: 5%; sting: 5%; other: 2%), cutaneous features were present in 83%, a past history of asthma was reported in 37%, adrenaline was used in 39%, and follow-up was arranged for 81% (only 28% with an allergy clinic).

CONCLUSIONS. The incidence of generalized allergic reactions of 9.3 in 1000 was greater than in the adults.

REVIEWER COMMENTS. Food, drug, and stinging-insect reactions are the primary causes of anaphylaxis in children (as in adults). Although skin symptoms are present in the majority, the lack of such symptoms should not exclude the diagnosis. All children who suffer an anaphylactic event deserve a consult to an allergist who can confirm the diagnosis, determine or confirm the cause, and instruct the patient on avoidance measures, emergency treatment for subsequent events should they occur, and provide a prognosis regarding possible resolution.

ATOPIC DERMATITIS
Age Related, Structured Educational Programmes for the Management of Atopic Dermatitis in Children and Adolescents: Multicentre, Randomised Controlled Trial

PURPOSE OF THE STUDY. To determine the effects of age-related, structured educational programs on the management of moderate-to-severe atopic dermatitis in childhood and adolescence.

STUDY POPULATION. A total of 992 of 1010 patients who were eligible for the study were given random group assignment. Children aged 3 months to 18 years were enrolled in group sessions of standardized intervention programs for atopic dermatitis once weekly for 6 weeks in a multicenter trial in Germany.

METHODS. The study was a randomized, controlled intervention trial. The 3 participating groups were parents of children with atopic dermatitis who were 3 to 7, 8 to 12, or 13 to 18 years old. Participants were recruited from 7 hospitals in Germany. The inclusion criteria were (1) diagnosis of atopic dermatitis according to predefined criteria, (2) eczema duration of at least 3 months, and (3) severity of eczema of at least 20 points on the scoring-of-atopic-dermatitis scale. Each treatment group received a tailored (age-specific) educational program once weekly for 2 hours over the course of 6 weeks. The control groups did not receive any education. Participants in the intervention and control groups were followed up at 6 and 12 months. Primary outcome measures were the differences in severity of eczema based on the scoring-of-atopic-dermatitis scale as well as parents’ quality of life over 12 months.

RESULTS. Significant improvements in severity of eczema were seen in all intervention groups compared with control groups after 12 months on the basis of the severity score. Moreover, improvement in quality of life for mothers of children aged 3 months to 7 years was significantly greater in the intervention group for all 5 subscales of the quality-of-life questionnaire and for mothers of children aged 8 to 12 years for 3 of the subscales.
CONCLUSIONS. Age-related educational programs for the control of atopic dermatitis in children and adolescents are effective in the long-term management of the disease.

REVIEWER COMMENTS. This study showed that educational interventions that use a multidisciplined approach that addresses psychosocial, pharmacologic, and nutritional factors served to decrease the severity of atopic dermatitis in the intervention groups. However, severity of disease was seen to decrease as well in the control groups that did not participate in the intervention programs despite having similar pharmacologic interventions in both groups. The authors attributed this finding to the assumption that the control groups were also highly motivated and tried to optimize therapies. Nonetheless, such standardized educational/support groups seem to have beneficial consequences in children as well as parents dealing with this chronic illness.

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Skin Colonization by *Staphylococcus aureus* in Patients With Eczema and Atopic Dermatitis and Relevant Combined Topical Therapy: A Double-Blind Multicentre Randomized Controlled Trial


PURPOSE OF THE STUDY. To investigate the colonizing features of *Staphylococcus aureus* in the lesional and nonlesional skin of patients with eczema and atopic dermatitis (AD) in China and to compare the therapeutic effect of mupirocin plus hydrocortisone butyrate with vehicle ointment plus hydrocortisone butyrate.

STUDY POPULATION. There were 327 patients with AD and eczema (177 male and 150 female); 75 were aged <10 years, 48 between 10 and 18 years, and 204 >18 years.

METHODS. A multicenter, double-blind randomized trial was conducted. Eczema area and severity index scores were evaluated before the start of the trial and on the 7th, 14th, and 28th day of treatment. Swabs for bacterial isolation were taken from lesional skin before the start of the trial and on the 7th, 14th, and 28th day of treatment and from nonlesional skin only before the start of the trial. A combination topical therapy with mupirocin plus hydrocortisone butyrate ointment was used in the experimental group, with vehicle ointment plus hydrocortisone butyrate ointment as a control.

RESULTS. Of 327 patients enrolled onto the study, bacteria were isolated from 74.8% of lesional and 34% of nonlesional skin samples from patients with AD, of which *S. aureus* accounted for 79.8% and 80.5%, respectively. The colonization density of *S. aureus* was markedly higher in lesional than in nonlesional skin and was positively correlated with lesion severity. Both groups had equivalent clearing of AD and improvement of skin lesions. The patients with severe AD improved faster with combination therapy compared with monotherapy with hydrocortisone butyrate ointment. However, the patients with severe AD were equivalent at days 14 and 28.

CONCLUSIONS. This study confirmed that lesional skin of patients with AD was more frequently colonized with *S. aureus* than was nonlesional skin. The more severe the eczema, the higher the colonization rate of *S. aureus*. *S. aureus* infection is related to the pathogenesis of eczema and AD. An antibiotic-corticosteroid combination and corticosteroid alone both provided good therapeutic effect in eczema and AD, and both reduced colonization by *S. aureus*. Early combined topical therapy is beneficial to patients with moderate-to-severe eczema and AD, and it is unnecessary to use antibiotics at later stages of disease or in mild eczema or AD.

REVIEWER COMMENTS. *S. aureus* colonization has been recognized as a long-standing issue in AD. This study confirmed a high rate of colonization and correlation with AD severity. The important new finding was that treatment with topical steroids only decreased *S. aureus* colonization without treatment of antibiotics. This is important as the rate of resistant *S. aureus* rises. Maintaining good control of AD will keep the use of unnecessary antibiotics down. Therefore, antibiotic treatment is probably just necessary for the patients with severe AD flares.

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The Role of Immune Response to *Staphylococcus aureus* Superantigens and Disease Severity in Relation to the Sensitivity to Tacrolimus in Atopic Dermatitis


PURPOSE OF THE STUDY. To examine the prevalence and role of *Staphylococcus aureus* superantigens on the pathophysiology and immunosuppressive drug sensitivity in patients with atopic dermatitis (AD).

STUDY POPULATION. Twenty-nine patients with AD and 13 healthy control patients were included in the study.

METHODS. Twenty-nine patients with AD were classified into 2 groups on the basis of their clinical AD scores: a low-score group (n = 14), corresponding to patients with mild-to-moderate AD, and a high-score group (n =
corresponding to patients with severe AD. Plasma antistaphylococcal enterotoxin B or toxic-shock syndrome toxin-1 (TSST-1) immunoglobulin E (IgE) levels were measured for the patients and healthy subjects by enzyme-linked immunosorbent assay. Also, individual drug sensitivity was estimated by determining the drug concentrations that would provide 50% inhibition (IC50) of peripheral blood mononuclear cell (PBMC) proliferation in vitro.

RESULTS. The levels of plasma antistaphylococcal enterotoxin B or TSST-1 IgE in the patients with severe AD were significantly higher than those in the patients with mild-to-moderate AD (P < .05 and P < .01, respectively). When stimulated with concanavalin A in vitro, PBMCs in the patients with severe AD exhibited low sensitivity to the suppressive efficacy of tacrolimus (FK506) as compared with the patients with mild-to-moderate AD (P < .01). Furthermore, there was a significant correlation between the IC50 values of FK506 and plasma anti–TSST-1 IgE levels (P < .01).

CONCLUSIONS. PBMCs in patients with severe AD exhibited lower sensitivity to FK506 and had higher plasma levels of anti–TSST-1 IgE as compared with the patients with mild AD. *S. aureus* superantigens seem to be one of the causes of decreased PBMC sensitivity to FK506; therefore, an alternative treatment would be useful on the basis of individual drug-sensitivity data and anti–TSST-1 IgE levels.

REVIEWER COMMENTS. Patients with AD commonly develop superinfections that require antimicrobial treatment. This study suggests that untreated superinfection may contribute to the ineffectiveness of topical medications that are commonly used as routine skin care for patients with AD. Attentiveness to the presence of concomitant skin infection is necessary for comprehensive skin care for patients with AD.
tion in a large subset of patients highlights the importance of the epidermal barrier in the pathogenesis of these disorders.

REVIEWER COMMENTS. The filaggrin gene encodes a structural protein that is essential for skin-barrier formation. Infants and children with atopic dermatitis are at high risk for developing additional atopic disorders, including food allergy, allergic rhinitis, and asthma. A disrupted skin barrier may be an important portal of entry for environmental and food allergens. In animal models, exposure through the skin predisposes to development of immunoglobulin E sensitization. Early intensive efforts to maintain and restore skin-barrier function may prevent subsequent development of allergic diseases and stop the progression of the atopic march.

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Clinical Effects of Probiotics Are Associated With Increased Interferon-\(\gamma\) Responses in Very Young Children With Atopic Dermatitis

PURPOSE OF THE STUDY. The authors recently demonstrated that young children with moderate-to-severe atopic dermatitis (AD) had significant clinical improvement in the severity and extent of their disease with the use of probiotics. The purpose of this study was to assess the effects of probiotics on underlying immune function and relate that to clinical improvement.

STUDY POPULATION. Fifty-six Australian children aged 6 to 23 months with moderate-to-severe AD (based on a modified scoring AD [SCORAD] index of ≥25).

METHODS. Subjects were randomly assigned to receive probiotics (\(1 \times 10^9\) colony-forming units of Lactobacillus fermentum; \(n = 26\)) or placebo (\(n = 27\)) twice daily for 8 weeks. Peripheral blood mononuclear cells were isolated from 53 children at baseline and at 8 and 16 weeks (8 weeks after the supplementation period). Cytokine (interleukin 5 [IL-5], IL-6, IL-10, IL-13, interferon \(\gamma\) [IFN-\(\gamma\]), and tumor necrosis factor \(\alpha\) [TNF-\(\alpha\)]) responses to allergens (egg ovalbumin, \(\beta\)-lactoglobulin, and house dust mite), vaccines (tetanus toxoid and diphtheria toxoid), intestinal flora (heat-killed \(L\) fermentum), skin flora (heat-killed Staphylococcus aureus), \(S\) aureus enterotoxin B (SEB), and mitogen (phytohemagglutinin) were assessed.

RESULTS. The children who received probiotics showed a significant increase in T-helper 1 cytokine IFN-\(\gamma\) responses to SEB and phytohemagglutinin at 8 and 16 weeks compared with baseline. The increase in IFN-\(\gamma\) response to SEB was directly proportional to the decrease in the severity of AD during the study period. After supplementation with probiotics (week 8) children had significantly higher TNF-\(\alpha\) responses to heat-killed \(L\) fermentum and heat-killed \(S\) aureus compared with those in the placebo group. This was not sustained at 16 weeks. IL-13 (a T-helper type 2 cytokine) responses to ovalbumin decreased significantly during the supplementation period, but this was not sustained after its discontinuation. No other effects of probiotics were seen on allergen-specific responses.

CONCLUSIONS. Probiotics led to an increase in IFN-\(\gamma\) responses to nonspecific stimuli (SEB and phytohemagglutinin) and an increase in TNF-\(\alpha\) responses to skin and intestinal flora. Clinical improvement in AD severity with probiotics was associated with significant increases in the T-helper 1 IFN-\(\gamma\) responses and altered responses to skin and intestinal flora but not consistent effects on allergen-specific responses.

REVIEWER COMMENTS. It is interesting to note that this study did not show any consistent effects of probiotics on allergen-specific responses, which suggests more of an impact on innate immune pathways rather than allergen-specific ones. The results of this study show some promise for the use of probiotics in children with AD. However, there are many variables that need to be addressed, such as impact of underlying food allergy, exposure to antibiotics, and environmental factors. Larger studies are needed to further demonstrate clinical efficacy (short-term and long-term), to determine optimal timing and dosing of treatment, to further investigate immunologic mechanisms, and to determine the impact of probiotic treatment on later development of other atopic disorders (eg, asthma) in young children with AD.

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Allergic Rhinitis and Its Consequences on Quality of Sleep: An Unexplored Area

PURPOSE OF THE STUDY. Allergic rhinitis (AR) is common and has been shown to impair social life and sleep. Patients with severe symptoms may have more sleep disturbances than those with a mild form of the disease, but this has never been assessed with a validated tool. The objective of this study was to assess, in patients with AR, whether duration and severity of AR are associated with sleep impairment.

METHODS. A nationwide controlled, cross-sectional epidemiologic study was conducted. A representative sample of 260 French ear, nose, and throat and allergy specialists enrolled 591 patients aged 18 to 50 years with AR of at least 1 year’s duration. Sleep disorders, sleep quality, and AR were assessed by using validated tools (Sleep Disorders Questionnaire, Epworth sleepiness scale, and score for allergic rhinitis). The severity of AR was assessed by using the allergic rhinitis and its impact on asthma classification.

RESULTS. All dimensions of sleep were impaired by AR, particularly by the severe type. Sleep was significantly more impaired in patients with severe AR than in those with the mild type. The duration of AR (intermittent or persistent) had no effect on sleep.

CONCLUSIONS. These data underline the close relationship between AR and sleep and highlight the need for clinicians, particularly general practitioners, to be attentive in this respect.

Reviewer Comments. This was the DREAMS study (Etude Descriptive des Rhinites Allergiques et des Modifications du Sommeil), and although that is really cute, I am not sure it is truly fair to use the authors’ native French to make an English acronym. Anyway, the main weakness here is that they did not perform sleep studies on the patients. Nonetheless, they used validated instruments (questionnaires) to establish the severity of the AR and its impact on sleep quality. There is no reason to think that similar effects would not also occur in children with AR. The study also points out the importance of understanding the effects of AR on many quality-of-life indicators.

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Intracranial Complications of Sinusitis in Children and Adolescents and Their Outcomes

PURPOSE OF THE STUDY. To evaluate the presentation, imaging, microbiology, treatment, and outcome of intracranial complications of sinusitis in children.

STUDY POPULATION. The study included 25 consecutive children and adolescents treated for intracranial complications of sinusitis over a 5-year period.

METHODS. This was a retrospective chart review of patients who were identified by screening admission diagnoses for central nervous system infections including intracranial abscesses, meningitis, encephalitis, and dural sinus thrombophlebitis. These records were cross-referenced for both procedure codes for external and endoscopic sinus surgery and diagnosis of acute or chronic sinusitis.

RESULTS. Twenty-five consecutive patients were identified, with ages ranging from 4 to 18 years; 19 patients were male and 6 were female. There were 35 intracranial complications: 13 epidural abscesses, 9 subdural empyemas, 6 meningitis, 2 dural sinus thromboses, and 1 middle cerebral artery ischemia. Nine patients (36%) had >1 intracranial complication. Ten patients (44%) also had at least 1 extracranial complication: 5 with orbital cellulites, 4 with orbital/periorbital abscess, 1 with forehead abscess, and 1 with forehead edema. Seventy percent of the patients with extracranial complications had epidural abscess as their intracranial complication. In addition, 12 patients (48%) presented with neurologic signs and symptoms, most commonly change in mental status (9 patients) or hemiparesis (5 patients). Of the 13 who presented without neurologic signs and symptoms, 9 (69%) had epidural abscess as their only intracranial complication. Fifteen patients had computed tomography imaging with contrast, identifying 12 (63%) of 19 complications in those patients. MRI was performed in 19 patients, identifying 26 (93%) of 28 complications in those patients. Cultures grew multiple organisms in more than one half of the patients, 53% of which were Streptococcus species. Outcomes were divided into 3 groups. No patient in group 1 (14 patients) had neurologic deficits or events. All the patients in group 1 underwent endoscopic sinus surgery (100%), and 7 (50%) underwent a neurosurgical procedure. By definition, there were no short-term or long-term sequelae for the children in group 1. Group 2 included 8 patients who experienced short-term neurologic sequelae only. Seven patients of group 2 underwent endoscopic sinus surgery (88%), and 5 (63%) underwent a neurosurgical procedure. Group 3 included 3 patients who experienced permanent neurologic deficits (bilateral sensorineural hearing loss for one and hemiparesis, expressive aphasia, and seizures for the other) or death. Two patients in group 3 underwent endoscopic sinus surgery (67%), and 1 (33%) underwent a neurosurgical procedure.

CONCLUSIONS. Intracranial complications of sinusitis in children present diagnostic challenges, because many patients lack a history of sinusitis and present with...
vague, nonlocalizing signs and symptoms. Aggressive medical and surgical management may limit morbidity and improve outcomes. Early imaging is crucial to diagnosis, and MRI is the most useful test.

REVIEWER COMMENTS. Intracranial complications of sinusitis remain uncommon; even in this review from a tertiary pediatric center only 5 patients per year were identified. A high index of clinical suspicion, particularly in adolescent boys, should lead to early imaging for diagnosis. Medical therapy combined with neurosurgical and otolaryngological surgical interventions may improve outcomes and reduce short-term and long-term sequelae.

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Outcome of Endoscopic Sinus Surgery in Children With Allergic Rhinitis

PURPOSE OF THE STUDY. To compare results of endoscopic sinus surgery for treatment of chronic rhinosinusitis in children with and without documented allergy.

STUDY POPULATION. One hundred forty-one children (aged 3–13 years) with chronic rhinosinusitis who were followed for at least 12 months after endoscopic sinus surgery and had symptoms assessed by caregiver questionnaire were included in this study. All children were evaluated for allergy, immunoglobulin deficiency, and cystic fibrosis before surgery. A total of 77 children had documented allergy, and 64 had negative allergy evaluations. The allergic and nonallergic children were similar with regard to gender distribution, tobacco exposure, and disease severity, but asthma was more than twice as prevalent in the allergic group (56% vs 23%). Children with cystic fibrosis, immunodeficiency, fungal infection, or previous sinus surgery were excluded from the study. Surgery usually consisted of middle meatal antrostomy and anterior ethmoidectomy.

METHODS. Symptoms were evaluated by the caregiver using a nonvalidated questionnaire before surgery and every 3 months for at least 12 months after surgery. The results of the questionnaire 12 months after surgery were used to create 2 groups: (1) cured or improved subjects were categorized as successful, and (2) subjects with unchanged or worsened symptoms and those who required additional surgery were categorized as treatment failures. Medical treatment for sinusitis included long-term antibiotics, intranasal steroids, decongestants, antireflux treatment, systemic steroids, and allergy management. Allergy management consisted of antihistamines and intranasal steroids in all allergic children and immunotherapy in 25%. One third of allergic patients underwent endoscopic sinus surgery before initiation of allergy treatment.

RESULTS. The overall success rate for endoscopic sinus surgery was 80%. The allergic group had a 77% success rate after sinus surgery, whereas the nonallergic group had an 84% success rate, a difference that was not statistically significant. Multivariate analysis was performed, and the presence of allergy did not predict a poorer outcome. Allergic children who underwent sinus surgery without preoperative allergy treatment had a 62% success rate, compared with a success rate of 84% for children who were treated for allergy before surgery.

CONCLUSIONS. The presence of allergy does not predict poorer outcomes after sinus surgery in children. Preoperative treatment of such allergy improves surgical results.

REVIEWER COMMENTS. This article demonstrated that endoscopic sinus surgery can effectively treat refractory sinusitis in children even when allergy is documented. The standard practice of allergy evaluation and treatment before sinus surgery in children was also supported, although the details of such evaluation were not addressed in this article. Because this was a cohort study, not a randomized, controlled trial, we cannot assess the effects of allergy management alone on children with chronic sinusitis. It is curious that the group of children who had allergy treatment before surgery had better surgical results at a 12-month follow-up than the others with allergy, because we would suspect that all children diagnosed with allergy would be treated for allergy at some point before or after surgery. The indications for endoscopic sinus surgery in children, and the extent of such surgery, remain debated. This article adds to evidence that such surgery is effective for refractory sinusitis, even in allergic children.

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Asthma

**PATHOPHYSIOLOGY**

**Reduced Lung Function at Birth and the Risk of Asthma at 10 Years of Age**


**PURPOSE OF THE STUDY.** To evaluate whether reduced lung function at birth predicts the development of asthma and markers of obstructive airway diseases by 10 years of age.

**STUDY POPULATION.** A prospective cohort of 616 10-year-old Norwegian children from the Environmental and Childhood Asthma (ECA) study who were initially enrolled as healthy term infants and had undergone lung-function testing and passive respiratory mechanics evaluation shortly after birth.

**METHODS.** Lung function at birth was measured by calculating the fraction of time to peak expiratory flow to total expiratory time ($T_{PEF}/T_{E}$) on the basis of tidal breathing flow-volume loops. Respiratory mechanics at birth were assessed by calculating respiratory system compliance and resistance during passive maneuvers. Data at the 10-year follow-up were collected during 2 clinical visits including forced expiratory flow-volume loops, methacholine-challenge tests, a treadmill exercise test, and skin-prick testing for common inhalant and food allergens. Parents also completed a validated International Study of Asthma and Allergies in Childhood questionnaire on airway symptoms, asthma-medication use, and previous physician-diagnosed asthma. The follow-up assessments and interviews were blinded with regard to the lung-function measurements at birth.

**RESULTS.** In this cohort, the prevalence of a history of asthma was 20.2%, and prevalence of current asthma was 11.1%. Children with a $T_{PEF}/T_{E}$ at or below the median at birth were more likely at 10 years of age to have a history of asthma (24.3% vs 16.2%; $P = .01$), current asthma (14.6% vs 7.5%; $P = .005$), severe bronchial hyperresponsiveness (9.1% vs 4.9%; $P = .05$), and inhaled corticosteroid use (5.9% vs 2.4%; $P = .02$). Children with respiratory system compliance at or below the median were more likely to have a history of asthma (27.4% vs 14.8%; $P = .001$) and current asthma (15.0% vs 7.7%; $P = .009$). Decreased lung-function measurements did not consistently correlate with percent predicted forced flow-volume loops and exercise testing.

**CONCLUSIONS.** Reduced lung function at birth may be a risk factor for the development of asthma by 10 years of age.

**REVIEWER COMMENTS.** Other studies to date have shown that infants with reduced lung function have an increased risk for wheezing and asthma in the first few years of life. This study suggests that measuring lung function at birth may be useful in predicting which infants will develop asthma by late childhood. Knowing these risks may allow for directed therapy and prevention.

**Lung Function and Exercise Capacity in Young Adults Born Prematurely**


**PURPOSE OF THE STUDY.** To determine long-term effects of prematurity on lung function (volumes, diffusing capacity) and exercise capacity in ex-preterm infants compared with healthy peers.

**STUDY POPULATION.** Preterm participants ($n = 42$) and healthy term controls ($n = 48$) were recruited for lung-function and exercise tests.

**METHODS.** Part of a prospective nationwide Dutch study, children born in 1983 with a gestational age of <32 weeks and/or a birth weight under 1500 g were followed up to 19 years of age. Measurements included spirometry, diffusing capacity ($DL_{CO}$), and bicycle ergometer test.

**RESULTS.** Most lung-function measurements were within the reference ranges for both groups. Preterm birth was associated with lower forced expiratory volume in 1 second (preterm infants: 95% predicted; controls: 110% predicted) and $DL_{CO}$, single breath corrected for hemoglobin (88% predicted vs 96% predicted compared with control subjects at follow-up). Exercise capacity was 15% lower in ex-preterm infants than in control subjects. The anaerobic threshold, maximum minute ventilation, and maximum heart rate as percentage predicted were significantly lower in ex-preterm infants compared with control subjects.

**CONCLUSIONS.** Long-term effects of prematurity were airway obstruction and a lower diffusing capacity compared with control subjects, although mean lung-function parameters were within the reference ranges. Ex-preterm infants had a lower exercise level, which could not be explained by impaired lung function or smoking habits but might be a result of impaired physical fitness.

**REVIEWER COMMENTS.** We all see ex-preterm patients in our practices, and there have been conflicting data on lung function as adolescents. No previous studies on exercise capacity have been performed. Without the control group included, one could have concluded that almost all participants had lung-function measurements within the reference ranges. Ex-preterm infants reported fewer...
hours of exercise per week than the control subjects, which might explain their lower level of physical fitness. Diminished exercise capacity did not seem to be a result of impaired lung function or limited ventilation. We might want to encourage all children who were born prematurely to participate in more physical activity and sports at an early age, because this might possibly improve the exercise performance of those in this group.

CONCLUSIONS. Many adults with a history of moderate-to-severe allergic asthma in childhood have irreversible lung-function deficits. Childhood parameters that might identify such individuals at a young age include spirometry, duration of asthma, methacholine sensitivity, and birth prematurity.

REVIEWER COMMENTS. The authors pointed out that their findings mesh with others’ observations of early disease magnitude, including measurable airway obstruction, which serves as a major predictor of continuation of significant disease into adulthood. Should not every child on maintenance asthma-drug therapy have spirometry results documented, if not monitored? Because all subjects in the current study were allergic, allergy itself did not stand out here as a risk factor, although it most definitely was. To date, no drug-therapy intervention convincingly alters this disease entrenchment.

Irreversible Lung Function Deficits in Young Adults With a History of Childhood Asthma

PURPOSE OF THE STUDY. Asthma is traditionally characterized as reversible airway obstruction. Yet, it is readily apparent that some individuals develop varying degrees of fixed obstruction associated with structural changes in the airway and that such a course is often marked early in life. These investigators sought to study the frequency, severity, and reversibility of pulmonary deficits in adults with a history of previously well-characterized moderate-to-severe childhood allergic asthma.

STUDY POPULATION. Subjects (N = 121) previously enrolled onto a randomized trial of immunotherapy for childhood asthma were recalled. This original group, aged 5 to 12 years at randomization between 1984 and 1994, had physician-diagnosed asthma and required daily medications for at least 1 year before enrollment. The original study evaluations included daily symptom diaries, home visits, allergy skin testing, and methacholine challenges with associated spirometry. The primary outcome variable was daily medication-useage score as a measure of disease severity. No differences between the placebo and active-immunotherapy groups were appreciated over the course of the study; both groups saw decreases in medication use and methacholine sensitivity.

METHODS. With the current study, an attempt was made to contact all 121 original study subjects, now aged 18 to 31 years. Subjects underwent spirometry and allergy skin testing, and interim medical histories were taken. Individuals with postbronchodilator forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), or FEV1/FVC of ≤5th percentile or at least 2 of these parameters at <10th percentile were categorized as abnormal. These subjects were prescribed 1 mg/kg per day prednisone for 1 week before follow-up pulmonary-function testing, physical examination, and a chest radiograph to assess steroid responsiveness of lung deficits.

RESULTS. Of the 84 subjects reevaluated, 40 (48%) had ≥1 abnormal spirometric index (P < .0001). Of these 40 subjects, 28 were reassessed after prednisone, and 21 (75%) did not improve. Adult and childhood spirometric results were positively correlated. Abnormal adult spirometric results were associated with a longer duration of asthma at enrollment in the original trial, increased childhood methacholine sensitivity, and birth prematurity. Childhood immunotherapy status was unrelated to adult lung function.

Allergy Skin Test Responses During Experimental Infection With Respiratory Syncytial Virus

PURPOSE OF THE STUDY. To determine if a viral upper respiratory infection affects allergy skin-test responsiveness.

STUDY POPULATION. Sixteen adults experimentally exposed to respiratory syncytial virus (RSV).

METHODS. Subjects without concurrent upper or lower airway disease were cloistered and inoculated with 106 plaque-forming units of RSV type B. Daily physical examination and symptom scores were recorded. Nasal lavages were performed and stored at −70°C for RSV-antigen assay and culture. Blood samples were obtained for immunoglobulin E (IgE) measurement on days 0, 2, 4, 6, 8, 10, and 21. Skin-prick testing was performed for 17 locally relevant aeroallergens and controls on days 0, 3, 6, and 21.

RESULTS. Eight patients had ≥1 positive skin-test result at baseline and were considered atopic. Eleven (5 atopic, 6 nonatopic) had evidence of postinoculation RSV infection. Atopic patients had a higher IgE level at baseline as
compared with nonatopic subjects (123 ± 80 vs 45 ± 36 IU/mL; P < .01). There was no change in total IgE level in those in the nonatopic group, but the atopic subjects had a nonsignificant increase in IgE level on days 8 and 10 (146 ± 112 IU/mL). Of the 8 nonatopic patients, only 3 had negative skin-test results to all antigens on all 3 postinoculation test days. The mean number of positive wheal responses to allergens for all patients was 1.7 ± 2.3, 4.4 ± 3.8, 3.6 ± 3.5, and 3.9 ± 3.6 at baseline and days 3, 6, and 21, respectively (P < .01 versus baseline for all pairings). For patients with positive skin-test results at baseline, mean wheal and flare area provoked by those allergens increased after RSV exposure. The increased number of positive responses to skin testing was noted for both seasonal and perennial aeroallergens.

CONCLUSIONS. The results may have some implication in explaining complications of RSV infection such as otitis media, asthma exacerbation, and subsequent development of asthma.

REVIEWER COMMENTS. There has long been a chicken-and-egg question when it comes to RSV infection in childhood and subsequent development of asthma. That is, does RSV predispose to later recurrent wheezing illnesses, or does the predisposition to wheeze lead to worse outcomes with RSV infection? Are children with an atopic predisposition more likely to have a severe RSV infection, or are those with severe infection more likely to develop atopy? This small study did not answer the question, but it provides a hint that RSV infection itself might affect immunologic responsiveness to aeroallergens, at least in the short-term. The study results cannot be extrapolated to make any long-term conclusions. Furthermore, the study was undertaken in healthy adults. It would be unethical to intentionally infect infants and toddlers with RSV at an age when they might be most susceptible to the risks of environmental influences on the development of atopy and to the risks of the infection itself.

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Suppression of IFN-Gamma Production in Atopic Group at the Acute Phase of RSV Infection

PURPOSE OF THE STUDY. Several studies have suggested that respiratory syncytial virus (RSV) bronchiolitis induces a change in the cytokine-production profile in childhood. The authors of this study sought to determine if the RSV-induced cytokine production was affected by the patient’s atopic background.

STUDY POPULATION. Fourteen children between 1 month and 14 years of age who were admitted to the hospital with RSV infection and divided into 2 groups: those who were nonatopic and those who were atopic.

METHODS. Interferon-γ (IFN-γ) and interleukin 4 (IL-4) in the supernatant of peripheral blood mononuclear cells was measured after culture for 24 hours in the presence of phytohemagglutinin, IL-12, or IL-18.

RESULTS. In RSV-infected infants with atopic diseases, IFN-γ production from IL-12– or especially IL-18–stimulated peripheral blood mononuclear cells was subtotally suppressed in the acute phase, whereas in RSV-infected infants without atopic diseases, IFN-γ production was not suppressed in the acute phase.

CONCLUSIONS. The IFN-γ suppression observed in the atopic group was not caused by the immaturity of the infants’ immune system, because reduced IFN-γ production to RSV was not observed in the infants in the nonatopic group. IFN-γ suppression in regard to RSV infection might be caused by some genetic factor involved in the development of atopic disease, such as IL-18 signal cascade.

REVIEWER COMMENTS. Several studies have suggested a link between RSV infection and the development of persistent wheezing later in childhood. However, a causal role for RSV infection in early life in the development of asthma is not clear. The results of this study indicate that there may be a genetic predisposition to T-helper 2–type immune responses to RSV in atopic children, which might play a role in the development of recurrent wheezing in this subset of children.

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Asthma Severity and Atopy: How Clear Is the Relationship?

PURPOSE OF THE STUDY. The term “atopy” can refer to allergic conditions such as allergic rhinitis, asthma, eczema, and food allergy, which cluster in families. It can also be defined as the tendency to generate an immunoglobulin E (IgE) response to specific allergens. Is there a relationship between such IgE responses and the severity of asthma?

STUDY POPULATION. The study included 400 children (aged 7–18 years) with asthma (documented episodes of wheezing in the previous 12 calendar months and physician diagnosis).

METHODS. Patients completed a standardized observer-administered International Study of Asthma and Allergies in Childhood questionnaire and underwent baseline spirometry, skin-prick testing (SPT) to dust mites, grass mix, cat, dog, cockroach and Alternaria, and measure-
agement of total serum IgE level. Atopy was defined as at least 1 SPT wheal >3 mm or a total serum IgE level of >100 IU/mL.

RESULTS. Total IgE was associated with increased asthma-severity score, decreased forced expiratory volume in 1 second ( FEV₁ ) ( mean IgE with FEV₁ < 80% predicted: 812; mean IgE with FEV₁ > 80%: 449 ), and risk of hospital admission ( mean IgE with hospitalization in last year: 726; no hospitalization: 392 ). Increasing skin-prick–test reactivity was associated with increased risk of hospital admission ( mean sum of SPT wheals with hospitalization in last year: 12.1 mm; no hospitalization: 6.5 mm ).

CONCLUSIONS. In children with asthma, increasing atopy is associated with increasing asthma severity.

REVIEWER COMMENTS. The majority of children with asthma have allergy, and the more allergy they have, the worse their asthma is. This is almost certainly a causal relationship; not surprisingly, inhaling things to which you are allergic can worsen your asthma. This reinforces the importance of assessing the allergic status of all children allergic can worsen your asthma. This reinforces the importance of assessing the allergic status of all children with asthma and reducing the exposure for those whose allergies are amenable to environmental control (dust mites, furry pets, mold, and cockroach).

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β2-Adrenoceptor Polymorphisms and Asthma From Childhood to Middle Age in the British 1958 Birth Cohort: A Genetic Association Study

PURPOSE OF THE STUDY. To determine if functionally relevant polymorphisms in the β2-adrenoceptor gene ( ADRB2 ) could predict prognosis in childhood asthma and determine long-term asthma prevalence.

STUDY POPULATION. Participants of a previously studied United Kingdom birth cohort ( N = 8018 ) that had been followed to 35 years were followed for an additional 10 years. The participants were identified before the age of 16.

METHODS. Parental interviews were conducted at ages 7, 11, and 16 years followed by patient interviews at ages 23, 33, and 42 years regarding history of wheezing and asthma. Those with a childhood history of wheezing had spirometry performed at age 34 to 35, and repeated at age 44 to 45. DNA blood samples were also obtained at ages 44 to 45. The variants in the coding region selected for genotyping were Arg16Gly, Gln27Glu, and Thr164Ile. A separate population of severely asthmatic subjects was recruited to search for potential novel polymorphisms within the ADPB2 gene. The effect of ADPB2 variants on the prevalence and severity of asthma and/or wheezing in childhood (7 years old) and adulthood (at 42 years old) and the persistence of wheezing illness from childhood (age 0–16 years) into adulthood (42 years old) were studied.

RESULTS. No single-nucleotide polymorphism was associated with lifetime onset of asthma or onset of asthma during any specific age range during childhood or adulthood. In comparing the frequency and prevalence of the 3 genotypic variants to the prognosis of children with wheeze or asthma, asthma persistence was associated with both the Arg16 and Gln27 alleles. The association with asthma prognosis could not be related to allergy. No significant associations were found with spirometry results and the polymorphisms. No new coding variants were discovered. Meta-analyses of previously published studies, together with the data from this study, showed that the previously described associations of the Gln27Glu and Arg16Gly variants with either asthma or severity, in both children and adults, were lost by inclusion of the results of this study.

CONCLUSIONS. The Arg16 and Gln27 polymorphisms may have a small effect on prognosis of wheezing in childhood with persistent asthma and/or wheezing. However, asthma prevalence in the British population was not related to any β2-adrenoceptor polymorphisms.

REVIEWER COMMENTS. Although previous studies have focused on correlating genotypic determinations in position 16 and 27 of ADPB2 with asthma severity, this unique birth-cohort study examined these genotypic associations with asthma prevalence and prognosis. The small prognostic effect of the Arg16 and Gln27 polymorphisms (being more common in those with persistent wheezing or asthma) seen in this study needs to be confirmed by additional studies. If confirmed, one could genotypically identify children with asthma who are more likely to have persistence of symptoms. In addition, one could determine if long-term asthma outcomes after early and persistent therapeutic interventions in children were genotype related.

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Endotoxin Exposure Is a Risk Factor for Asthma: The National Survey of Endotoxin in United States Housing

PURPOSE OF THE STUDY. Studies have shown that endotoxin exposure associated with living in farm environments correlates with protection from atopy and asthma. Other studies offer conflicting data. The authors considered the possibility that regional sampling within the United States might explain such discrepancies.
STUDY POPULATION. Household dust samples were assayed from 831 housing units that were selected as demographically representative of the 96 million homes in the United States.

METHODS. Data gathered on all household occupants included diagnosed hay fever, diagnosed asthma, asthma symptoms in the past year, current asthma-medication use, and wheezing (ever, in the past month, and in the past year). Field-workers distributed questionnaires and collected dust samples, which were processed for endotoxin. Adjusted odds ratios (ORs) were calculated, controlling for census region, season, frequency of indoor cigarette smoking, education, poverty, race, ethnicity, presence of a ≤6-year-old child, and exposure to dust mite, cat, and dog allergens.

RESULTS. The highest endotoxin concentrations were found in dust from kitchen and living room floors (geometric means: 80.5 and 63.9 EU/mg, respectively). The lowest concentration was found in the bedding (18.7 EU/mg). In multivariate analysis, endotoxin exposure was significantly associated with multiple asthma outcomes, with the strongest for bedroom-floor and bedding endotoxin concentrations. No protective effects of endotoxin were seen. Instead, bedroom-floor-endotoxin concentrations above the first quartile (>16.6 EU/mg) had adjusted ORs of 1.95 to 2.78 for asthma symptoms in the past year, wheezing in the past month, and wheezing at any time compared with those in the first quartile. Similarly, bedding concentrations above the second quartile (>19.6 EU/mg) demonstrated adjusted ORs of 2.01 to 2.05 for wheezing at any time, in the past year, and in the past month compared with those in the first 2 quartiles. The authors noted that the endotoxin levels in the samples were higher than in similar data from Europe. Subanalysis showed no significant adjusted ORs for children, indicating that adults were responsible for the endotoxin effects found. Allergic subjects had no increase in asthma symptoms compared with nonallergic subjects with higher endotoxin exposure.

CONCLUSIONS. In a broad sample of US housing, a significant correlation between household endotoxin and asthma outcomes was demonstrated, driven largely by adults. No protective effect of endotoxin exposure was seen. Current endotoxin exposure had little impact on allergy status. Instead, household endotoxin exposure seemed to be a significant risk factor for increased asthma prevalence.

REVIEWER COMMENTS. These data from the National Survey of Lead and Allergens in Housing demonstrate a positive correlation between asthma symptoms in occupants and increasing endotoxin exposure. The implications and sources of higher endotoxin exposures in the United States, noted by the authors, must be considered in this and other studies. Because this study was cross-sectional rather than longitudinal, it could not assess the impact of early endotoxin exposure on the development of asthma and atopy. Thus, the study suggests that endotoxin is a risk factor for asthma and wheezing, but it neither supports nor contradicts the hygiene hypothesis of the development of atopy.

PURPOSE OF THE STUDY. The cysteinyl leukotrienes (cysLTs), derived from the 5-lipoxygenase pathway, play an important role in asthma as smooth muscle constrictors of airways and microvasculature. This study investigated a potential additional role of cysLTs in the Th1 helper 2 (Th2) cell-dependent pulmonary inflammation using an ovalbumin-sensitization and -challenge protocol with mice that lacked LTC4 synthase (LTC4S), the terminal pathway enzyme for cysLT biosynthesis.

METHODS. LTC4S-null mice and wild-type mice underwent intraperitoneal ovalbumin sensitization, followed on days 40, 43, and 46 by intranasal ovalbumin or saline challenge. Pulmonary histology was examined 48 hours after the last challenge. Total and ovalbumin-specific serum immunoglobulin (Ig) levels, cytokine mRNA expression in the lung, cytokine production by parabronchial lymph node cells after in vitro ovalbumin restimulation, delayed-type hypersensitivity, and airway hyperresponsiveness to methacholine 24 hours after the last challenge were measured also.

RESULTS. In the LTC4S-null mice, antigen-induced pulmonary inflammation (eosinophil infiltration and goblet cell hyperplasia) and airway hyperresponsiveness to methacholine were significantly reduced. In addition, antigen-specific serum immunoglobulin E and G1 and Th2 cell cytokine messenger RNA expression in the lung were reduced in LTC4S-null mice compared with wild-type controls. The production of Th2 cytokines by antigen-restimulated parabronchial lymph node cells from LTC4S-null mice was also significantly reduced compared with those from wild-type controls; however, there was no suppression of cutaneous delayed-type hypersensitivity in LTC4S-null mice.

CONCLUSIONS. These findings support a role for cysLTs in the development and/or amplification of a pulmonary Th2 response.

REVIEWER COMMENTS. Two types of leukotriene-based medications have been used to treat patients with bronchial asthma: (1) leukotriene inhibitors that block the actual
by differences in child or family characteristics. These racial disparities could not be completely explained by influencing factors that might explain those differences.

PERCENT OF THE STUDY. To evaluate the differences in asthma prevalence and emergency department (ED) visits between non-Hispanic black and white children, as well as the factors that might explain those differences.

STUDY POPULATION. Cross-sectional study of 14,487 non-Hispanic black children and 49,042 non-Hispanic white children interviewed from 1997 to 2003 as part of a large, nationally representative sample.

METHODS. Information was collected as part of the National Health Interview Survey, a cross-sectional, in-person, household interview administered annually by the Centers for Disease Control and Prevention. Data were obtained on lifetime asthma, current asthma, ED visits in the previous year, age, gender, birth weight, family income, rural versus urban environment, type of health insurance, accessibility of routine medical care, and maternal history of asthma, smoking, depression, and BMI.

RESULTS. Being black was associated with a 20% greater likelihood of having current asthma as well as a greater likelihood of having gone to the ED for asthma treatment in the past year. Furthermore, this increased asthma risk was greatest in younger children and remained even after child and family characteristics were controlled for.

CONCLUSIONS. Black children were more likely to have asthma and to have experienced ED visits in the past year than were otherwise comparable white children; these racial disparities could not be completely explained by differences in child or family characteristics.

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Racial Disparities in Childhood Asthma in the United States: Evidence From the National Health Interview Survey, 1997 to 2003
McDaniel M, Paxson C, Waldfogel J. Pediatrics. 2006;117(5). Available at: www.pediatrics.org/cgi/content/full/117/5/e868

PURPOSE OF THE STUDY. To evaluate the validity and reliability of the asthma-control test (ACT) and assess its responsiveness to changes in asthma control over time in a sample of patients who were new to the care of an asthma specialist.

STUDY POPULATION. Participants were asthmatic subjects (N = 313) aged ≥ 12 years who had not consulted an asthma specialist within 5 years and had a previous diagnosis of asthma.

METHODS. This prospective trial was conducted in 6 asthma specialty practices. Participants were evaluated at 2 physician office visits (a baseline visit and a follow-up visit separated by 4–12 weeks) in which they completed the ACT, the Asthma Control Questionnaire (ACQ), and prebronchodilator measurements of forced expiratory volume in 1 second (FEV1). The ACT is a 5-item patient-administered survey for assessing asthma control. Each of the 5 questions is given a score from 1 to 5. Responses from the ACT are summed to yield a score that ranges from 5 (poor control) to 25 (complete control). Asthma specialists, who were blinded to the

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DIAGNOSIS AND MANAGEMENT

Asthma Control Test: Reliability, Validity, and Responsiveness in Patients Not Previously Followed by Asthma Specialists

PURPOSE OF THE STUDY. To evaluate the validity and reliability of the asthma-control test (ACT) and assess its responsiveness to changes in asthma control over time in a sample of patients who were new to the care of an asthma specialist.

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METHODS. This prospective trial was conducted in 6 asthma specialty practices. Participants were evaluated at 2 physician office visits (a baseline visit and a follow-up visit separated by 4–12 weeks) in which they completed the ACT, the Asthma Control Questionnaire (ACQ), and prebronchodilator measurements of forced expiratory volume in 1 second (FEV1). The ACT is a 5-item patient-administered survey for assessing asthma control. Each of the 5 questions is given a score from 1 to 5. Responses from the ACT are summed to yield a score that ranges from 5 (poor control) to 25 (complete control). Asthma specialists, who were blinded to the
ACT and ACQ results, rated asthma control on a 5-point Likert scale (not completely controlled to completely controlled) based on history, physical examination, FEV₁ scores, and National Asthma Education and Prevention Program–defined goals for asthma control. Reliability, validity, and responsiveness were all tested via comparison of the ACT results to the specialists’ evaluation, the ACQ scores, and the FEV₁ scores.

RESULTS. Participants (N = 313) had a mean age of 35 years (12–84 years). At baseline, specialists rated asthma control as well controlled or completely controlled (48%), somewhat controlled (29%), and not controlled (23%). The reliability of the ACT was tested by internal consistency and test-retest methods. The internal consistency was .85 for the initial visit (n = 313) and .79 for the follow-up visit (n = 248). The test-retest assessment among 86 patients with the same specialist rating for asthma was .77. The criterion validity was based on comparisons between the ACT scores at the baseline visit and the specialists’ assessment as well as the ACQ scores and FEV₁ values. All of these comparisons were found to be statistically significant. The discriminant validity was measured in 3 ways: the asthma specialists’ rating, percent predicted value of FEV₁, and treatment recommendation of the asthma specialists. As predicted, patients with low ACT scores correlated with diagnoses of poorer control by asthma specialists. Patients with low FEV₁ scores also scored lower on the ACT, and patients who required an increase in their therapy had lower scores on this questionnaire. The responsiveness of the ACT was also measured by assessing the changes in scores between the initial and follow-up visits. Moderate correlations existed between the ACT and the asthma specialist’s score, whereas changes in the ACT and ACQ were found to be highly consistent. Changes in FEV₁ and ACT were only minimally correlated. An ACT score of ≥19 identified patients with poorly controlled asthma (71% sensitivity; 71% specificity).

CONCLUSIONS. The ACT was reliable, valid, and responsive to changes in asthma control over time in a sample of patients who were new to the care of an asthma specialist.

REVIEWER COMMENTS. These authors have further shown the value of the ACT in assessing asthma control in the practice of asthma specialists. In a day when physicians are pressed for time when evaluating patients, it is important to find effective tools that are reliable, valid, responsive, and practical to assist in patient evaluations. Additional work is needed to assess the usefulness of the ACT within primary care, where it may prove to be even more valuable in assessing asthma control.

The Influence of Variation in Type and Pattern of Symptoms on Assessment in Pediatric Asthma

PURPOSE OF THE STUDY. To examine the asthma-related health burden in US children.

STUDY POPULATION. Participants were US children (aged 4 to 18 years) with current asthma during February to May, 2004, identified in a telephone-based survey. Asthma was defined as ever having a physician diagnosis of asthma and either using current asthma medication or having asthma symptoms in the past year.

METHODS. In this telephone-based study, 41 433 households were screened to provide 1089 children reporting current asthma and 801 completed interviews. Interviews were completed by parents for children 4 to 15 years old (84.6%) and the children themselves when they were 16 to 18 years old (14.6%). Symptoms, perceived level of control, activity limitation, health care use, medications, disease management, and knowledge were assessed. Global asthma-symptom burden was composed of short-term symptom burden (4-week recall), long-term symptom burden (past year), and functional impact (activity limitation) based on National Asthma Education and Prevention Program (NAEPP) guidelines. Asthma was classified on the basis of symptoms in 3 categories: mild-intermittent, mild-persistent, and moderate/severe-persistent (combined into 1 category) asthma.

RESULTS. Eighty percent of the children were classified as having mild-intermittent asthma on the basis of daily symptoms; however, this percentage decreased to 64% when nighttime symptoms were considered. In contrast, on the basis of the global asthma-symptom burden, only 13% of the children were classified as having mild-intermittent disease, whereas 62% were classified as having moderate/severe disease. Of children with moderate/severe asthma, 54% reported complete asthma control despite meeting criteria for more moderate/severe-persistent disease. Asthma impact on daily activity was substantial, with 47% of the children avoiding exertion and 34% staying inside to control asthma symptoms.

CONCLUSIONS. The majority of children had not achieved the goals of asthma treatment based on NAEPP guidelines. In addition, parents and their children overestimated the child’s asthma control and commonly restricted activities to control asthma symptoms.

REVIEWER COMMENTS. Why is there a rift between what patients or their parents perceive as their level of asthma control and their actual control measured against NAEPP-guideline goals? The level of control perceived by pa-
tients and their parents seems worse when more detailed or specific questions are asked about asthma burden. As demonstrated by this study, limitation in activity level or staying indoors are “common” methods to control asthma symptoms despite contradictory reporting that exercising and participating in outdoor activities are important to children. Unfortunately, many children are not meeting the NAEPP guidelines’ goals of removing self-imposed limitations to control a child’s asthma. It is notable that this study did not account for current asthma medications that could result in underclassification of disease burden. This study provides another wake-up call that asking specific questions during patient encounters and education regarding symptom-control expectations are worthwhile, because there can be misperception of control by patients and their parents.

Classification of Asthma Severity in Children: The Contribution of Pulmonary Function Testing

PURPOSE OF THE STUDY. To evaluate whether adding lung-function measurements to clinical history changes asthma-severity classification and, thus, treatment decisions.

STUDY POPULATION. Inner-city children with asthma from 2 asthma study cohorts: 257 children from cohort 1 (1992–1994) and 383 from cohort 2 (1998–2001). On the basis of the age range of the available reference for pulmonary-function values, analyses were restricted to children aged 8 to 11 years.

METHODS. Data collected from both studies included a comprehensive history, allergy skin testing, and pulmonary-function tests. Each child’s asthma severity was classified according to the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 2 guideline on the basis of their symptom frequency alone. Participants were classified into 3 severity levels: mild-intermittent, mild- persistent, and moderate-to-severe–persistent asthma. Then, those participants with abnormal results of the pulmonary-function test (forced expiratory volume in 1 second [FEV₁] and/or peak expiratory flow [PEF] rate) were reclassified on the basis of symptom-frequency data plus pulmonary-function results.

RESULTS. Among children with symptoms consistent with mild-intermittent asthma, 22.8% in cohort 1 and 27.7% in cohort 2 would be reclassified as having moderate-to-severe–persistent asthma. Among children with symptoms consistent with mild-persistent asthma, 31.2% in cohort 1 and 33.3% in cohort 2 would be reclassified as having moderate-to-severe–persistent asthma. Among children who were already classified as having moderate-to-severe–persistent asthma according to their symptoms alone, 22.3% in cohort 1 and 44.2% in cohort 2 had abnormal pulmonary function.

CONCLUSIONS. Approximately one third of the children in each cohort were reclassified to higher NAEPP asthma-severity categories when pulmonary function was considered in addition to symptom frequency. The results demonstrate that the current NAEPP severity-assessment algorithm is highly dependent on the availability of symptom-frequency and pulmonary-function data.

Exhaled Nitric Oxide in Asthma: Variability, Relation to Asthma Severity, and Peripheral Blood Lymphocyte Cytokine Expression

PURPOSE OF THE STUDY. To measure and compare exhaled nitric oxide (eNO) levels in patients with asthma and healthy volunteers, to study peripheral blood lymphocyte cytokine expression, and to study the relationship between eNO and intracellular cytokine expression.

STUDY POPULATION. A total of 36 subjects were enrolled onto the study, with 19 asthmatic patients and 17 healthy control subjects.

METHODS. At least once per week for 4 weeks, patients with asthma visited the clinic and underwent a detailed history, physical examination, spirometry, and eNO-level measurement. These patients were maintained on established pharmacologic therapy regimens. A blood
sample was taken and analyzed by flow cytometry. eNO was measured by using an NO analyzer. Univariate linear regression analysis was used to determine correlations between continuous variables and eNO concentrations.

RESULTS. eNO levels were significantly elevated in patients with moderate-to-severe asthma compared with those in healthy subjects (18.53 ± 2.00 vs 5.90 ± 0.90 ppb). With treatment, eNO levels in patients with moderate-to-severe asthma decreased to levels near those of the healthy subjects by 4 weeks. Interferon γ expression was decreased in patients with moderate-to-severe asthma. An elevated eNO level was also associated with decreased interleukin 4 and interleukin 13 cytokine expression in CD8 lymphocytes.

CONCLUSIONS. eNO levels were elevated in patients with moderate-to-severe asthma. With 4 weeks of treatment, eNO levels in patients with moderate-to-severe asthma were no different from those in the control subjects. There was decreased interferon γ expression by the CD4- and CD8-positive peripheral blood lymphocytes of patients with moderate-to-severe asthma. Elevated eNO levels were associated with suppression of both T-helper 1 and 2 cytokine expression by the peripheral blood lymphocyte, suggesting a systemic immunomodulatory effect.

REVIEWER COMMENTS. This study adds to the growing information on the utility of eNO levels to monitor asthma-treatment response. It demonstrates how eNO can be used to measure the reduction in airway inflammation as a response to treatment primarily in patients with moderate-to-severe asthma. At this point, it is not clear what the implications are of the association between elevated eNO levels and cytokine suppression.

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Cardiopulmonary Exercise Testing in Children and Adolescents With Asthma Who Report Symptoms of Exercise-Induced Bronchoconstriction
Joyner BL, Fiorino EK, Matta-Arroyo E, Needleman JP. J Asthma. 2006;43:675–678

PURPOSE OF THE STUDY. To use cardiopulmonary exercise testing (CPET) to establish the cause of exercise limitation in a population of children with asthma who were reporting symptoms of exercise-induced bronchoconstriction (EIB).

STUDY POPULATION. A total of 42 children (aged 7 to 19 years) who continued to report exercise-associated symptoms attributed to asthma despite daily controller therapy were included in the study. There were 22 boys and 20 girls. All patients were receiving daily inhaled corticosteroids and had normal pulmonary function at the time of the study. Patients were excluded if they had underlying cardiac disease, had another chronic lung disease, or were unable to ride the cycle ergometer.

METHODS. Each patient’s BMI was calculated, and baseline spirometry was performed. Then, the patients performed cycle ergometry with a ramp protocol to voluntary exhaustion to determine maximal oxygen consumption (V˙O2). Spirometry was repeated at intervals of 5 and 20 minutes. A decrease of 10% in forced expiratory volume in 1 second was considered a positive finding of EIB.

RESULTS. Ten patients (24%) developed EIB after CPET. There were no significant differences in BMI, BMI z score, V˙O2, or initial pulmonary function between the subjects who developed EIB and those who did not.

CONCLUSIONS. Exercise limitation without EIB was found in both obese and nonobese patients, suggesting that poor fitness is a problem independent of body habitus. Including CPET in the management of children with suspected EIB would provide a better understanding of the etiology of their symptoms and facilitate more appropriate treatment.

REVIEWER COMMENTS. This study illustrates how a patient’s BMI does not directly correlate with fitness levels. Nonobese individuals can be just as out of shape as obese individuals. Given the trend toward more obesity in this country, it is important to not let any generalizations based on body habitus affect our judgment as physicians. Therefore, when a nonobese individual presents with symptoms similar to EIB, it may be prudent to have them undergo CPET before labeling them as asthmatic.

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The Impact of Spirometry on Pediatric Asthma Diagnosis and Treatment

PURPOSE OF THE STUDY. To evaluate the use of spirometry as a diagnostic tool in a pediatric asthma-management program at an inner-city community health clinic.

STUDY POPULATION. The study profiled 56 pediatric patients who presented with respiratory symptoms that were indicative of an acute asthma exacerbation.

METHODS. Clinicians recorded each patient’s history of asthma symptoms as well as heart rate, respiratory rate, and pulse oximetry. Patients then were assessed for current asthma symptoms and given an initial assessment of asthma, upper respiratory infection, or both. An initial treatment plan for nonreactive airway management, al-
buterol, yellow-zone management, and/or prednisone/ prelone treatment was recorded. After the initial symptom-based diagnosis, a pulmonary-function test was performed by using spirometry measurements. The clinician concluded the visit by making a final assessment of asthma or upper respiratory infection and assigned a final treatment plan that was based on standardized asthma plans.

RESULTS. The most frequently reported physical symptom was general coughing (73.2%), followed by nighttime cough (50.0%), wheezing (35.7%), and trouble sleeping because of cough (21.4%). Approximately two thirds of the patients in this population had abnormal values of forced expiratory volume in 1 second. Physicians changed 30.4% of the patients’ treatment plans after viewing spirometry results.

CONCLUSIONS. Spirometry is an objective tool that can help prevent misclassification of asthma severity and inappropriate use of asthma medication among pediatric patients with asthma. The use of spirometry made an impact in asthma diagnosis at this inner-city clinic: nearly one third of the patients had their treatment plans changed after the spirometry results were viewed.

REVIEWER COMMENTS. The emphasis of this study was to examine the impact of spirometry results on physician behavior in the acute setting. It demonstrates that when clinicians follow the National Asthma Education and Prevention Program guidelines for recommended spirometry use, there were considerable differences in recommendations for treatment. Ensuring appropriate diagnosis cannot solely rely on patients’ signs and symptoms; thus, pediatricians should consider spirometry in asthmatic children.

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

PURPOSE OF THE STUDY. To assess how preevaluation pulmonary-function tests (PFTs) influenced management decisions in children with asthma, beyond what was obtained from history and physical examination alone.

STUDY POPULATION. Children with asthma (N = 367) aged 4 to 18 years.

METHODS. Physicians and nurse practitioners in the outpatient pulmonary office evaluated the children and made initial treatment recommendations before reviewing the specific spirometry results. Any changes based on the test results were documented.

RESULTS. Spirometry results were abnormal in 45% of the visits, related to underlying asthma severity but not to clinical findings. PFT results changed management decisions in 15% of the visits. This frequency was not affected by the patient’s age, disease severity, symptom control, or examination findings. When spirometry results did not change treatment decisions, the provider was more likely to maintain therapy (58%) than to increase (17%) or decrease (24%) therapy. In contrast, when spirometry results did change treatment decisions, the provider was more likely to increase therapy (75%) than to maintain (20%) or decrease (5%) therapy.

CONCLUSIONS. Without PFTs, providers often overestimated the degree of asthma control. This incorrect assessment could have resulted in suboptimal therapy.

REVIEWER COMMENTS. This was a very practical clinical study that addressed a common clinical scenario that physicians who treat asthma face daily in clinical practice. Ideally, the patient’s presenting clinical history, physical examination, and PFT result should all be factored into the final clinical decision regarding asthma therapy. The data from this investigation demonstrate that spirometry results were abnormal in almost one half of the visits, and this was related to underlying asthma severity and not clinical findings. When the spirometry results did not enter into the management decision, therapy was generally maintained; however, when spirometry results were factored in, the provider was more likely to increase therapy. With this in mind, proper interpretation of PFT data should help prevent overestimation of the degree of asthma control and help prevent suboptimal therapy. An obvious extension of this investigation would be the examination of serial PFTs in patients with asthma to identify clinically relevant trends in these data to assist in the best possible decision-making regarding ongoing asthma therapy and control.

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Predictors of Early Hospital Readmission for Asthma Among Inner-City Children

PURPOSE OF THE STUDY. To identify modifiable predictors of early readmission in inner-city children with asthma.

STUDY POPULATION. All pediatric patients aged 0 to 21 years who were discharged with a primary diagnosis of asthma during the study period were identified from a single hospital. Case patients were those who were readmitted with asthma within 30 days of discharge, and controls were those who were not readmitted. A total of 152 case patients and 293 controls who met the inclusion criteria were used in this study.

METHODS. Medical chart reviews were performed on the selected patients. Information was collected on demo-
RESULTS. Case patients were more likely to have been hospitalized for asthma in the past 12 months (odds ratio [OR]: 2.22; 95% confidence interval [CI]: 1.40–3.50), to have visited the emergency department for asthma in the past 12 months (OR: 3.28; 95% CI: 1.55–6.94), to have a history of an ICU admission for asthma (OR: 1.87; 95% CI: 1.26–3.78), to have received a pulmonary consultation during the index admission (OR: 1.87; 95% CI: 1.12–3.10), and to have been prescribed inhaled corticosteroids before the index admission (OR: 1.61; 95% CI: 1.02–2.52). Multivariate analysis revealed that a history of asthma hospitalization within the past 12 months was an independent predictor of early readmission (OR: 1.89; \( P = .021 \)).

CONCLUSIONS. A history of asthma hospitalization within the past 12 months was associated with early readmission. Modifiable factors such as medical treatment and management during and at discharge from the index admission did not predict early asthma readmission.

REVIEWER COMMENTS. In this largely minority population, with >50% covered by Medicaid, early readmission was increased in those with markers of more severe and persistent asthma. History of an asthma-related emergency department visit in the last year, ICU admission for asthma, or pulmonary consultation was associated with readmission. Children with a prescription for inhaled corticosteroid (ICS) before hospitalization were more likely to require readmission, yet no protective effect was identified for ICS prescription at the time of discharge. On multivariate analysis, early readmission was associated with hospitalization for asthma in the preceding 12 months. Although limited by its retrospective nature, this study indicates that children who frequently use tertiary care for asthma are at increased risk for early readmission and identifies at-risk asthmatic children who may benefit from targeted interventions at hospital discharge.

Aerosol Therapy by Pressured Metered-Dose Inhaler-Spacer in Sleeping Young Children: To Do or Not to Do?

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Improved Preventive Care for Asthma: A Randomized Trial of Clinician Prompting in Pediatric Offices

PURPOSE OF THE STUDY. To determine if clinician prompting regarding asthma severity and guideline recommendations at the time of an office visit improves the delivery of preventive asthma care.

STUDY POPULATION. Children aged 2 to 12 years (N = 226) with persistent asthma from 2 inner-city pediatric practices in Rochester, New York. Children were at the clinic for a well-child check, asthma care, or non–asthma-related illness care and were randomly assigned to 1 of 2 groups: clinician-prompting group (CPG) or standard-care group (SCG).

METHODS. A baseline survey was conducted to obtain information regarding household demographics, medication use, and environmental tobacco-smoke exposure. Parents of the children who were randomly assigned to the CPG were instructed to give a prompt sheet to their clinician along with a blank asthma action plan form. Parents of the children who were assigned to the SCG also completed baseline assessment interviews but were not given a prompt sheet, and no information regarding the interview was shared with the clinician. Follow-up information was collected within 60 days through telephone interviews.

RESULTS. The children in the CPG were more likely to have any preventive action related to asthma taken at the visit compared with children in the SCG (86.6% vs 69.3%). Children in the CPG were also more likely to have received an asthma action plan (50.0% vs 23.7%), recommendation for a specific asthma follow-up visit (53.6% vs 36.8%), discussion regarding asthma (75.0% vs 63.2%), and smoke-reduction counseling (57.5% vs 35.4%) compared with those in the SCG. There were no statistical differences in referrals for specialty care, treatment of comorbid conditions, or changes in preventive medications between the 2 groups.

CONCLUSIONS. Clinician prompting regarding asthma severity and care guidelines at the time of an office visit increased the likelihood of delivering preventive asthma care.

REVIEWER COMMENTS. Several studies have demonstrated that health care providers often underestimate asthma severity and have demonstrated poor adherence to National Asthma Education and Prevention Program guidelines. Successful management of asthma requires both accurate determination of asthma severity and proper treatment. This study demonstrates a method that may increase the likelihood of delivering preventive asthma care at non–asthma-related office visits by prompting clinicians. However, as the authors pointed out, although prompting improved the delivery of preventive asthma care, a large percentage of patients in the CPG did not have follow-up–visit recommendations (46.4%), received no asthma action plan (50%), and received no discussion related to asthma (25%). This study demonstrates that a better system needs to be implemented to increase the rate of delivering appropriate preventive care for patients with asthma.

Improved Asthma Outcomes in a High-Morbidity Pediatric Population: Results of an Emergency Department-Based Randomized Clinical Trial

PURPOSE OF THE STUDY. To determine if an emergency department–based asthma follow-up clinic could improve outcomes within a high-morbidity pediatric population.

STUDY POPULATION. Four hundred eighty-eight patients (aged 12 months to 17 years) from an emergency department at an urban tertiary care pediatric hospital with previous physician-diagnosed asthma and ≥1 unscheduled visit in the last 6 months and/or ≥1 hospitalization in the last 12 months.

METHODS. The subjects were recruited while they were still in the emergency department for their acute care visits. The subjects were randomly assigned to either a single visit to an asthma clinic located in the emergency department, where they met with an asthma educator and a physician, or the control group, which received printed information about asthma. Follow-up telephone interviews were conducted at 1, 3, and 6 months after enrollment.

RESULTS. One hundred seventy-two (70.5%) of the subjects who were randomly assigned to the intervention attended the clinic, and 167 of these subjects were prescribed inhaled corticosteroids. Compared with children in the control group, those in the intervention group had significantly fewer unscheduled visits for asthma care (mean: 1.39 vs 2.34; relative risk: 0.60); at 6 months, reported significantly more use of inhaled corticosteroids (49.3% vs 26.5%; relative risk: 2.03); reported “no limitation in daytime quality of life” significantly more often...
(43.8% vs 34.4%; relative risk: 1.36); and reported “no functional limitations in quality of life” significantly more often (49.8% vs 40.8%; relative risk: 1.33).

CONCLUSIONS. A single follow-up visit to an emergency department–based asthma clinic resulted in significant improvements in care and outcomes for a high-morbidity pediatric population.

REVIEWER COMMENTS. This study was unique in that the emphasis was on follow-up in a clinic in the emergency department where care was first given, rather than a primary care office. This intervention seems to have been more successful than previously published emergency department–based studies that focused on improving rates of follow-up with primary care providers. There are a number of possible explanations for these findings, including the fact that many families use the emergency department as a de facto primary care office and the comprehensive nature of the emergency department–clinic visit. Costs were not analyzed, and there may be other barriers to other emergency departments adopting an intervention of this type, but these results are promising.

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MEDICAL THERAPIES

Early Intervention of Recent Onset Mild Persistent Asthma in Children Aged Under 11 yrs: The Steroid Treatment As Regular Therapy in Early Asthma (START) Trial

PURPOSE OF THE STUDY. To determine the long-term efficacy of regular inhaled low-dose budesonide in children aged <11 years with recent-onset mild-persistent asthma.

STUDY POPULATION. Children aged 5 to 10 years with current symptoms of mild-persistent asthma during the 3 months preceding trial entry. Patients had no symptoms for >2 years before study entry and had received neither inhaled corticosteroids (ICSs) for ≥30 days nor depot corticosteroid injection in the previous year.

METHODS. Patients were randomly assigned to receive once-daily budesonide 200 µg (1000 children) or placebo (974 children). Patients were followed at weeks 6 and 12 and then subsequently every 3 months for a 3-year period. Patients and their caregivers kept a record of asthma symptoms between visits. At each visit, spirometry was performed, and data were collected on medication compliance and asthma control. The primary end point was the time to the first severe asthma-related event (SARE) or introduction of corticosteroid treatment other than the study medication.

RESULTS. There was a 40% relative-risk reduction of SAREs in the treatment group over the 3-year study visit. Fewer children in the budesonide group required treatment with other corticosteroids as compared with those in the placebo group (12.3% vs 22.7%). There was a trend toward decreased β2-agonist use, decreased systemic corticosteroid use, and improved lung function in the children in the treatment arm.

CONCLUSIONS. The early addition of once-daily budesonide treatment in young children with mild-persistent asthma improves asthma control and lung function and decreases the risk of SAREs.

REVIEWER COMMENTS. Early asthma intervention in children is a topic of much debate, particularly in the very young with mild symptoms. Oftentimes, caregivers are faced with the difficult task of deciding on the right time to initiate an ICS, and the decision may be delayed until a serious event such as hospitalization occurs. This study demonstrates the benefits of using an ICS as early intervention in children <11 years of age to improve lung function and decrease the risks of serious and potentially life-threatening asthma exacerbations. Unlike previous studies in pediatric populations with mild asthma, researchers with this study enrolled patients with relatively newly diagnosed asthma, perhaps before the onset of chronic irreversible inflammatory changes such as basement-membrane thickening. These findings support early intervention to improve lung function and to potentially prevent loss of lung function in hopes of improving long-term outcomes.

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Intermittent Inhaled Corticosteroids in Infants With Episodic Wheezing

PURPOSE OF THE STUDY. To determine the effectiveness of inhaled corticosteroid (ICS) in the treatment of wheezing in infants and if early ICS treatment will delay or prevent progression to persistent asthma.

STUDY POPULATION. Pregnant women (N = 798) with the diagnosis of asthma were enrolled onto a cohort study in Denmark. There were 411 newborns enrolled by 1 month of age.

METHODS. The patients were randomly assigned to ICS or placebo with their first episode of wheezing at a median of 10.7 months. Treatment with budesonide 400 µg per day with a spacer or placebo with spacer was begun after
the third day of the first wheezing episode and continued for at least 2 weeks. Terbutaline with the same delivery system was provided for as-needed use. Symptoms and β-agonist use were recorded daily for the 3 years of the study. One-hour study visits were conducted every 6 months. Nasal aspirates for viral culture and infant lung-function tests were monitored.

RESULTS. A total of 294 infants had at least 1 treatment with a total of 1661 episodes (577 episodes were not verified by an investigator). During the entire study, 83% of the ICS and 82% of the placebo days were symptom free. Twenty-four percent of the patients who received ICS and 21% who received placebo developed persistent symptoms. A respiratory virus was isolated in 369 (63%) of 583 episodes, but there was no relation to treatment outcome. Over the 3 years of the study, growth and bone mineral density (ultrasound technique) were not different in the groups.

CONCLUSIONS. Early intervention with ICS did not effect the duration of acute illnesses or progression to persistent disease.

REVIEWER COMMENTS. The results of this very important study were confounded by the effect of delaying 3 days to initiate therapy, the unclear efficacy of the delivery system, and that 40% of the events were not confirmed by the investigators.

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Long-term Inhaled Corticosteroids in Preschool Children at High Risk for Asthma

PURPOSE OF THE STUDY. To determine the role of inhaled corticosteroid (ICS) in preventing the development of asthma in a group of high-risk children before the development of symptomatic disease or abnormal lung function.

STUDY POPULATION. Subjects were 285 children aged 2 to 3 years at high risk for developing asthma.

METHODS. Subjects were assigned to fluticasone propionate (FP) 88 μg twice per day with a pressurized metered-dose inhaler with spacer or placebo for a 2-year treatment period. The patients were observed without treatment for 1 year.

RESULTS. During the 2-year treatment period, there was significant improvement in symptom-free days for those in the FP group (86.8%–85.9%). Children in the FP group had more episode-free days, decreased exacerbations, and decreased need for extra controller medication. Those in the ICS group had a 1.1-cm decrement in growth after the first 2 years of the study, but this difference decreased to 0.7 cm after the 1-year observation period.

CONCLUSIONS. Although ICS had a significant effect on the burden of asthma during the treatment period, there was no evidence that a long-term effect was carried over to the 1-year observation period.

REVIEWER COMMENTS. The burden of childhood asthma is benefited with administration of ICS, but there is no evidence that long-term disease modification occurs.

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Rapid Effects of Inhaled Corticosteroids in Acute Asthma: An Evidence-Based Evaluation
Rodrigo GJ. Chest. 2006;130:1301–1311

PURPOSE OF THE STUDY. To analyze available evidence on the early (1–4 hours) clinical impact of inhaled corticosteroids (ICSs) for adults and children with an acute asthma exacerbation in the emergency department (ED).

STUDY POPULATION. A total of 470 adults (≥18 years old) and 663 children (6 months to 17 years old) seen in the ED or an equivalent care setting with a diagnosis of acute asthma.

METHODS. A search was conducted of Medline (1966 to February 2006) and Embase (1974 to February 2006) databases, the Cochrane Controlled Trials Register, bibliographic reviews of primary research, review articles, and citations from texts. Randomized, double-blind, placebo-controlled trials conducted in the ED or equivalent care setting comparing ICSs to placebo or systemic corticosteroids were analyzed. Primary outcome measures included hospital admission and ED discharge rates. Secondary outcomes were spirometric measures, clinical symptoms, heart and respiratory rates, oxygen saturation, and adverse effects, all measured from 1 to 4 hours of the protocol.

RESULTS. Fifty articles were identified on the initial search, and 17 of these randomized, double-blind, placebo-controlled studies (6 included adults and 11 included children) met the above-stated criteria. Eight studies compared ICSs with placebo, 3 compared ICSs plus systemic corticosteroids (SCSs) with SCSs, and 6 compared ICSs with SCSs. ICS doses used in the trials ranged from 400 μg to 2 mg dispensed by inhaler or nebulizer, and the ICSs used included fluticasone (3 studies), budesonide (8), flunisolide (2), dexamethasone (1), and beclomethasone (3). “Multiple-dose” protocols administered ≥3 doses of ICS at ≥30-minute intervals, and “single-dose” protocols administered ≤2 doses at ≤30-minute intervals or ≥1 dose at >30-minute intervals. Six studies examined the discharge rates 2 to 3 hours after multidose ICS treatment and found that a signifi-
cantly greater proportion of ICS-treated patients were discharged early from the ED compared with those treated with either placebo or SCS (odds ratio: 4.7). Patients who received multiple ICS doses along with β agonists also had improvement in spirometric and clinical scores, with evidence of a dose-response relationship. There was a significantly lower admission rate in the patients treated with multiple-dose ICs. The number of patients needed to treat with ICs to prevent 1 hospital admission was 10.

CONCLUSIONS. This study suggests that ICS treatment provides early beneficial effects (1–2 hours) when they were used in multiple-dose amounts administered in time intervals of ≤30 minutes.

REVIEWER COMMENTS. This meta-analysis suggests that ICs given early in multiple doses with β agonists may have a place in the ED for treatment of acute exacerbations of asthma. Previous studies have shown that asthmatic patients have a significant increase in airway mucosal blood flow compared with nonasthmatic patients. Repeated high doses of ICs could work by decreasing airway blood flow, leading to enhanced bronchodilator action when administered simultaneously with β agonists. Additional study is needed to determine the most effective dose and delivery system in different patient populations to obtain an optimal effect.

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Secondary Prevention of Asthma by the Use of Inhaled Fluticasone Propionate in Wheezy Infants (IFWIN): Double-Blind, Randomised, Controlled Study

PURPOSE OF THE STUDY. To determine if the early use of inhaled fluticasone propionate in wheezy infants helps to prevent loss of lung function and progression of asthma later in childhood.

STUDY POPULATION. High-risk children (N = 1073) identified by having 1 atopic parent were followed prospectively until 2 wheezing episodes occurred or there was 1 wheezing episode longer than 1 month. Of these patients, 206 who met the inclusion criteria were randomly assigned: 104 to placebo and 102 to treatment. The median age was 1.2 years (range: 0.5–4.9 years). Eighty-six percent continued to be followed by their fifth birthday.

METHODS. Children were excluded if they had wheeze caused by bronchiolitis, were preterm (<34 weeks’ gestation), had other chronic lung disease or chronic illness, had previous inhaled corticosteroid (ICS) use, or were unable to use the inhaler. The treatment group was started on fluticasone propionate 100 µg twice daily. Randomly assigned patients were followed by monthly telephone calls for the first 3 months, if controlled, and then every 3 months until their fifth birthday. If symptoms were not under control by 3 months, then open-label fluticasone propionate 100 µg was added. Treatment was adjusted to the minimum necessary to control symptoms. Participants were allowed to use β agonists as needed. Parents were asked to keep daily diaries of symptom scores, reliever use, and unscheduled visits. At the age of 5, specific airway resistance (sRAW), forced expiratory volume in 1 second (FEV1), airway reactivity, and postbronchodilator lung function were measured and compared.

RESULTS. There was no significant difference between those in the treatment group versus placebo in the proportion of children with current wheeze, physician-diagnosed asthma, use of asthma medication, or current wheeze, even when factoring the addition of those participants who added open-label medication. There was also no significant difference in FEV1 (baseline or postbronchodilator), sRAW, or airway reactivity at 5 years of age in these groups. The 2 groups were similar in the number of children who required, and in the length of time to adding, open-label drug. Symptom scores, use of reliever medication, and unscheduled visits to the family doctor were similar until the third month, when children in the treatment group had lower median daily symptom scores, a trend toward less reliever medication, and significantly fewer visits than those in the placebo group. In the 2 open-label drug groups, there was a greater risk of current wheeze, current use of asthma medications, and current wheeze with asthma medications compared with those in the placebo group, although there was no difference in baseline or postbronchodilator FEV1. However, there was a significantly higher sRAW in the treated groups, which represented decreased lung function.

CONCLUSIONS. The use of ICs in young children at risk for asthma with the earliest sign of recurrent wheezing had no significant effect on the natural history of wheezing, lung function, or airway reactivity by 5 years of age and only showed a small improvement on symptom scores and unscheduled physician visits after the third month of the study. Higher postbronchodilator sRAW showing reduced lung function was seen in children in the treated group compared with those in the placebo group.

REVIEWER COMMENTS. Evidence for the efficacy of ICs in infants and very young children remains unclear. It has been suggested that early use of ICs could be detrimental to the lung development on the basis of the sRAW scores of ICs-treated patients. However, children in both
the treatment and placebo groups required the addition of fluticasone equally, which suggests that perhaps those in the treatment group had worse disease. Prestudy lung function was not tested, and individual atopic status was not assessed to determine if these 2 groups were truly equivalent. Studies are needed to determine if atopy is a confounding factor and whether controlling for allergen exposure in addition to ICS has an effect on asthma outcomes. This study and other similar studies suggest that ICS can improve asthma symptoms, but early use does not modify the disease.

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**High-Dose Inhaled Fluticasone Does Not Replace Oral Prednisolone in Children With Mild to Moderate Acute Asthma**


**PURPOSE OF THE STUDY.** To evaluate whether there is a significant difference in the degree of impairment in forced expiratory volume at 1 second (FEV₁) in children with mild-to-moderate acute asthma treated with either inhaled fluticasone or oral prednisolone.

**STUDY POPULATION.** Sixty-nine children aged 5 to 17 years with a previous history of wheezing who presented to a tertiary care pediatric emergency department (ED) with acute asthma and an FEV₁ between 50% and 79% predicted.

**METHODS.** This randomized, double-blind, double-dummy trial randomly assigned patients to receive either 2 mg of fluticasone via metered-dose inhaler (MDI) in the ED along with 500 μg of fluticasone via Diskus twice daily for 5 days (n = 35) or 2 mg/kg oral prednisolone in the ED along with 1 mg/kg prednisolone once daily for 5 days (n = 34). All children received scheduled, nebulized albuterol and ipratropium bromide in the ED and were given scheduled salmeterol and rescue albuterol on ED discharge. FEV₁ was measured at baseline, 4 hours, and 48 hours.

**RESULTS.** At 4 hours, the patients in the prednisolone group had a significantly greater increase in FEV₁ (29.8% ± 15.5%) compared with those in the fluticasone group (19.1% ± 12.7%; P = .001). By 48 hours, the difference in FEV₁ between the groups was no longer statistically significant. In addition, the number of unscheduled asthma visits by 48 hours after ED discharge was significantly greater in the fluticasone group (4 of 32) than the prednisolone group (0 of 34).

**CONCLUSIONS.** Children with mild-to-moderate acute asthma improve faster on oral prednisolone than inhaled fluticasone.

**REVIEWER COMMENTS.** Systemic corticosteroids are both historically and currently the mainstay treatment for acute asthma, given their ability to reduce hospitalizations, decrease relapses, regain asthma control, and improve lung function. However, the risks associated with the frequent use of oral corticosteroids have led researchers to search for an alternative treatment for acute asthma. Although previous studies have shown oral corticosteroids to be superior to inhaled steroids in severe acute asthma, the question remains as to whether inhaled corticosteroids could be used in mild and moderate asthma exacerbations. This study addressed this question and determined that oral corticosteroids are superior to inhaled steroids, even for mild exacerbations of asthma, in regard to relapse rate and time to FEV₁ improvement. These findings support the current use of oral steroids for treatment of mild-to-moderate acute asthma.

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**Assessment of Adrenal Suppression in Children With Asthma Treated With Inhaled Corticosteroids: Use of Dehydroepiandrosterone Sulfate as a Screening Test**


**PURPOSE OF THE STUDY.** To evaluate dehydroepiandrosterone sulfate (DHEA-S), a corticotropin-dependent adrenal androgen precursor, as a possible marker for adrenal function and hypothalamic-pituitary-adrenal axis suppression in children treated with inhaled corticosteroids (ICSs) compared with low-dose (0.5 μg/m² up to 1.0 μg) and standard-dose (250 μg) cosyntropin-stimulation testing.

**STUDY POPULATION.** Twenty-two patients with moderate-to-severe persistent asthma receiving a medium-to-high dose of ICSs for at least 6 months were enrolled (definition of median-to-high dose of ICS: budesonide >400 μg/day or fluticasone >176 μg/day for children <6 years old or >200 μg/day for those ≥6 years). Patients had received no more than 2 courses of systemic corticosteroid exposure of <10 days' duration in the previous 6 months and no systemic corticosteroid in the 1 month before enrollment. The average age of the patients was 8.6 years (range: 2–12 years).

**METHODS.** After a 12-hour fast, morning cortisol, corticotropin, DHEA-S, and fasting blood sugar levels were measured. Cortisol was measured after the stimulation tests. A cortisol level of ≤18 μg/dL was considered abnormal (adrenal suppression).
RESULTS. Of 22 patients, 13 (59%) had an abnormal response to low-dose cosyntropin. One patient had an abnormal standard-dose cosyntropin test result. The normal and abnormal low-dose cosyntropin responders did not differ in age, height, BMI, predicted forced expiratory volume in 1 second, or morning cortisol, corticotropin, or fasting blood sugar levels. There was no difference between normal and abnormal low-dose cosyntropin responders in relation to type of ICS (fluticasone, fluticasone-salmeterol, or budesonide) or dose. DHEA-S levels were significantly lower in abnormal low-dose cosyntropin responders compared with normal responders (31 vs 91 µg/dL; P = .004). Age- and gender-specific mean DHEA-S z scores were significantly lower in abnormal low-dose cosyntropin responders. Receiver-operating-characteristic (ROC) curves for DHEA-S z scores were calculated to obtain optimal cutoff values for DHEA-S. The ROC curve for DHEA-S z scores reached 100% sensitivity with a DHEA-S z score of less than −1.5966 and 100% specificity with a DHEA-S z score >0.0225.

CONCLUSIONS. Fifty-nine percent of the children on a medium-to-high dose of ICS had biochemical evidence of adrenal suppression according to the low-dose cosyntropin-stimulation test. Low DHEA-S levels can be used as a screening test to identify children who need more formal testing of the hypothalamic-pituitary-adrenal axis. The half-life of DHEA-S (10–20 hours) is substantially longer than that of cortisol (<2 hour) and, therefore, has less diurnal variation or fluctuating concentration depending on exogenous stress and time of day.

REVIEWER COMMENTS. The cosyntropin-stimulation test is cumbersome, labor intensive, and not practical as a screening test, so the DHEA-S test may be more useful. The number of patients on a moderate dose of ICS found to have biochemical adrenal suppression by low-dose cosyntropin tests (59%) is higher than seen in most other studies. The authors speculated that the higher rates of adrenal suppression may be associated with “real-world” ICS use versus study-protocol use. The clinical significance of this biochemical suppression is not clear.

The Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol

PURPOSE OF THE STUDY. To compare the safety of salmeterol or placebo added to usual asthma care.

STUDY POPULATION. Subjects who were >12 years old with asthma (as judged by the study physician) and were currently receiving a prescription asthma medication.

METHODS. This was a multicenter, randomized, double-blind, parallel group, placebo-controlled observational surveillance study conducted at 6163 US sites with 1316 investigators between 1996 and 1999 (phase 1) and 2000 and 2003 (phase 2). The primary purpose was to compare respiratory and asthma-related outcomes in subjects who were receiving usual asthma pharmacotherapy plus placebo or usual care plus salmeterol. Subjects were recruited by large-scale advertisement and assigned geographically to the closest site (phase 1) and directly by study investigators (phase 2). A single clinic visit was performed to determine eligibility, obtain consent and baseline data, and dispense a 28-week supply of study medications and instructions. Subjects were told to continue their baseline asthma medications, and those without a short-acting β agonist were given albuterol. Telephone follow-up was obtained every 4 weeks. Adherence was not measured or reinforced.

RESULTS. Almost 25% of the subjects dropped out of the study before 28 weeks. At baseline, nearly all of the subjects were taking short-acting β agonists, but only 47% were taking inhaled corticosteroids (ICSs) (49% of white subjects and 38% of black subjects). The study was terminated in 2003 because of safety concerns and difficulty with recruitment (of planned 60,000 subjects). There were 50 combined respiratory-related deaths or life-threatening experiences in the salmeterol group versus 36 in the placebo group (relative risk [RR]: 1.4; 95% confidence interval [CI]: 0.91–2.14). There were 24 respiratory-related deaths in the salmeterol group and 11 in the placebo group (RR: 2.16; 95% CI: 1.06–4.41). There were 13 asthma-related deaths in the salmeterol group (6 white and 7 black) and 3 in the placebo group (RR: 4.37; 95% CI: 1.25–15.34). The increased risk was primarily in black subjects with combined asthma-related deaths or life-threatening experiences of 19 in the salmeterol group versus 4 in the placebo group (RR: 4.92; 95% CI: 1.68–14.45). Half of the black subjects and 71% of the white subjects who had asthma-related deaths were not on ICS at baseline, but the impact of ICS on prevention of asthma or respiratory death or life-threatening experiences could not be analyzed because of the study design. The death rate for subjects exposed to salmeterol in the Salmeterol Multicenter Asthma Research Trial was 1.98 per 1000 person-years.

CONCLUSIONS. The authors concluded that there were small but statistically significant increases in respiratory- and asthma-related deaths and combined asthma-related deaths or life-threatening experiences in the total pop-
Montelukast Improves Regional Air-Trapping Due to Small Airways Obstruction in Asthma


PURPOSE OF THE STUDY. To assess the effects of montelukast on regional air-trapping, airway hyperresponsiveness, and small-airway physiology using quantitative image analysis with high-resolution computed tomography (HRCT).

STUDY POPULATION. Sixteen patients (7 women, 9 men) aged 18 to 65 with no use of inhaled corticosteroids for the past 2 months, a forced expiratory volume in 1 second (FEV₁) of >60% predicted, a provoked dose that causes a 20% decrease in FEV₁, and a clinical diagnosis of asthma.

METHODS. The study was designed as a randomized, double-blind, placebo-controlled crossover trial. Subjects received either montelukast 10 mg or a placebo given once daily in the evening for 4 weeks. The subjects then crossed over to the alternate treatment for 4 more weeks. Regional air-trapping was assessed by HRCT at residual volume before and after methacholine challenge and was performed at baseline and after each of the drug phases was complete. Other indices of hyperresponsiveness and physiology were measured as well.

RESULTS. Significantly less regional air-trapping was seen on the premethacholine images of patients treated with montelukast. However, no effect on increases in regional air-trapping was seen on the postmethacholine images in these same patients. There were no differences seen in global indices of small-airways physiology between montelukast and placebo. Montelukast resulted in improved quality-of-life scores.

CONCLUSIONS. Montelukast improved small-airways disease in asthmatic subjects, but this improvement can only be detected by HRCT, not by physiologic studies.

Lack of Tolerance to the Protective Effect of Montelukast in Exercise-Induced Bronchoconstriction in Children


PURPOSE OF THE STUDY. To evaluate montelukast’s ability to inhibit exercise-induced bronchoconstriction in children at various time points over a treatment period of 28 days.

STUDY POPULATION. Thirty-two children, ranging in age from 6 to 12 years, with mild-to-moderate asthma.

METHODS. This study was designed as a multicenter, double-blind, randomized, parallel-group, placebo-controlled study. Subjects received either montelukast 5 mg or a placebo given once daily in the evening for 4 weeks. Exercise challenge and a pulmonary-function test were performed at baseline and then again at days 3, 7, and 28.

RESULTS. Montelukast provided significantly more protection against exercise-induced bronchoconstriction than placebo at each time point after treatment began. In addition, there was no significant difference in the percentage decrease of forced expiratory volume in 1 second for each drug at each of the days measured.
CONCLUSIONS. Montelukast provided significant protection for children with mild-to-moderate asthma against exercise-induced bronchoconstriction for a period of 28 days with no tolerance observed to the medication’s effects.

REVIEWER COMMENTS. The results of this study parallel those that were run in adults. Montelukast offered effective protection against exercise-induced bronchoconstriction in children as well. The study also confirmed that long-term use is not required for results to be seen, and the protection conferred does not diminish for at least a 28-day period. Longer studies up to ≥12 weeks, parallel adult studies, are warranted for further evaluation of montelukast’s effects. This study was also limited in its sample size and involved only subjects with mild-to-moderate asthma. It would be worthwhile to determine if montelukast would be of the same benefit to severely asthmatic patients. It should be noted that approximately a quarter of the children in the study were taking inhaled steroids on a regular basis, and these patients responded to montelukast in the same way as those who were not on any such medications. This study makes a case for montelukast to be a preferential therapeutic option in children.

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Antibiotic Treatment of Wheezing in Children With Asthma: What Is the Practice?
Kozyrskyj AL, Dahl ME, Unger WJ, Becker AB, Law BJ. Pediatri. 2006;117(6). Available at: www.pediatrics.org/cgi/content/full/117/6/e1104

PURPOSE OF THE STUDY. To evaluate time trends and determinants of antibiotic use in children with wheezing episodes.

STUDY POPULATION. Children with asthma were identified from population-based health care and prescription databases in Manitoba, Canada, during fiscal years 1995–2001. Asthma was defined as at least 1 physician or hospital visit for asthma or at least 1 prescription for an asthma drug.

METHODS. In this descriptive study, using general estimating equations, annual population-based rates of antibiotic prescriptions for wheezing episodes were modeled by age and antibiotic class. Population-based rates for antibiotic use for wheezing were defined as the annual number of antibiotic prescriptions dispensed per 1000 children with asthma. Linear hierarchical rankings were used to calculate odds ratios for receiving an antibiotic prescription according to child demographics and physician factors.

RESULTS. Antibiotic prescription rates for wheezing decreased 28% from 708 prescriptions per 1000 children with asthma in 1995 to 511 prescriptions per 1000 children with asthma in 2001. However, an increase in prescriptions was observed for broader-spectrum macrolides (azithromycin and clarithromycin) in preschool-aged children (a 15-fold increase) and in all children (an eightfold increase). Immediate prescriptions (defined as within 2 days of the visit) were given in 23% of physician encounters for wheezing. Sixty-four percent of the visits resulted in an antibiotic prescription within 7 days of the visit. General practitioners prescribed antibiotics for wheezing more often than pediatricians, as did older compared with younger physicians. Physicians trained outside Canada and the United States were 40% more likely to prescribe antibiotics. Visits for younger children and visits during winter months more frequently resulted in antibiotic prescriptions.

CONCLUSIONS. Antibiotic prescription rates for wheezing episodes declined in the late 1990s, but broader-spectrum antibiotic prescription rates increased.

REVIEWER COMMENTS. Antibiotic use in asthma has gained renewed interest because of the antiinflammatory properties of certain antibiotic classes such as the macrolides. Coupled with the better-tolerated and more-convenient dosing of newer antibiotics (primarily azithromycin), they may provide a future therapeutic option in the treatment of asthma. Nonetheless, little is published about the prescribing patterns of antibiotics for wheezing and asthma. Coexisting maladies such as otitis or pneumonia are not specifically addressed in this publication but may account for the increase in prescription rates at 7 days postvisit. In addition, the possible contribution of antibiotics in the inception of asthma by participating in the “hygiene hypothesis” provides additional interest in these data. Finally, the perceived dangers of resistance with antibiotic use continue to make their use controversial in the treatment of asthma exacerbations.

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Effect of Clarithromycin on Cytokines and Chemokines in Children With an Acute Exacerbation of Recurrent Wheezing: A Double-Blind, Randomized, Placebo-Controlled Trial

PURPOSE OF THE STUDY. To evaluate the effect of clarithromycin on serum and nasopharyngeal cytokine and chemokine concentrations in children with an acute exacerbation of recurrent wheezing.
STUDY POPULATION. Forty-three children (mean age: 8.8 years) with a history of recurrent wheezing or asthma were enrolled when presenting to the emergency department of Children’s Medical Center (Dallas, TX) with an acute exacerbation of wheezing.

METHODS. Study participants were randomly assigned to receive oral clarithromycin or placebo for 5 days. All participants received systemic steroids for 5 to 6 days and aerosolized β agonists. On enrollment (visit 1), after 3 to 5 days (visit 2), and after 3 to 8 weeks (visit 3), children were clinically evaluated and respiratory samples (nasopharyngeal swab and aspirate) were obtained. Nasopharyngeal swabs were tested for Chlamydia pneumoniae and Mycoplasma pneumoniae. Nasopharyngeal aspirates were analyzed for cytokine and chemokine concentrations (tumor necrosis factor α [TNF-α], interferon γ, interleukin-1β [IL-1β], IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, granulocyte/macrophage colony-stimulating factor, regulated upon activation, normal T cells expressed and secreted [RANTES], eotaxin, macrophage inflammatory protein 1α, macrophage inflammatory protein 1β, and monocyte chemotactic protein 1). Serum was analyzed for cytokine concentrations (TNF-α, interferon γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, and granulocyte/macrophage colony-stimulating factor).

RESULTS. Evidence of M pneumoniae infection was found in 20 patients (48%), and C pneumoniae was found in 12 patients (28%). Nine patients had dual infection. No significant differences in nasopharyngeal aspirate or serum cytokine or chemokine concentrations were found between patients with evidence of C pneumoniae and/or M pneumoniae infection and those without evidence of infection before treatment with clarithromycin or placebo. No difference in asthma severity was found. No difference in resolution of symptoms was noted in patients treated with clarithromycin versus placebo. No correlation was identified between asthma severity and nasopharyngeal concentrations of cytokines and chemokines. Correlation was found between serum IL-10 concentration and asthma severity (P = .02). Nasopharyngeal concentrations of TNF-α, IL-1β, and IL-10 were significantly and persistently lower in children treated with clarithromycin compared with placebo. These results were not attempted or recorded in all cases. The subsequent survey consisted of 2 parts: a preliminary survey of the use of intravenous MgSO4 in the hospital and a second part regarding interest in research in this area.

CONCLUSIONS. Five days of clarithromycin therapy significantly decreased nasal concentrations of TNF-α, IL-1β, and IL-10 out to 3 to 8 weeks, indicating that macrolides may have a long-lasting effect on immune mediators beyond the time that therapy is completed.

The Use of Magnesium Sulfate in Acute Asthma: Rapid Uptake of Evidence in North American Emergency Departments

PURPOSE OF THE STUDY. Magnesium sulfate (MgSO4) has been shown to be an effective acute bronchodilator in both children and adults with severe acute asthma, yet little is known about its actual clinical use.

STUDY POPULATION. Between 1997 and 2001, ~10 000 patients were enrolled onto observational asthma studies in the Multicenter Airway Research Collaboration, which is part of the Emergency Medicine Network (EMNet), a collaboration of 140 mostly academic medical institution emergency departments (EDs) in the United States and Canada. In 2001, a survey was conducted of all site investigators regarding MgSO4 use in this patient group.

METHODS. At the time of the study, physicians were unaware of the study and did not use a particular protocol at each site. Chart review was conducted on patients 2 to 54 years of age who were currently having an asthma exacerbation. Patients were managed at the discretion of the treating physician, and cases in which intravenous MgSO4 was used were identified. Pulmonary-function studies, usually peak expiratory flows (PEFs), were recorded as early during the ED evaluation as possible but were not attempted or recorded in all cases. The subsequent survey consisted of 2 parts: a preliminary survey of the use of intravenous MgSO4 in the hospital and a second part regarding interest in research in this area.

RESULTS. From 10 169 ED visits, 9745 (96%) charts documented information regarding administration of MgSO4 for the patients while in the ED. Of these, 240 (2.5%) patients received this drug. The use was 10 times higher among patients who were subsequently admitted versus nonadmitted patients. No specific data as to the number of children so treated were presented. Logistic regression identified several factors associated with MgSO4 use:
increasing age, female gender, past history of intubation, duration of symptoms <24 hours, higher initial respiratory rate, low PEF or missing PEF data, and greater use of β agonists and systemic corticosteroids in the ED. In response to the survey, site leaders listed severity and failure to respond to initial β agonists as factors that would prompt MgSO₄ use. They disagreed with the use of MgSO₄ in all asthmatic patients in the ED. Site leaders also described far less use of this agent both prehospital and in the ICU.

CONCLUSIONS. Most ED physicians accept the efficacy of MgSO₄ in acute asthma, but its use remains relatively uncommon. In both practice and theory, these physicians seem to restrict its use to patients with severe acute asthma. Patterns of use will likely continue to evolve as knowledge of the efficacy and safety of MgSO₄ in acute asthma management disseminates.

REVIEWER COMMENTS. Because the use of MgSO₄ was so much higher in admitted patients, does this not beg the question as to whether it should be used even more aggressively in the ED and in the subsequently hospitalized child with status asthmaticus? Also, considering the apparent safety of MgSO₄ in either the intravenous or nebulized form, should this drug be part of the outpatient treatment protocol for the child with relatively severe bronchospasm who first presents in the office of the pediatrician or allergist?

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Five-Year Follow-up on the PAT Study: Specific Immunotherapy and Long-term Prevention of Asthma in Children

PURPOSE OF THE STUDY. The Preventive Allergy Treatment (PAT) study was designed to investigate the preventive effect of specific immunotherapy (SIT) on the development of asthma in children suffering from allergic rhinoconjunctivitis. SIT was performed as a 3-year course of subcutaneous immunotherapy with extracts of grass and/or birch pollen. The PAT study showed that SIT can prevent the development of asthma in children suffering from seasonal allergic rhinoconjunctivitis. This article was a follow-up evaluation on the development of asthma in these children 2 years after discontinuation of SIT versus no treatment.

STUDY POPULATION. Children aged 6 to 14 with rhinoconjunctivitis triggered by allergy to grass and/or birch pollen were enrolled onto the PAT study. A total of 183 of the 205 children (now aged 11–20 years) from the PAT study were included in this 5-year follow-up evaluation.

METHODS. Of the initially randomly assigned 205 patients, there were 183 patients (95 receiving SIT, 88 controls) suffering from rhinoconjunctivitis caused by allergy to grass and/or birch who underwent conjunctival provocation testing, methacholine bronchial provocation testing, evaluation for asthma, and recording of rhinitis and conjunctivitis visual analog scores. Asthma was defined as recurrence of at least 2 of the 3 following symptoms within the last 12 months that were not only triggered by infection and responded to treatment with β agonists: cough, wheeze, and shortness of breath.

RESULTS. Of the 183 patients evaluated after 5 years, 142 had no asthma at inclusion, and 8 children dropped out of the study. Patients without asthma before the start of SIT (n = 142) were analyzed for the development of asthma, which was the primary end point of this study, after the 5-year period. Of the 75 patients who received SIT, 15 developed asthma, whereas 29 of the 76 control patients developed asthma (P < .01). On the basis of the visual analog scores of conjunctivitis and rhinitis, the SIT-treated group had a significant improvement from baseline to 5 years compared with the controls (P < .001). The conjunctival sensitivity measured by provocation tests were significantly reduced in the active group compared with the control group (P < .001).

CONCLUSIONS. This study showed that the benefits of SIT (ie, the reduction of symptoms and prevention of asthma) persisted 2 years after termination of treatment of children with allergic rhinoconjunctivitis caused by grass and/or birch.

Reviewer Comments. Although the results that allergen immunotherapy may reduce the symptoms of allergic disease and the onset of asthma are encouraging, the manner in which asthma was defined in this study, based primarily on subjective findings, limited the significance of the results. Furthermore, in the United States, we generally perform SIT with more than just timothy grass (Phleum pratense) and birch pollen (Betula verrucosa) because of multiple aeroallergen sensitization; therefore, it is difficult to generalize the findings of this study to our typical patient population.

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Allergy Immunotherapy as an Early Intervention in Patients With Child-Onset Atopic Asthma
Nagaya H, Maren S, Nagaya N. Int Arch Allergy Immunol. 2006;139:9–15

PURPOSE OF THE STUDY. In patients with bronchial asthma, an effective treatment is required at early stages of the disease to prevent irreversible structural changes of the airways. The objective of this study was to evaluate the beneficial effects of routine immunotherapy as an early intervention on forced expiratory volume in 1 second (FEV1) in patients with childhood-onset atopic asthma.

STUDY POPULATION. Forty-three patients with child-onset atopic asthma who had received regular immunotherapy injections and periodic FEV1 measurements.

METHODS. Beneficial effects of successful immunotherapy on FEV1 were analyzed retrospectively in 43 unselected patients who received standard subcutaneous immunotherapy with periodic FEV1 measurements and became asymptomatic.

RESULTS. Although there was no significant correlation between the duration of asthma symptoms before immunotherapy and the changes in FEV1 before and after immunotherapy in the 43 unselected patients, there was a significant inverse correlation between these 2 parameters in 23 patients whose asthma duration was <20 years. Because the FEV1 increased after immunotherapy in all 14 patients whose asthma duration was <5 years, the 43 patients were divided into group, 1 including these 14 patients, and group 2, including 29 patients whose asthma duration was >5 years. The FEV1 decreased in 7 of the 29 asymptomatic patients in group 2. There was no difference in the initial FEV1 between the
Grass Pollen Immunotherapy as an Effective Therapy for Childhood Seasonal Allergic Asthma


PURPOSE OF THE STUDY. There is abundant evidence to support the use of specific immunotherapy (SIT) in the treatment of allergic rhinoconjunctivitis. Studies that have looked at the role of SIT for the treatment of seasonal allergic asthma are lacking. This study evaluated the safety and effectiveness of SIT for the treatment of seasonal allergic asthma in children.

STUDY POPULATION. A total of 39 of 161 screened subjects 3 to 16 years old were enrolled onto the study from the allergy clinic at St Mary’s Hospital (London, United Kingdom). All of them had history of grass-pollen–induced asthma that required 200 µg of inhaled beclomethasone (or equivalent) daily. All subjects had a positive skin-prick–test response: a positive specific immunoglobulin E level (Pharmacia CAP) to a relevant grass pollen (*Phleum pratense*). Subjects also had a positive conjunctival provocation test. Subjects were excluded if they previously had been treated with grass-pollen immunotherapy or had a history of perennial asthma requiring inhaled corticosteroids, significant perennial allergic rhinitis, or sensitization to a pet present in the household.

METHODS. The study was a single-center, randomized, double-blind, placebo-controlled study over 2 successive pollen seasons. Subjects were randomly assigned to receive SIT or placebo. The primary outcome was the asthma-symptom–medication score during the second pollen season. Secondary outcome measures included lung function, cutaneous, conjunctival, and bronchial allergen reactivity, and both exhaled nitric oxide and sputum eosinophil levels.

RESULTS. The use of SIT was associated with a substantial reduction in asthma-symptom–medication score as compared with placebo (P = .04). There was significant reduction in cutaneous (P = .002), conjunctival (P = .02), and bronchial (P = .01) reactivity to allergen after SIT compared with placebo. Children in the 2 groups had similar levels of airway inflammation, although less inhaled steroids were required for those in the active group. No serious adverse events were reported, and no subjects withdrew because of adverse events.

CONCLUSIONS. SIT is effective and well tolerated in children with seasonal allergic asthma to grass pollen.

Long-term Immunologic Effects of Broad-Spectrum Aeroallergen Immunotherapy


PURPOSE OF THE STUDY. To evaluate the long-term clinical effects, skin tests, and specific immunoglobulin E (IgE) levels from subjects who had previously received broad-spectrum aeroallergen immunotherapy several years earlier.

STUDY POPULATION. Eighty-two polysensitized subjects who had previously been enrolled onto a randomized, double-blind, placebo-controlled trial of specific immunotherapy for treatment of childhood allergic asthma were reevaluated in adulthood (mean follow-up interval: 10.8 years) by puncture skin tests and CAP-RAST levels for major aeroallergens. All subjects originally completed at least 18 months
(median: 27 months) of maintenance active immunotherapy treatment or placebo injections without subsequent immunotherapy.

RESULTS. At adult follow-up, 36% of all skin tests to treatment allergens among subjects who received immunotherapy \((n = 41)\) had significantly reduced intensity versus 26% of skin tests among placebo recipients \((n = 41); P = .03\). No significant differences were noted for individual treatment allergens. No significant differences were observed in the long-term changes of serum-specific IgE antibody levels for all or individual treatment allergens between immunotherapy treatment and placebo groups \((P = .43)\). The treatment and placebo groups had a similar acquisition of new skin-test sensitivities from time of randomization in the original childhood trial to debriefing \((15% \text{ vs } 20%; P = .28)\) and to adult follow-up \((30% \text{ vs } 31%; P = .75)\).

CONCLUSIONS. Immunotherapy suppresses skin-test sensitivity 8 to 16 years after discontinuation of treatment, but long-term effects on specific IgE levels in serum are not observed. Broad-spectrum immunotherapy does not seem to affect the acquisition of new inhalant sensitivities.

REVIEWER COMMENTS. In this study, allergic-asthmatic children who participated in a double-blind, placebo-controlled immunotherapy trial were reevaluated as adults to determine if immunotherapy had long-lasting effects. This study revealed that asthmatic children who received immunotherapy to multiple allergens for a median of 27 months had limited long-term effects on the results of testing parameters routinely used in allergy practice. The long-term efficacy of immunotherapy and optimal duration of therapy are issues that remain open.

成果和结论。在成年随访中，36%的皮肤测试反应在治疗组中显著降低，而仅26%的皮肤测试反应在安慰剂组中（\(n = 41\) vs \(n = 41\), \(P = .03\))。个体治疗变应原的血清特异性IgE抗体水平没有显著差异。在免疫疗法治疗组和安慰剂组之间，没有观察到长期变化。广谱免疫疗法似乎不干扰新吸入性变应原的获得。本研究结果表明，对多种变应原的免疫疗法治疗在治疗后8-16年对皮肤测试反应的抑制作用是显著的，但对血清特定IgE水平的长期影响在未观察到。广谱免疫疗法似乎不干扰新吸入性变应原的获得。

评论者评论。在这项研究中，参与了双盲、安慰剂对照的免疫疗法试验的哮喘儿童在成年后被重新评估，以确定免疫疗法是否有长期疗效。这项研究揭示了哮喘儿童接受免疫疗法对多种变应原的治疗，27个月的中位随访时间，有有限的长期影响。研究结果表明，免疫疗法的长期疗效和治疗的最佳持续时间是存在的问题，这些问题仍需进一步研究。

Usefulness of Specific Immunotherapy in Patients With Atopic Dermatitis and Allergic Sensitization to House Dust Mites: A Multicentre, Randomized, Dose-Response Study


PURPOSE OF THE STUDY. To evaluate whether allergen specific immunotherapy (SIT) improves eczema in patients who are sensitized to house dust mites.

STUDY POPULATION. Adults with chronic atopic dermatitis and a scoring atopic dermatitis (SCORAD) index of ≥40 who were sensitized to house dust mites as verified by CAP-RAST testing.

METHODS. Double-blind placebo-controlled multicenter study in which patients were randomly assigned to receive subcutaneous SIT of a house dust-mite preparation at maintenance doses of 20, 2000, and 20,000 SQ-U (manufacturer’s units) for 1 year. Treatment involved weekly injections and 2 plateau phases during up-dosing in the 2000 and 20,000 SQ-U dosing categories. SCORAD values were assessed by dermatologists who were blinded to the patients’ treatment status. Patients were allowed to also use emollients, topical corticosteroids (up to European class 3), and antihistamines during the study period. House dust-mite–specific and total immunoglobulin E (IgE) levels, as well as eosinophil cationic protein levels, were measured. Patients kept daily records regarding the condition of their skin and use of other medications.

RESULTS. Of 89 patients originally enrolled, 51 completed the study. A dose-dependent decrease in SCORAD index was observed, with the difference being statistically significant in the 2000 and 20,000 SQ-U groups. Patients who received higher doses of SIT also showed decreased use of topical corticosteroids. Levels of allergen-specific IgE, total IgE, and eosinophil cationic protein were unchanged by treatment. Less than 1% of the injections resulted in systemic reactions (mild urticaria and itching).

CONCLUSIONS. One year of treatment with subcutaneous SIT in patients with allergic sensitization to house dust mites can lead to an improvement in eczema severity and a reduction in the need for topical corticosteroids.

REVIEWER COMMENTS. The occurrence of adverse effects, most importantly an exacerbation of atopic dermatitis, observed in this study was remarkably less than that seen in other studies using SIT in patients with atopic dermatitis. Additional studies are warranted to identify which subgroup of patients with atopic dermatitis are most likely to benefit from SIT and least likely to experience adverse effects. It will also be important to determine if patients with multiple sensitizations, and therefore multiple possible triggers for their disease, are less likely to respond to SIT and whether SIT for other Aeroallergens is as useful.

Sublingual Immunotherapy With Once-Daily Grass Allergen Tablets: A Randomized Controlled Trial in Seasonal Allergic Rhinoconjunctivitis


PURPOSE OF THE STUDY. To examine the efficacy and safety of sublingual immunotherapy (SLIT) in seasonal allergic rhinoconjunctivitis using timothy-grass–allergen tablets.
STUDY POPULATION. The study included 855 patients aged 18 to 65 from 55 centers in Canada and Europe with seasonal allergic rhinoconjunctivitis induced by grass pollen.

METHODS. A double-blind, randomized, parallel-group, placebo-controlled trial was conducted during 2002–2003. Patients had a history of allergic rhinoconjunctivitis during grass-pollen season for at least 2 years with a positive skin-prick-test result and serum-specific immunoglobulin E (IgE) to Phleum pratense. Individuals were randomly assigned to receive placebo or 2500, 25 000, or 75 000 SQ-T sublingual tablets administered daily. Daily diaries of symptoms (0–3) and rescue-medication use from pre– through post–grass-pollen season were kept, and a rhinoconjunctivitis quality-of-life (QoL) questionnaire was completed. Well days were calculated as those with a symptom score of ≤2 and no rescue-medication use.

RESULTS. A total of 790 (92%) participants completed the trial that included a mean duration of treatment of 18 weeks. Treatment with 75 000 SQ-T tabs revealed an improvement in symptom score (16%; P = .0710) and medication score (28%; P = .0470) when compared with placebo. The QoL score and number of well days also revealed improvement of 17% (P = .006) and 18% (P = .041), respectively. The 2 lower doses did not demonstrate significant change from placebo. Preseason treatment for 8 weeks with the 75 000 SQ-T dose showed an increased improvement of symptom score (21%; P = .002) and medication score (29%; P = .012) compared with placebo. In the 75 000 SQ-T group, specific IgG to P pratense was increased after 8 weeks of treatment and tripled posttreatment. Specific IgE levels increased after treatment initiation but remained unchanged thereafter. Therapy was well tolerated with only mild-to-moderate symptoms (consisting of primarily oral pruritis and throat irritation) noted in 53% of the patients.

CONCLUSIONS. Grass-pollen SLIT has a dose-dependent efficacy, is well tolerated, and provides improved QoL for patients with seasonal allergic rhinoconjunctivitis.

REVIEWER COMMENTS. SLIT for grass-pollen allergy holds promise as an alternative future therapy to subcutaneous immunotherapy that is attractive on many levels. Grass-pollen SLIT may have broader coverage range because of improved accessibility and more convenient administration, less discomfort than injections, and decreased risk of IgE-mediated severe systemic reactions. Preseason coverage with SLIT may improve symptoms and reduce medication requirements for treatment of seasonal allergic rhinoconjunctivitis.

Clinical Efficacy and Safety of Sublingual Immunotherapy With Tree Pollen Extract in Children

PURPOSE OF THE STUDY. To investigate the clinical efficacy, safety, and dose-response relationship of sublingual immunotherapy (SLIT) in children suffering from rhinoconjunctivitis with or without asthma.

STUDY POPULATION. Eighty-eight children (aged 5–15 years) in Finland with a history of tree-pollen–induced allergic rhinoconjunctivitis with or without seasonal asthma. Skin-prick test, specific immunoglobulin E, and conjunctival provocation test were used to confirm allergy to tree pollen.

METHODS. Randomized, double-blind, placebo-controlled dose-response study using a glycerinated mixture of pollen from birch, hazel, and alder trees. Three groups receiving SLIT 5 days per week for up to 18 months were given an accumulated weekly dose of 24 000 U (dose group 1), an accumulated weekly dose of 200 000 U (dose group 2), or placebo.

RESULTS. In the birch-pollen season, dose group 2 showed a significant reduction in both symptom (P = .01) and medication (P = .04) scores compared with those in the placebo group, but dose group 1 showed only a significant reduction of symptom scores (P = .03). No serious adverse events were reported. Oral local reactions were the most common adverse effect, ranging from 25% of patients in the placebo group to 50% in group 2.

CONCLUSIONS. SLIT with tree-pollen extract provided dose-dependent benefits in tree-pollen–allergic children in terms of significantly reduced symptoms and medication use. The treatment was well tolerated.

REVIEWER COMMENTS. The use of allergen-specific immunotherapy by the sublingual route, SLIT, has been increasing in clinical practice in Europe. SLIT is especially attractive for use in children, because it is a noninjection form of immunotherapy. This study showed a modest reduction (~40%) in both symptom and medication scores. This is an interesting disease-modifying therapy that will need more studies to characterize efficacy and safety and to compare the results to that of subcutaneous immunotherapy before wider use can be recommended.
Immunotherapy With a Ragweed-Toll-Like Receptor 9 Agonist Vaccine for Allergic Rhinitis


PURPOSE OF THE STUDY. The conjugate compound of the ragweed antigen, Amba1, and an immunostimulatory DNA sequence containing a CpG motif is associated with a suppression of T-helper 2 cellular and cytokine responses via binding to toll-like receptor 9 (TLR9). This study investigated whether Amba1-immunostimulatory oligodeoxyribonucleotide conjugate (AIC) is a safe and effective immunotherapy for ragweed-sensitized patients.

STUDY POPULATION. A randomized, double-blind, placebo-controlled, phase 2 clinical trial in which 25 participants with a history of fall allergic rhinitis aged 23 to 60 years were assigned to receive a vaccine containing either AIC or placebo.

METHODS. Participants received a total of 6 weekly injections before the ragweed season. The primary clinical end point was the change in albumin level in nasal secretions assessed by a posttreatment nasal allergen challenge. Postchallenge rhinitis symptoms were also scored. Secondary clinical end points included the rhinitis visual analog score, daily nasal symptom diary score, use of relief medication, a rhinoconjunctivitis quality-of-life questionnaire, and skin-test sensitivity. Immunologic evaluation included measuring Amba1- and ragweed-specific immunoglobulin (Ig) G and IgE and cytokine levels.

RESULTS. There was no affect on the primary end point with AIC treatment. However, during the 2 posttreatment ragweed seasons, subjects in the group that received AIC had better peak-season rhinitis visual analog scores, peak-season daily nasal-symptom diary scores, and midseason rhinoconjunctivitis quality-of-life scores. Those in the AIC group also had decreased peak-season use of relief medications and antihistamine and decongestant use in the second season posttherapy. AIC was associated with a rise in the Amba1-specific IgE level after treatment but was not associated with an increase in the Amba1-specific IgE level during either posttreatment ragweed season. There were no vaccine-associated serious adverse reactions.

CONCLUSIONS. AIC may have a potential therapeutic role in the treatment of ragweed-allergic individuals.

IgG-Blocking Antibodies Inhibit IgE-Mediated Anaphylaxis in Vivo Through Both Antigen Interception and FcγRIIβ Cross-linking


PURPOSE OF THE STUDY. It has been hypothesized that at least part of the mechanism of successful allergen immunotherapy is the induction of specific immunoglobulin (Ig) G that can “block” IgE-dependent responses by competitively preventing IgE binding and/or by signaling via inhibitory FcγRIIβ on basophils and mast cells, thereby downregulating FcεRI-dependent signaling. In vivo evidence of this blocking function has been lacking. The authors of this study carefully addressed whether and how specific IgG can inhibit IgE-mediated anaphylaxis by using a murine model.

METHODS. The authors had previously established a model of anaphylaxis by immunizing BALB/c mice with goat antimouse IgD antibody (GoaMD), which elicits a strong T-helper 2 response with high levels of IgE, IgG1, and mastocytosis. In this study they very cleverly modified the model by conjugating GoaMD with the hapten trinitrophenyl to generate a trinitrophenyl-specific IgG and IgE response to allow for more detailed evaluation of the role of different antibody isotypes with the same epitope specificity. They used a number of tools including antibody blocking of FcγRs, FcRIII-deficient knockout mice, and pharmacologic inhibition to discriminate between IgE- and IgG-dependent anaphylaxis. Assessment of anaphylaxis was by temperature drop and hemoconcentration. IgG-trinitrophenyl antibody complexes were measured by enzyme-linked immunosorbent assay (ELISA). In some experiments, interleukin 4 secretion was measured from whole blood by ELISA.

RESULTS. In immunized mice, the authors showed that IgE-dependent anaphylaxis is primarily inhibited by IgG preventing antigen-induced cross-linking of cell-associated IgE. In FcγRIII-deficient mice (ie, those capable of only IgE-dependent anaphylaxis), blockade of the FcγRIIβ inhibitory receptors did not exacerbate antigen-induced anaphylaxis, and IgG–antigen complexes could be detected in whole blood within 5 minutes of antigen administration. Furthermore, animals passively sensi-
CD137-Mediated Immunotherapy for Allergic Asthma


PURPOSE OF THE STUDY. Allergen-specific CD4+ T-helper 2 (Th2) cells are thought to be at the center of asthma pathogenesis because of their ability to secrete cytokines such as interleukin 4 (IL-4), IL-5, and IL-13, which result in many of the features of allergic inflammation. CD4+ cells recognize the allergen-derived target presented with class II on antigen-presenting cells along with costimulatory signals. One recently described costimulatory molecule is CD137. Studies using murine disease models have shown that stimulation of CD137 on T cells can modulate the immune system in beneficial ways, such as promoting tumor regression and suppressing autoimmunity. The authors of this study investigated the effect of CD137 stimulation on a murine model of allergic asthma.

METHODS. Allergic airway inflammation was induced in BALB/cByJ mice in the well-established manner involving systemic immunization to ovalbumin with alum followed by repeated aerosolized ovalbumin exposure. Control, nonspecific, antibody-treated mice were compared with mice treated with a single dose of agonistic anti-CD137 antibody given either before ovalbumin sensitization or after establishment of airway inflammation. Immunologic responses to ovalbumin were measured by ovalbumin-induced proliferation, in vitro cytokine production, and ovalbumin-specific immunoglobulin E and G1 titers. Changes in frequency of lymphocyte populations (CD4+, CD8+, CD19+, and CD4+CD25+) were measured by flow cytometry of total splenocytes. Adoptive transfer experiments were also conducted with CD4+ cells into severe combined immunodeficiency animals after control or anti-CD137 treatment.

RESULTS. A single dose of anti-CD137 treatment was effective in prevention of ovalbumin-induced airway inflammation and in vitro recall responses to ovalbumin continued to show suppressed Th2 cytokine responses (IL-4, IL-5, IL-13) and elevated Th1 (interferon γ [IFN-γ]) even after chronic ovalbumin exposure. Anti-CD137 given as a single dose after establishment of airway inflammation induced significant reduction of inflammation, even when given at a time point associated with chronic inflammation (32 weeks). In vitro cytokine responses were modulated by anti-CD137 treatment, which resulted in lower levels of ovalbumin-induced Th2 cytokines and elevated levels of IFN-γ in both lung and spleen cells. Anti-CD137 treatment was also associated with an increase of CD8+ cells and a decrease of CD19+ cells. The anti-CD137 affect was not entirely accounted for by this increase in CD8+ or IFN-γ, because inhibition of either resulted in only a partial reversal of its effect. Consistent with this, adoptively transferred CD4+ cells from animals that had been treated with anti-CD137 induced lower levels of airway inflammation compared with control-treated CD4+ cells.

CONCLUSIONS. CD137 is a potentially important target molecule for the modulation of Th2 inflammation.

REVIEWER COMMENTS. Asthma morbidity continues to rise in the pediatric population. This was the first report of the potential importance of the CD137 costimulatory pathway in the pathogenesis of Th2-driven airway inflammation. CD137 activation has been shown to be associated with both promotion of Th1 and regulatory T-cell activity in various disease models, and clinical trials targeting this pathway are likely to come soon for tumor immunology. Much more study is required, but this may emerge as an important new target for suppressing allergic inflammation.
Novel Approach to Inhibit Asthma-Mediated Lung Inflammation Using Anti-CD147 Intervention

PURPOSE OF THE STUDY. Extracellular cyclophilins are known to promote chemotaxis of various leukocyte subsets through interaction with the cell surface signaling receptor CD147. Increased levels of extracellular cyclophilins have been reported in various inflammatory diseases. This study investigated whether extracellular cyclophilin-CD147 interaction plays a role in the recruitment of leukocytes in asthmatic lung inflammation.

METHODS. A mouse model of allergic asthma was created by intraperitoneal ovalbumin injection into newborn mice, followed by intranasal ovalbumin challenge on days 7 to 10. For in vivo inhibition studies, anti-CD147 was administered intraperitoneally on days 6 to 11. Bronchial hyperreactivity was assessed on day 12. After sacrifice on day 12, the following were examined: histology on bronchoalveolar lavage (BAL) and lung biopsy, cytokine levels after restimulation of pulmonary lymphocytes with ovalbumin antigen, cyclophilin (Cyp) A and CypB levels in BAL fluid by Western blot analysis, chemotaxis of eosinophils and CD4+ splenocytes to CypA and CypB, and CD147 expression levels on CD4+ T cells by fluorescence-activated cell sorter analysis.

RESULTS. The mouse model of asthma-mediated lung inflammation was confirmed by the findings of elevated eosinophils and lymphocytes in the BAL of ovalbumin mice, elevated interleukin 5 (IL-5) and IL-13 in lung cell supernatant from ovalbumin mice cells restimulated with antigen, and airway hyperresponsiveness to methacholine in ovalbumin mice. The main study findings were: (1) extracellular CypA and CypB levels were significantly increased in the airways of asthmatic mice; (2) CD147 was expressed by mouse eosinophils and CD4+ T cells and upregulated in activated CD4+ T cells; (3) CypA and CypB induced CD147-dependent chemotaxis of activated mouse CD4+ T cells but not eosinophils; (4) in vivo anti-CD147 monoclonal antibody (mAb) treatment resulted in a significant (up to 50%) decrease in the numbers of eosinophils and CD4+ T cells in lung tissues of ovalbumin mice, as well as a reduction in antigen-specific T-helper 2 (Th2) cytokine (IL-5 and IL-13) secretion; and (5) anti-CD147 mAb treatment reduced airway epithelial mucin production and bronchial hyperreactivity.

CONCLUSIONS. This study suggests that extracellular cyclophilins, through interaction with CD147, play a role in asthma-mediated lung inflammation and that anti-CD147 intervention significantly reduces several parameters of this inflammation.

Neonatal-Onset Multisystem Inflammatory Disease Responsive to Interleukin-1β Inhibition

PURPOSE OF THE STUDY. Neonatal-onset multisystem inflammatory disease (NOMID) is a chronic inflammatory disease that develops in infancy and is characterized by an urticarial rash, arthropathy, and central nervous system disease, including aseptic meningitis, cerebral atrophy, mental retardation, seizures, and vision and hearing loss. Approximately 60% of patients have a mutation in the cold-induced autoinflammatory syndrome 1 (CIAS1) gene, which is involved in the interleukin 1β (IL-1β) pathway. This study evaluated the effect of anakinra (Kineret, Amgen), an IL-1 receptor antagonist, on the various clinical and laboratory aspects of NOMID.

STUDY POPULATION. A cohort of 18 patients aged 4 to 32 years with clinical NOMID (67% with mutations in CIAS1) who had active disease despite treatment with other antiinflammatory agents.

METHODS. Patients were given a daily subcutaneous dose of anakinra. The drug was withdrawn from 11 patients at 3 months with the development of a clinical flare. Thereafter, all patients were continued on daily treatments up to 24 months. Clinical and laboratory assessments were made at 1, 3, and 6 months during therapy with anakinra. Primary end points included changes in a disease-specific daily diary score and changes in the serum levels of acute-phase reactants.

RESULTS. All patients had an immediate response to anakinra with resolution of rash and conjunctivitis. There

REVIEWER COMMENTS. The pathogenesis of allergic asthma involves the recruitment of eosinophils and Th2 lymphocytes to airways and lung tissues, with resultant elaboration of cytotoxic proteins, mediators, and cytokines that induce disease pathology, such as increased mucus and bronchial hyperreactivity. Much attention has focused on chemokines that attract these inflammatory cells through interaction with chemokine receptors on leukocytes. The important chemokine-like activity of extracellular cyclophilins, via their interaction with CD147, was investigated in this study, and anti-CD147 treatment was found to significantly reduce leukocyte recruitment to inflamed lung tissues. Given the pathogenesis of allergic asthma, the targeting of cyclophilin–CD147 interaction using anti-CD147 mAb represents a potentially novel asthma therapy.

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was an improvement in diary scores at 3 months that was maintained at 6 months. Serum amyloid A, C-reactive protein, and the erythrocyte sedimentation rate significantly declined with treatment. All the patients had headache at baseline, which resolved or improved with therapy, and cochlear and leptomeningeal lesions were improved on MRI. Serum levels of IL-1β, which were initially higher than those in healthy controls, decreased over the first 6 months of therapy. All the patients who underwent a treatment withdrawal experienced rapid improvement of their symptoms after resuming anakinra. Other than injection-site reactions, which resolved with continued treatment, there were no serious adverse events.

CONCLUSIONS. Anakinra may be a safe and effective treatment for patients with NOMID.

REVIEWER COMMENTS. This study suggests that anakinra may have a role in the treatment of other diseases in which IL-1β mediates inflammation (eg, systemic juvenile rheumatoid arthritis). Additional studies are needed to determine its long-term effects and clinical application. This study is an example of how specific immunomodulatory therapy may be useful in treating those diseases that have a defined molecular pathophysiologic profile.

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PRIMARY IMMUNODEFICIENCY

Memory Switched B Cell Percentage and Not Serum Immunoglobulin Concentration Is Associated With Clinical Complications in Children and Adults With Specific Antibody Deficiency and Common Variable Immunodeficiency


PURPOSE OF THE STUDY. To compare the associations of clinical complications of antibody deficiency with (1) measures of memory B-cell development and (2) serum immunoglobulin (Ig) concentrations.

STUDY POPULATION. Twenty-seven children (aged 2–16 years) and 28 adults (aged 22–65 years) with diagnoses of specific antibody deficiency defined as having normal Ig levels and impaired responses to pneumococcal immunization (specific antibody deficiency [SAD], 21 patients) or common variable immunodeficiency defined as hypogammaglobulinemia with more generally impaired vaccine responses (common variable immunodeficiency [CVID]; 34 patients) were studied. Nineteen patients who underwent evaluation and were found to have normal Ig levels and fully intact vaccine responses served as a “control” group.

METHODS. Serum Ig levels were measured by standard clinical laboratory methods; memory B-cell populations were assessed by flow cytometry using labeled monoclonal antibodies to detect cell-surface CD19, CD27, and IgD. (CD19 is a marker for all B cells. CD27 is a marker for the memory subset of cells. Cells that do not express IgD have undergone class-switching and express IgG, IgA, or IgE. CD19+CD27+IgD− cells are called “switched” memory B cells and are indicators of normal B-cell activation and development in germinal centers in lymph nodes or other secondary lymphoid tissues.) These laboratory findings were separately correlated with clinical characteristics.

RESULTS. The only significant laboratory differences between the SAD and CVID groups were the serum concentrations of IgG and IgA, which was expected because of the laboratory definitions of these entities. There were no differences in memory B-cell populations nor the occurrence of splenomegaly, bronchiectasis, and autoimmune disease (enteropathy, cytopenias, arthritis, diabetes) between the groups with SAD and CVID. However, when patients with each of these complications (without regard to immunodeficiency diagnosis) were compared with those without, a significantly ($P < .01$) lower percentage and number of switched memory B cells was found in the affected patients. The statistical significance was unchanged after adjustment for age. Serum Ig levels were not different in patients with or without each of these complications, even after adjusting for age.

CONCLUSIONS. Measurement of switched memory B cells is a more accurate predictor of clinical complications of humoral immunodeficiency than is the classification of SAD and CVID or measurement of serum Ig.

REVIEWER COMMENTS. Measurement of memory B-cell populations has emerged in the past 5 years as a potentially clinically useful predictor of complications for patients with CVID, with reports of findings similar to those in this article. This study extends this observation to another diagnosis: SAD. This study was also the first to compare children and adults with these 2 diagnoses with respect to clinical and laboratory features. Although the numbers are relatively small, neither the diagnostic assignment nor measurement of serum Ig concentration (related by the clinical/laboratory definitions of these syndromes) allows one to predict the occurrence of the complications studied. Even across diagnoses, the determination of switched memory B-cell percentage emerges as a robust indicator of associated complications. This laboratory test is likely to become a part of the routine evaluation of humoral immunodeficiency.

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Infants Presenting With Recurrent Infections and Low Immunoglobulins: Characteristics and Analysis of Normalization


PURPOSE OF THE STUDY. To determine the outcomes of infants and young children with recurrent infections found to have low levels of ≥1 immunoglobulin (Ig) class (IgG, IgA, or IgM) without other screening laboratory indicators of immunodeficiency.

STUDY POPULATION. Forty-nine infants who presented for evaluation at <24 months of age and had IgG, IgA, or IgM levels of <2 SD below the age-adjusted mean, intact antibody response to tetanus and diphtheria, intact cellular immunity, and no other immunodeficiency diagnoses.

METHODS. Retrospective review of medical charts at a single institution from 1977 to 2005.

RESULTS. Boys accounted for 70% of the patients. Recurrent otitis media was the predominant presentation (78%). Significant associated features were recurrent wheezing with infection (61%) and atopy (27%). Multiple isotypes were reduced in 65% of the patients; low
IgA was most prevalent (96%). Only half of the patients had achieved normalization of Ig levels at the end of the observation period. Of these, 84% had become normal by 5 years of age. Of the patients who had not yet normalized at the end of the study, 54% were >5 years old. Two met criteria for selective IgA deficiency. Higher levels of Igs at presentation were associated with shorter times to normalization. Boys who presented at younger ages normalized more quickly than those who presented later. The opposite was true for girls. On average, the time to normalization for girls was 10-fold longer than the time for boys. Serious infections or death were not observed.

CONCLUSIONS. Most patients with this phenotype are boys with recurrent otitis media, wheezing episodes, and atopy. Girls with this presentation may be at greater risk for prolonged immunodeficiency. A “definitive” diagnosis of transient hypogammaglobulinemia can only be conferred retrospectively (ie, after Ig levels have normalized).

REVIEVER COMMENTS. There were several interesting new observations in this group of patients. In particular, the gender differences in time to normalization stand out; the immunologic significance of this finding is not known. The authors correctly pointed out that patients must be followed at least until clinical resolution, if not actual normalization, of Ig values. Only half of the patients normalized during the observation period. It is possible that other specific immunodeficiency diagnoses may be conferred on some of the patients who are still hypogammaglobulinemic. The authors did not comment on whether some patients who initially presented in this way subsequently developed additional clinical and/or laboratory features leading to the diagnosis of other immunodeficiencies. Without knowing this, it is impossible to estimate the predictive value of intact vaccine responses in this setting (ie, how often do we “miss” a different specific immunodeficiency diagnosis if we stop after this initial evaluation). However, these and other reports suggest that the majority of these patients follow a relatively benign course.

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Clinical and Laboratory Characteristics of 75 Patients With Specific Polysaccharide Antibody Deficiency Syndrome

PURPOSE OF THE STUDY. To study the clinical and laboratory characteristics of patients with specific polysaccharide antibody deficiency syndrome.

STUDY POPULATION. This was a retrospective review of records obtained over 8 years of patients from the Mayo Clinic (Rochester, MN) who were found to have recurrent infection defined as ≥4 infections per year and an immunoglobulin G (IgG) level of >500 mg/mL.

METHODS. Serious infections were defined as pneumococcal sepsis, meningitis, pneumonia, or deep-seated abscess. Specific polysaccharide antibody deficiency syndrome (SPADS) is empirically defined as <9 of 12 serotype responses to vaccination with Pneumovax (titers checked preimmunization and 2–4 weeks postimmunization ×2), and no other documented, established primary or secondary immunodeficiency syndrome. An adequate response to pneumococcal serotypes contained in the vaccine was defined as reaching the protective level defined by the laboratory assay. Loss of immune response 6 months after vaccination was also assessed in patients with recurrent infection. In such patients, vaccination was repeated and serologies were remeasured.

RESULTS. Seventy-five patients met the inclusion criteria. The median age at presentation was 42 years (range: 0–76 years), and the median age at diagnosis was 48 years (range: 4–81 years). The median interval between onset of symptoms and diagnosis of SPADS was 4 years. Sixty-nine percent of the patients were female, and 83% were white. The most common documented infections (in order of occurrence) were sinus infection, pneumonia, bronchitis, and ear infections; only 7% of the patients had documented sepsis, meningitis, or deep-tissue abscesses. Eight percent had autoimmune disorder or rheumatic disease. Sixteen percent of the patients had 0 of 12 responses to Pneumovax; 72% had 1 to 6 of 12 responses; and 12% had 7 to 8 of 12 responses. Patients under 18 years of age tended to have less response. The median IgG2 level (150 mg/dL) for patients with 0 responses to Pneumovax tended to be lower compared with patients with >1 response (193 mg/dL; P = .06). When measured, the majority (31 of 35) of the patients had protective levels of antibody to tetanus and diphtheria (18 of 19). In vitro lymphocyte-stimulation test results were normal in the vast majority of patients when measured. Thirty patients were treated with a standard intravenous Ig (IVIg) therapy, 400 mg/kg per month for an undetermined time period. Patients with a higher number of infections (P = .003) and fewer responses to Pneumovax (P = .01) were more likely to receive IVIg. Of the patients receiving IVIg, the number of infections after treatment was significantly lower (median: 1 vs 8; P < .001).

CONCLUSIONS. SPADS is a disorder of humoral immunity that is seen in patients with recurrent infections. Response to unconjugated pneumococcal vaccine is abnormal despite normal total IgG levels. Other immune abnormalities are not typically seen. Patients with more frequent infections have less responses to Pneumovax and may clinically respond to IVIg therapy.
as postimmunization antibody concentration of fines response to pneumococcal polysaccharide vaccine sis and management of primary immunodeficiency de- well established. The practice parameter for the diagno- normal response to pneumococcal vaccination was not response to protein antigens). The definition of an ab- tion of SPADS (some with autoimmune disease, poor response to protein antigens). The definition of an ab- normal response to pneumococcal polysaccharide vaccine as postimmunization antibody concentration of >1.3 μg/mL or fourfold rise over baseline. Children younger than 2 years should not be given a diagnosis of SPADS, because they have a physiologic impairment of antibody production to unconjugated polysaccharide antigens. Prospective studies for a more specific definition and response to treatment are needed for patients with specific antibody deficiency and normal IgG levels.

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HUMAN IMMUNODEFICIENCY VIRUS

Immune Reconstitution Syndrome After Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus-Infected Thai Children


PURPOSE OF THE STUDY. Immune reconstitution inflammatory syndrome (IRIS) is a clinical phenomenon characterized by paradoxical worsening of the clinical status of patients with HIV who receive highly active antiretroviral therapy. It is presumed that this is a result of improvement in cellular immune functions and secondary immunopathology in response to organisms that had not been recognized previously. This syndrome has been well described in adult patients. The purpose of this study was to describe IRIS after initiation of highly active antiretroviral therapy in HIV-infected children.

STUDY POPULATION AND METHODS. There were 153 HIV-infected children enrolled at initiation of antiretroviral therapy and then followed prospectively.

RESULTS. Of the 153 children, 29 (19%) experienced 32 episodes of IRIS. The median time of onset was 4 weeks after initiation of antiretroviral therapy. Fourteen episodes were caused by mycobacterial organisms, 7 by varicella-zoster virus, 7 by herpes simplex virus, 3 by Cryptococcus neoformans, and 1 by Guillain-Barré syndrome. In general, treatment was not interrupted, and only 2 patients were treated with short courses of corticosteroids. However, 3 patients died as a result of IRIS or its complications. It is important to note that patients who reactivated mycobacterial disease had substantially lower CD4+ T-cell counts at the time that their antiretroviral therapy was started, compared with patients who reactivated herpes viruses.

CONCLUSIONS. IRIS is common among HIV-infected children who initiated antiretroviral therapy in an advanced stage of HIV disease.

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PD-1 Expression on HIV-Specific T Cells Is Associated With T-Cell Exhaustion and Disease Progression


Upregulation of PD-1 Expression on HIV-Specific CD8+ T Cells Leads to Reversible Immune Dysfunction


PURPOSE OF THE STUDIES. Recent evidence from a mouse model of chronic viral infection suggests a crucial role for the programmed death 1 (PD-1)/programmed death 1 ligand (PD-L1) signaling pathway in downregulating the functions of virus-specific CD8+ T cells. PD-1 is an inhibiting receptor that negatively regulates activated T cells, and it is markedly upregulated on the surface of “exhausted” virus-specific CD8+ T cells in mice. HIV similarly induces a virus-specific impairment of T-cell functions. The purpose of these 2 studies was to investigate the expression of PD-1 on HIV-specific T cell in patients infected with the virus.

STUDY POPULATION AND METHODS. Both studies evaluated subjects with HIV and healthy controls and compared PD-1
expression in these individuals on virus-specific T cells. A panel of MHC class I tetramers were used to identify HIV-specific CD8^+ T cells. PD-1 expression was then measured on tetramer-positive cells. PD-1 expression was also analyzed on cytomegalovirus-specific, Epstein-Barr virus–specific, and vaccinia virus–specific CD8^+ T cells from HIV-negative controls.

RESULTS. The findings in these studies were remarkably similar. PD-1 was significantly upregulated on HIV-specific T cells, and expression correlated with impaired HIV-specific CD8^+ T-cell function as well as predictors of disease progression: HIV viral load, a reduced capacity for cytokine production, and decreased proliferation of HIV-specific CD8^+ T cells. Cytomegalovirus-specific CD8^+ T cells from the same donors did not upregulate PD-1 and seemed to maintain functional integrity. Blockade of the PD-1/PD-1L pathway result reversed immune dysfunction.

CONCLUSIONS. The PD-1/PD-1L pathway is associated with significant HIV-specific T-cell exhaustion. The accumulation of HIV-specific dysfunctional T cells in an infected host may prevent the renewal of a functionally competent HIV-specific CD8^+ T-cell response.

REVIEWER COMMENTS. HIV has proven remarkably adept at inhibiting the very system that evolved to control it. Expression of a negative regulator of activated T cells, PD-1, is markedly increased on HIV-specific CD8^+ T cells when HIV engages the T-cell receptor. Such T cells have been termed “exhausted” because they fail to respond as fully activated effector cytotoxic T cells. Surprisingly, blockade of PD-1 engagement with its ligand results in a restoration of T-cell function. This observation suggests a target for enhancing the function of exhausted T cells in HIV-infected individuals. However, much has to be learned about the importance of this pathway in the control of normal T-cell activation. T-cell activation seems to be an intrinsic component of HIV pathogenesis; therefore, blocking this activation may be useful. However, it would be potentially dangerous to be unable to turn off an activated immune response to a routine infection.

A Prospective Controlled Study of Neurodevelopment in HIV-Uninfected Children Exposed to Combination Antiretroviral Drugs in Pregnancy

PURPOSE OF THE STUDY. The effective treatment of HIV-infected women with antiretroviral agents has dramatically reduced the incidence of HIV infection in their newborn infants. However, an ongoing concern has been the potential adverse effects of the antiretroviral agents themselves on the neurodevelopment of HIV-uninfected children who were exposed to combination HIV medications. The purpose of this study was to investigate the neurodevelopment of HIV-infected children exposed to combination anti-HIV therapy in pregnancy compared with children not exposed to this therapy.
STUDY POPULATION. A total of 39 antiretroviral therapy–exposed and 24 control children were assessed.

METHODS. This was a prospective, controlled, cross-sectional study. The Bailey Scales of Infant Development and Vineland Adaptive Behavior scales were performed at 18 to 36 months of age. Control children were born to HIV-uninfected women with similar anticipated social and economic backgrounds. Results were compared by using analysis of covariance and χ² analysis.

RESULTS. All scores were lower for children who were exposed prenatally to antiretroviral therapy. However, when maternal substance use during pregnancy was controlled for, there were no significant differences between the groups in any of the domains assessed. Children in both groups who were exposed to maternal substance use scored significantly lower in most domains than children who were not exposed.

CONCLUSIONS. HIV and antiretroviral therapy–exposed HIV-uninfected children had lower development and adaptive behavior scores compared with children who were not exposed to HIV or anti-HIV drugs. It is important to note that these differences were not significant when maternal substance use was considered. In this prospective study, exposure to perinatal anti-HIV therapy was not associated with neurodevelopmental abnormalities.

REVIEWER COMMENTS. This small study demonstrated that maternal substance use impacted the neurodevelopment of children to a far greater extent than exposure to anti-HIV drugs. In this study, at least, any negative impact of antiretroviral drugs on infant neurodevelopment was masked by the maternal substance use. This is not to say that exposure to combination anti-HIV medications may not have an impact on childhood development. Studies with similar designs to this one, in larger numbers of children for whom maternal substance use is not a confounding factor, will be required to address this issue fully.

PURPOSE OF THE STUDY. Chemokine receptor 5 (CCR5) is critical for survival of mice infected with West Nile virus (WNV). CCR5Δ32 is a defective CCR5 found predominantly in white individuals. Approximately 1% of the white population in the United States have homozygous CCR5Δ32 and completely lack CCR5 function. Individuals with CCR5Δ32 have an innate resistance to infection with HIV, because most HIV that is transmitted sexually or perinatally uses the CCR5 as a coreceptor with CD4 for HIV attachment to target cells. CCR5 inhibitors are in development, because most individuals with homozygous CCR5Δ32 seem to be immunologically normal. The purpose of this study was to determine if the presence of CCR5Δ32 homozygosity increases the risk for symptomatic WNV infection.

STUDY POPULATION AND METHODS. Three cohorts of patients were studied: 2 WNV-positive and 1 WNV-negative but with symptomatic illness in which WNV was considered. Genotypes of CCR5 were defined for each subject in the 3 cohorts.

RESULTS. In the group of healthy white random blood donors, CCR5Δ32 homozygotes represented 1% of the total. In contrast, CCR5Δ32 homozygotes represented over 4% of white subjects in the one WNV cohort and 8% in the second cohort. CCR5Δ32 homozygosity was significantly associated with fatal outcome in one of the cohorts.

CONCLUSIONS. The authors concluded that CCR5 mediates resistance to symptomatic West Nile infection.

REVIEWER COMMENTS. The immune system has evolved over the millennia to provide generally protective functions for the human host. That a particular chemokine receptor was maintained throughout this evolutionary process suggests a survival advantage. One percent of the white population in the United States have a genotype that eliminates functional CCR5. This mutation emerged in northern Europe and probably had no significant negative impact on that population. However, it seems that host defense against WNV depends on sufficient CCR5 engagement. CCR5 blockade is an emerging strategy in the treatment of HIV infection. It is possible that blockade of CCR5 will subsequently result in an increase risk for invasive WNV infection. If the CCR5 inhibitors continue through development, this potential complication must be anticipated.

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CCR5 Deficiency Increases Risk of Symptomatic West Nile Virus Infection

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Cost of Influenza Hospitalization at a Tertiary Care Children’s Hospital and Its Impact on the Cost-Benefit Analysis of the Recommendation for Universal Influenza Immunization in Children Age 6 to 23 Months

PURPOSE OF THE STUDY. To calculate the costs of influenza hospitalization at a tertiary care children’s hospital as the basis of a cost/benefit analysis of the new influenza vaccine recommendation for children 6 to 23 months old.

STUDY DESIGN. The investigators reviewed the medical charts of all patients diagnosed with influenza and admitted to Children’s Memorial Hospital in Chicago, Illinois, in 2002. Total hospital costs were obtained from the business development office.

RESULTS. Thirty-five charts were analyzed. Both of the 2 patients who required mechanical ventilation and 4 of the 6 patients admitted to the ICU had high-risk underlying medical conditions. Nine children were 6 to 23 months old; 4 of these 9 had no preexisting medical conditions. Had all 18 high-risk children over 6 months old been protected from influenza, approximately $350,000 in hospital charges could have been saved.

CONCLUSIONS. Preventing the additional 4 hospitalizations in the otherwise low-risk children 6 to 23 months old for whom vaccine was currently recommended would have cost approximately $281,000 ($46 per child) more than the hospital charges saved. When all children 6 to 23 months old were considered, influenza vaccination would have been less costly than other prophylactic measures. Addition of indirect costs, deaths, outpatient costs, and the cost of secondary cases would favor the cost/benefit ratio for influenza vaccination of all children 6 to 23 months old.

REVIEWER COMMENTS. A few years ago when recommendations were made to immunize all children 6 to 23 months of age with the influenza vaccine, they were not initially accepted with open arms because of an already-busy infant-immunization schedule. This article provided interesting data regarding actual charges of hospitalization for care of children with influenza. Analyzing the ages and underlying medical conditions of these children, as well as using conservative estimates of vaccine efficacy and only direct costs of hospitalization, the investigators predicted substantial cost savings from vaccinating children with underlying medical conditions and modest spending ($46 per child) when vaccinating healthy children 6 through 23 months of age. Recognized limitations of the investigation included extrapolation of findings from a tertiary care center and underrepresentation of children without underlying conditions. Hopefully, in the future, we will have more data such as these that will be useful in assessing the cost/benefit ratio of influenza vaccination recommendations in pediatric patients.

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Wait-and-See Prescription for the Treatment of Acute Otitis Media: A Randomized Controlled Trial
Spiro DM, Tay KY, Arnold DH, Dziura JD, Baker MD, Shapiro ED. JAMA. 2006;296:1235–1241

PURPOSE OF THE STUDY. Acute otitis media (AOM) is the most common diagnosis for which antibiotics are prescribed for children. Previous trials that have evaluated a “wait-and-see prescription” (WASP) for antibiotics, with which parents are asked not to fill the prescription unless the child either is not better or is worse in 48 hours, have excluded children with severe AOM. None of these trials were conducted in an emergency department. The purpose of this study was to determine if treatment of AOM using a WASP significantly reduces use of antibiotics compared with a standard prescription (SP) and to evaluate the effects of this intervention on clinical symptoms and adverse outcomes related to antibiotic use.

STUDY POPULATION. Children with AOM aged 6 months to 12 years seen in an emergency department in 1 year.

METHODS. A randomized, controlled trial was conducted; patients were randomly assigned to receive either a WASP or an SP. All patients received ibuprofen and otic analgesic drops for use at home. A research assistant who was blinded to group assignment conducted structured telephone interviews 4 to 6, 11 to 14, and 30 to 40 days after enrollment to determine outcomes and monitor filling of the antibiotic prescription and clinical course.

RESULTS. Overall, 283 patients were randomly assigned to either the WASP (n = 138) or SP (n = 145) group. Substantially more parents in the WASP group did not fill the antibiotic prescription (62% vs 13%; P < .001). There was no statistically significant difference between the groups in the frequency of subsequent fever, otalgia, or unscheduled visits for medical care. Within the WASP group, both fever (relative risk: 2.95; 95% confidence interval: 1.75–4.99; P < .001) and otalgia (relative risk: 1.62; 95% confidence interval: 1.26–2.03; P < .001) were associated with filling the prescription.
CONCLUSIONS. The WASP approach substantially reduced unnecessary use of antibiotics in children with AOM seen in an emergency department and may be an alternative to routine use of antimicrobial agents for treatment of such children.

REVIEWER COMMENTS. This study added a few new twists to 2 previous, similar studies: (1) the patients had no previous relationship with the prescribing physician; (2) the patients, overall, were sicker, being seen in an ED; and (3) otic analgesics and ibuprofen were allowed. The use of antibiotics by those in the WASP group was 56% less than those in the SP group. We try in our practice to use a similar approach in our patients who also present with symptoms of acute sinusitis. Still, I wonder how many patients who do not use their prescription just save it for their next episode.

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