with DBPCFCs still considered the “gold standard” for this diagnosis.

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

**LAURA GOBER, MD**  
MARY BETH BOLLINGER, DO  
Baltimore, MD

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


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

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

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

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

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

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

**JOHN E. DUPLANTIER, MD**  
Indianapolis, IN

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


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

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

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

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

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

**Reviewer’s Comments.** Although subsequent food-allergic reactions were similar to previous ones, more severe reactions can occur. Many patients erroneously believe that subsequent reactions will automatically be more severe over time and this study dispels that notion. However, the results also support the instruction to families that subsequent reactions could be more severe. In the same context, the study results highlight the importance of educating patients on food-allergen avoidance and how to identify and treat allergic reactions, including the use of self-injectable epinephrine.

**HELEN SKOLNICK, MD**  
Princeton, NJ

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


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

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

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

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

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

John James, MD
Fort Collins, CO

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


**Purpose of the Study.** To develop a peptide microarray-based immunoassay to map IgE-binding segments (epitopes) of peanut allergens by using microarrayed epitopes of sequential recombinant proteins onto glass slides and used for immunolabeling.

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

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

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

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

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

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

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


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

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

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

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

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

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

Frederick E. Leickly, MD
Indianapolis, IN

ANAPHYLAXIS AND INSECT ALLERGY

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


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

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

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

**Results.** A total of 898 patients were identified, and a random sample of 70 (9%) cases with a coded diagnosis and 50 (43%) cases with a comment diagnosis underwent additional evaluation. Relevant information on the diagnosis was available for >90% of these cases. Criteria for anaphylaxis was met in 87 of the 120 cases, so that an estimated 675 cases of the total 783 were estimated to have confirmed anaphylaxis, resulting in an incidence of 8.4 cases per 100 000 person-years. Insect stings were responsible for 32% and medications for 30% of cases. Food was implicated in 29% of cases, and > half of these were due to a tree nut or peanut. Severity of the cases was categorized into 3 types: localized urticaria and did not require treatment in an emergency department; the reaction was considered to be moderate if the symptoms were primarily limited to gastrointestinal symptoms; the reaction was considered to be severe if there was hypotension or respiratory symptoms.

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

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

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


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

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

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

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

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

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

Elizabeth Matsui, MD
Baltimore, MD

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


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

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

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

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

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

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

Bradley E. Chippis, MD
Sacramento, CA

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


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

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

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

Results. Of the 1033 patients, 512 (50%) responded, with a mean follow-up period of 18 years, a mean duration of venom immunotherapy of 3.5 years in treated patients, and a sting incidence of 43%. Systemic reactions occurred less frequently in patients who had received venom immunotherapy (2 of 64 patients [3%]) than in untreated patients (19 of 111 patients [17%]; P = .007). Patients with a history of moderate-to-severe reactions had a higher rate of reaction if they had not been treated (7 of 22 patients [32%]) than if they had received venom immunotherapy (2 of 43 patients [5%]; P = .007). In patients who had been treated and had a history of mild (cutaneous) systemic reaction, none of the 21 subjects who received stings had a systemic reaction; however, there was no statistical significance between the rates of reaction when comparing the treated versus the untreated groups. Among the patients who had not received venom immunotherapy, there were no severe systemic reactions after a subsequent sting. Twenty-seven percent of patients who had moderate-to-severe initial reactions sustained subsequent reactions of similar severity (otherwise, the reactions were less severe), and 6.7% of patients with initial mild (cutaneous) systemic reactions developed moderate systemic reactions on subsequent stings (otherwise, the reactions were less severe than the original [87% had no subsequent systemic allergic reaction]).

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

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

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

The Upper Airway

THE DIAGNOSTIC ACCURACY OF COMPUTED TOMOGRAPHY IN PEDIATRIC CHRONIC RHINOSINUSITIS


Purpose of the Study. To determine the accuracy of computed tomography (CT) in the diagnosis of pediatric chronic rhinosinusitis (CRS).

Study Population. The sinus CT scans of 2 cohorts of children were evaluated and compared prospectively. The “diseased” cohort consisted of 66 children (mean age: 8 years) who were scheduled to undergo endoscopic sinus surgery for medically refractory CRS. The second “nondiseased,” control cohort consisted of 192 children (mean age: 9 years) who were undergoing CT scans for reasons other than sinusitis.

Methods. Sinus CT scans were scored according to the Lund-Mackay system. The Lund-Mackay staging system scores each sinus (anterior ethmoid, posterior ethmoid, maxillary, frontal, and sphenoid sinuses) according to the following scale: 0, no opacification; 1, partial opacification; 2, complete opacification. The ostiomeatal complex is scored as 0 (not occluded) or 2 (occluded). The left and right sides are staged separately. The scores are summed so that the total Lund score may range from 0 to 24 for each patient. The authors adapted the Lund-Mackay staging system for young children by assigning a null value to undeveloped sinuses. The corresponding Lund score was then scaled up to range from 0 to 24 by scaling with the factor 12/n, where n represents a number of scoreable (pneumatized) sinuses. The Lund scores of the diseased and control groups were compared. The diagnostic accuracy of the CT scan in distinguishing diseased patients from control patients was established by using the receiver operating characteristic curve. Sensitivity, specificity, and predictive value analyses were also conducted. The authors calculated predictive values at different base-rate prevalence values.

Results. The diseased group exhibited a mean Lund score of 10.4 (95% confidence interval [CI]: 9.2, 11.5), and the control group exhibited a mean Lund score of 2.8 (95% CI: 2.4, 3.2). The area under the curve for the receiver operating characteristic was 0.923 (P < .001), indicating excellent diagnostic accuracy for CT scans. Adopting a Lund score cutoff of 5 to represent true disease, the CT scan demonstrated a sensitivity and specificity of 86% and 85%, respectively. Lund scores of ≤2 have an excellent negative predictive value, whereas Lund scores of ≥5 have an excellent positive predictive value. The authors demonstrated a decline in diagnostic accuracy of the CT scan with decreasing base-rate prevalence of the disease by calculating positive and negative predictive values at base-rate prevalences of 0.2, 0.5, and 0.8.

Conclusions. The sinus CT scan demonstrates excellent diagnostic accuracy for the diagnosis of pediatric CRS, with excellent sensitivity and specificity. The predictive value depends substantially on the base-rate prevalence of CRS in the population being evaluated. The authors established Lund score ranges for CT scans of children with sinusitis: 0 to 2, normal; ≥5, positive for sinusitis; 3 to 4, equivocal.

Reviewers’ Comments. Although CT is considered the gold standard for diagnosis of CRS, its sensitivity, specificity, and diagnostic accuracy have not been well established in children. This study uses quantitative Lund
scores to differentiate pediatric patients with and without CRS based on radiographic criteria. Based on these data and analysis, we can use the CT scan to discriminate between children with and without CRS. Nevertheless, the positive and negative predictive values of this test are substantially dependent on the prevalence of CRS, and this must be factored into clinical decision-making. This study highlights the fact that CRS is primarily a clinical diagnosis, and both the decision to perform a sinus CT and the interpretation of the scan should include this clinical context.

Sara I. Pai, MD, PhD
David E. Tunkel, MD
Baltimore, MD

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


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

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

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

Results. Over a mean follow-up period of 22 months, children in the adenotonsillectomy group compared with children in the watchful-waiting group as follows: 2.97 fevers per person-year compared with 3.18 (difference: −0.21, 95% confidence interval [CI]), 0.56 throat infections compared with 0.77 (difference: −0.21, 95% CI), and 5.47 upper respiratory tract infections compared with 6.00 (difference: −0.53, 95% CI). The subgroup of patients with 3 to 6 throat infections in the preceding year did show more pronounced results than the subgroup of 0 to 2 infections. Health-related quality-of-life scores revealed no clinical differences at 2 years. The Brouillette score of obstructive sleep apnea was lower in the group receiving surgery after 6 months but not at 24 months.

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

Reviewers’ Comments. Adenotonsillectomy is one of the most common surgical procedures performed on children, and these authors noted a tonsillectomy rate in the Netherlands more than twice that seen in the United States. The children in this study do not have the well-established indications for adenotonsillectomy, namely very frequent pharyngitis or documented obstructive sleep apnea. It is certainly not a new concept that only modest benefits are afforded by adenotonsillectomy to children “moderately affected” by throat infection (see Pediatrics. 2002;110:7–15.)

This study supports continued use of well-defined severity criteria to select children for treatment with adenotonsillectomy, because sustained major benefits of surgery were not demonstrated in children with mild illnesses. However, more than 34% of the children randomized to observation in this study underwent adenotonsillectomy during the follow-up period. The analysis of outcomes was performed based on initial randomization, not on the eventual treatment. We are also concerned that children with mild obstructive symptoms of adenotonsillar hypertrophy may have upper airway resistance or obstructive sleep apnea of physiologic consequence. These children may need additional evaluation and/or consideration for adenotonsillectomy to avoid complications of upper airway obstruction.

Karin S. Hotchkiss, MD
David E. Tunkel, MD
Baltimore, MD

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


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

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

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

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

Conclusions. In atopic patients with OME, the allergic inflammation occurs on both sides of the eustachian tube,
in both the middle ear and the nasopharynx. The results of this study support the concept that the middle ear may be part of the united airway in atopic individuals.

**Reviewer's Comments.** OME affects 15% to 20% of children and is a major pediatric health care issue as well as a substantial economic burden (estimated costs are in the billions of dollars annually). Current management of OME is often unsuccessful, and significant numbers of refractory cases require surgical intervention. Extensive research has supported the concept of a “united airway,” in which a tight connection exists between the upper and lower airways in allergic disease. For example, local treatment of allergic rhinitis leads to a reduced bronchial hyperresponsiveness in patients with coexisting asthma. The results of this study support the concept that the middle ear might be part of the united airway in atopic individuals. Therefore, an integrated management approach to allergic OME should take into consideration the common underlying systemic inflammation and the unity of airways.

**Anna Nowak-Wegrzyn, MD**
New York, NY

EFFECTIVENESS OF SUBLINGUAL IMMUNOTHERAPY IN CHILDREN WITH SEVERE GRASS POLLEN ALLERGIC SYMPTOMS: A DOUBLE-BLIND PLACEBO-CONTROLLED STUDY


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

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

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

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

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

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

**David Fleischer, MD**
Robert A. Wood, MD
Baltimore, MD

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


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

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

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

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

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

**Allen Adinoff, MD**
Denver, CO

SUPPLEMENT
Asthma

PATHOPHYSIOLOGY

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


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


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

Results. Information on wheezing before and after the onset of puberty was available for 781 subjects. In this cohort, 401 (51%) never experienced wheezing, and 83 (11%) reported wheezing after the onset of puberty. Of the 297 who were wheezing before puberty, 131 (17%) had only infrequent wheezing, and 166 (21%) fulfilled the definition for asthma. Most children (92 of 131 [70%]) with infrequent wheezing experienced remission after puberty. Of those children with the diagnosis of asthma in the prepubertal period, 97 (58%) of the 166 had wheezing episodes after the onset of puberty, and 69 (42%) had remitting asthma. The early onset of puberty was associated with the persistence of asthma into adolescence and with children in the unremitting-wheezing and asthma groups having the onset of puberty significantly earlier than children in the corresponding remitting groups (unremitting wheezing/unremitting asthma = 11.74/11.95 years versus remitting wheezing/remitting asthma = 12.34/12.7 years). The mean body mass index was significantly higher in unremitting-wheezing/asthma groups compared with remitting groups at each point over 10 years of surveys. Other factors associated with the persistence of symptoms included the amount of wheezing in the per-pubertal period and the presence of active sinus disease and rhinitis in the year before the survey. There were a limited number for whom a measure of airway hyperresponsiveness was available. In the unremitting-wheezing group, 27% had a positive methacholine challenge, and in the unremitting-asthma group, 68% were positive. Persistence of wheezing and asthma into adolescence was also associated with a positive skin test to the mold Alternaria. Children sensitized before puberty were 1.6 to 2.0 as likely to experience unremitting wheezing/asthma into adolescence.

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

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

FREDERICK E. LEICKLY, MD
Indianapolis, IN

IS OBESITY ASSOCIATED WITH ASTHMA IN YOUNG CHILDREN?


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

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

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

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

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

Reviewer’s Comments. This article addresses a highly contentious issue, focusing on the possible association between obesity and asthma, which has been investigated in both pediatric and adult populations. Both asthma and obesity are common chronic conditions, and in recent years, the prevalence of both of these conditions has increased in North America. Although a number of published studies have documented a positive association between obesity and asthma prevalence and incidence in adults, results from pediatric studies have not been consistent. There has been no clear explanation or consensus for this discrepancy. In this investigation, To and colleagues did not find a significant statistical association between obesity and asthma prevalence and incidence in adults, results from pediatric studies have not been consistent. There has been no clear explanation or consensus for this discrepancy. In this investigation, To and colleagues did not find a significant statistical association between obesity and asthma prevalence and incidence in adults, results from pediatric studies have not been consistent. There has been no clear explanation or consensus for this discrepancy. In this investigation, To and colleagues did not find a significant statistical association between obesity and asthma prevalence and incidence in adults, results from pediatric studies have not been consistent. There has been no clear explanation or consensus for this discrepancy. In this investigation, To and colleagues did not find a significant statistical association between obesity and asthma prevalence and incidence in adults, results from pediatric studies have not been consistent. There has been no clear explanation or consensus for this discrepancy. In this investigation, To and colleagues did not find a significant statistical association between obesity and asthma prevalence and incidence in adults, results from pediatric studies have not been consistent. There has been no clear explanation or consensus for this discrepancy. In this investigation, To and colleagues did not find a significant statistical association between obesity and asthma prevalence and incidence in adults, results from pediatric studies have not been consistent. There has been no clear explanation or consensus for this discrepancy. In this investigation, To and colleagues did not find a significant statistical association between obesity and asthma prevalence and incidence in adults, results from pediatric studies have not been consistent. There has been no clear explanation or consensus for this discrepancy.

John James, MD
Fort Collins, CO
EFFECT OF BODY SIZE ON BREATHING PATTERN AND FINE-PARTICLE DEPOSITION IN CHILDREN

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

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

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

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

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

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

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

ELINOR SIMONS, MD
ROBERT A. WOOD, MD
Baltimore, MD

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


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

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

Results. Exercised, sensitized mice had a statistically significantly decreased cellular infiltrate, epithelial hyperplasia, and goblet cells and mucin production compared with sedentary, sensitized mice. Exercise also decreased the total BAL fluid protein in sensitized mice. Exercised, sensitized mice had significantly fewer macrophages, lymphocytes, neutrophils, and eosinophils in BAL fluid samples than sedentary, sensitized mice. Exercise also decreased KC (murine homolog of interleukin [IL]-8) levels in sensitized mice to the baseline levels observed in nonsensitized mice but had no effect on monocyte chemotactic protein 1 levels. Exercise did not reduce intercellular adhesion molecule 1 expression but did reduce vascular cell adhesion molecule 1 expression in lung epithelium of sensitized mice. Exercise also decreased BAL fluid levels of the T-helper 2 cytokines, IL-4 and IL-5, by 13- and 3-fold, respectively. Exercised, sensitized mice had lower levels of OVA-specific IgE levels but not total IgE levels than sedentary, sensitized mice ($P < .05$). Exercise also decreased nuclear translocation of NF-κB, a molecule that is involved in transcriptional activation of inflammatory genes.

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

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

ELIZABETH MATSUI, MD
Baltimore, MD

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

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

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

Methods. Fourth-grade children \( n = 1759 \) were recruited from elementary schools in 12 communities of southern California. Spirometric data were attained annually for 8 years. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV\(_1\)), and midexpiratory flow rate were evaluated. The attrition rate of subjects was \( \sim 10\% \) of subjects per year. Air pollution–monitoring stations were set up in the 12 study communities to measure exposures to ozone, acid vapor, nitrogen dioxide, particulate matter, elemental carbon, and organic carbon. Linear regression was used to examine the relationship of air pollution to the FEV\(_1\), and other spirometric measures.

Results. Over the 8-year period, deficits in the growth of FEV\(_1\) were associated with exposure to nitrogen dioxide \( (P = .005) \), acid vapor \( (P = .004) \), particulate matter with an aerodynamic diameter of \( <2.5 \mu m \) \( (PM_{2.5}) (P = .04) \), and elemental carbon \( (P = .007) \) even after adjustment for several potential confounders and effect modifiers. Associations were also observed for other spirometric measures. Exposure to pollutants was associated with clinically and statistically significant deficits in the FEV\(_1\) attained at the age of 18 years. For example, the estimated proportion of 18-year-old subjects with a low FEV\(_1\) (defined as a ratio of observed to expected FEV\(_1\) of \( <80\% \)) was 4.9 times as great at the highest level of exposure to \( PM_{2.5} \) as at the lowest level of exposure \( (7.9\% \text{ vs } 1.6\%; P = .002) \). Exposure to ozone was not proven to be a contributor to lung-function deficit.

Conclusions. The results of this study indicate that current levels of air pollution in the communities evaluated have chronic, adverse effects on lung development in children from the age of 10 to 18 years. This long-term exposure leads to clinically significant deficits in attained FEV\(_1\) as children reach adulthood.

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

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

CHARACTERIZATION OF A COMMON SUSCEPTIBILITY LOCUS FOR ASTHMA-RELATED TRAITS


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

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

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

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

Scott H. Sicherer, MD
Jennifer Maloney, MD

VASULAR ENDOTHELIAL GROWTH FACTOR (VEGF) INDUCES REMODELING AND ENHANCES Th2-MEDIATED SENSITIZATION AND INFLAMMATION IN THE LUNG


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

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

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

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

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

Reviewers’ Comments. Well-described airway pathology in asthma includes epithelial desquamation, goblet cell hyperplasia, collagen deposition below the basement membrane, smooth muscle hypertrophy/hyperplasia, and the growth and proliferation of new blood vessels. Al-
though its pathogenesis is still unclear, VEGF (an inducer of angiogenesis) recently attracted considerable attention as a major contributor to airway remodeling. VEGF was first discovered as a vascular permeability factor >20 years ago. Subsequently, it was revealed to be a potent inducer of endothelial cell activation and growth. Overexpression of VEGF and its receptor in the airways has been demonstrated in stable asthma and during asthma exacerbations and are reduced by conventional asthma therapies (ie, inhaled corticosteroids and leukotriene receptor antagonists). The findings of this study imply an essential role of VEGF in asthma pathogenesis with links to TH2-mediated airway inflammation and remodeling. The results of this study may also inform the link of respiratory syncytial virus infection and asthma development in children, because respiratory syncytial virus up-regulates VEGF production. This disclosed role of VEGF highlights a potential therapeutic role for a VEGF receptor antagonist in asthma.

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

VIRAL-INDUCED T HELPER TYPE 1 RESPONSES ENHANCE ALLERGIC DISEASE BY EFFECTS ON LUNG DENDRITIC CELLS


Purpose of the Study. To determine the role of interferon (IFN)-γ and dendritic cells in allergic pulmonary disease after influenza A infection.

Study Population. IFN-γ knockout and wild-type mice completely recovered from influenza A infection were studied.

Methods. Mice were inoculated intranasally with influenza A virus. The postinfluenza mice were then sensitized and challenged with allergen. Airway inflammatory cells, specific antibody responses, and pulmonary dendritic cell functions were examined. In some of the wild-type mice, a neutralizing IFN-γ monoclonal antibody was administered repeatedly after the viral inoculation.

Result. Pulmonary dendritic cells of postinfluenza mice enhanced allergen-specific T-helper (TH2) responses via an IFN-γ-dependent mechanism.

Conclusion. The TH1 immune response caused by an influenza infection perpetuates TH2-dependent allergic asthma by altering pulmonary dendritic cell function.

Reviewers’ Comments. The role of respiratory viral infections in the development of allergic sensitization and asthma has been perplexing. Acute viral respiratory tract infections are the primary cause of asthma exacerbations in children and adults; however, the influence of viral respiratory infections on subsequent allergic sensitization and disease in young children is unclear. Viral infections are simplistically thought to augment TH1 (interleukin [IL]-12 and IFN-γ) responses and, as a result, antagonize TH2 (IL-4, IL-5, and IL-13) responses and decrease the risk of developing atopic diseases and asthma (ie, the hygiene hypothesis). Based on mouse models of allergic asthma, the impact of influenza infection on TH2 development and allergic sensitization has resulted in both beneficial and detrimental outcomes. The factors accounting for the different results are likely to be differences in experimental methods, including the timing of infections relative to allergen sensitization, the type and dose of allergen used, and the strain of the mouse. The findings of the Dahl et al study indicate that a preceding influenza infection with subsequent TH1 immune responses can amplify subsequent TH2 immunity. Thus, the TH1-TH2 paradigm of mutual exclusivity (ie, TH1 inhibits TH2, and vice versa) seems to be overly simplistic in the circumstance in which TH1 begets TH2. Although the result of the study has not been observed or correlated in humans, the finding may provide a mechanistic explanation for a recent report of the increased risk of asthma/reactive airways disease in young children <36 months of age who received a live attenuated intranasal influenza vaccine (published by Bergen et al in Pediatrics Dis J. 2004;23:138-144).

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

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


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

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

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

Results. In allergen-driven cultures, CD4+CD25+ T cells from nonatopic donors showed little proliferation and suppressed CD4+CD25− T cell proliferation in a dose-dependent manner. CD4+CD25− T cells showed enhanced production of interleukin (IL)-5 compared with unseparated PBMCs (P = .0056). Compared with nonatopic individuals, suppression of allergen-driven proliferation of CD4+CD25− T cells by CD4+CD25+ T cells was lower in atopic patients (P = .012) and lowest in patients with hay fever who had active rhinitis (P = .0003). Suppression of IL-5 production was also lowest in patients with hay fever who had active rhinitis (P = .0166). When the patients with hay fever were studied outside of their allergy season, the suppression of proliferation was greater than during their allergy season but less than in nonatopic individuals (P = .0028) and similar to the atopic group.

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

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

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

DIAGNOSIS AND MANAGEMENT

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


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

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

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

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

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

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

John M. Kelso, MD
San Diego, CA

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


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

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

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

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

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

COUGHING IN PRE-SCHOOL CHILDREN IN GENERAL PRACTICE: WHEN ARE RAST’s FOR INHALATION ALLERGY INDICATED?


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

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

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

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

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

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

JULIE WANG, MD
SCOTT H. SICHERER, MD
New York, NY

BENEFITS OF A SCHOOL-BASED ASThma TREATMENT PROGRAM IN THE ABSENCE OF SECONdHAND SMOKE EXPOSURE: RESULTS OF A RANDOMIZED CLINICAL TRIAL


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

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

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

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

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

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


Purpose of the Study. To determine the prevalence of asthma among a population of homeless children.

Study Population. A total of 740 children whose families entered 3 family shelters in New York City, New York, from June 1998 to September 1999, representing 75% of all children entering these shelters.

Methods. On entry into the shelters, the investigators attempted to screen children with a 1-page, 11-item survey that included questions about daytime and nighttime symptoms, previous diagnosis of asthma, current medications, use of an emergency department for respiratory symptoms, and demographic characteristics. The asthma symptom questions were coded to allow for staging as outlined in nationally recognized guidelines. The validity of the screening instrument was assessed by comparing the screening results of 117 children with a clinical assessment by a pediatrician or pediatric nurse practitioner. With this assessment, the sensitivity of the screening instrument was 77%, and the specificity was 92%.

Results. The prevalence of asthma in the children who were screened was 39.8%, with 26.9% having a prior physician diagnosis of asthma and 12.9% having no prior diagnosis but symptoms consistent with moderate to severe asthma. Furthermore, 50.3% of these children had current symptoms consistent with mild intermittent to severe asthma. Of those children who were 5 years old, 34.2%, 9.8%, 30.1%, and 25.9% had current symptoms consistent with mild intermittent, mild persistent, moderate, and severe asthma, respectively. Of those children who were ≥5 years old, 45%, 17%, 18%, and 20% had current symptoms consistent with mild intermittent, mild persistent, moderate, and severe asthma, respectively. Of those children with a prior physician diagnosis of asthma, the percentage of patients receiving anti-inflammatory treatment was 4%, 11%, 16%, 28%, and 20% for patients with no symptoms and current symptoms consistent with mild intermittent, mild persistent, moderate, and severe asthma, respectively. Finally, 48.6% of children with current asthma symptoms consistent with severe asthma visited an emergency department in the last year for respiratory symptoms, whereas 54.9% of severe asthmatics (and 68% of mild persistent asthmatics) with a prior physician diagnosis of asthma visited an emergency department in the last year for respiratory symptoms.

Conclusions. The data suggest that the routine use of a screening instrument for asthma would identify many at-risk children, an essential first step to providing them with appropriate medical care. Another remarkable finding is the low rate of use of anti-inflammatory medication even among severe asthmatics. This finding, taken along with the high rate of use of emergency department care for respiratory symptoms, provides evidence for a high rate of undertreatment of asthma among homeless children.

Reviewer’s Comments. This study, which provides evidence for a surprisingly high rate of asthma among homeless children, as well as undertreatment with anti-inflammatory medication and overuse of the emergency department, should be viewed by health care providers as a call to action. The medical system seems to have failed these children, and new approaches to their care are worth considering, such as routine screening for asthma, regular visits with primary care providers, and education of caregivers about asthma.

A SCHOOL-BASED CASE IDENTIFICATION PROCESS FOR IDENTIFYING INNER CITY CHILDREN WITH ASTHMA: THE BREATHMOBILE PROGRAM


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

Study Population. Parents of schoolchildren in the Los Angeles, California, area.

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

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

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

Reviewer’s Comments. This article describes the utility of a brief survey in identifying children with asthma in an inner-city, primarily Hispanic population. This survey has been used by the Los Angeles Breathmobile to screen >25,000 children, and it has been the model for similar surveys used by the 4 other Breathmobile programs in the country. Jones et al should be commended for their trail-
IMPLICATION OF EVIDENCE BASED GUIDELINES FOR PAEDIATRIC ASTHMA MANAGEMENT IN A TEACHING HOSPITAL


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

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

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

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

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

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

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


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

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

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

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

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

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

JOHN E. DUPLANTIER, MD
Indianapolis, IN

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


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

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

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

Results. There were 263 potential asthma-related deaths identified, but only 61 met the criteria. Of these, 81% were subjects <21 years of age, and only 3% were >31 years of age. Sixty-nine percent of the subjects were male; 91% had a known history of asthma. There were 35 competitive and 26 recreational athletes. Only 51% of competitive athletes had their fatal event during participation in their organized sport, with 78% of these occurring during practice situations and the rest during active competition.

Basketball was the most common activity at time of death (21%) in both competitive and recreational groups, compared with track/running (11%), gym class (10%), football and recreational play (each 8%), and other (42%). Only 5% of the subjects had been using asthma-controller therapy, although the medication status of 18% of the subjects could not be determined. No mention was made of the use of an inhaled β₂-agonist before exercise.

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

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

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

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


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

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

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

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

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

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

HELEN SKOLNICK, MD
Princeton, NJ

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


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

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

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

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

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

Ariana D. Buchanan, MD
Larry W. Williams, MD
Durham, NC

Rhinitis Therapy and the Prevention of Hospital Care for Asthma: A Case-Control Study


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

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

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

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

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

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

Tamara T. Perry, MD
Little Rock, AR

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

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

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

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

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

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

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

**Reviewer’s Comments.** This article demonstrates one of the limitations of MDIs in the inability of patients to accurately assess when they are empty without counting each dose. It illustrates the need for better devices to track doses remaining (an advantage of dry-powder inhalers).
Methods. START was a randomized, 3-year controlled trial of budesonide versus usual asthma therapy in early-onset asthma among 7165 subjects. Three age groups (5–10, 11–17, and ≥18 years) were studied separately and collectively. All patients were allowed to receive other asthma treatments including inhaled and oral corticosteroids, according to local practice. The cost-effectiveness evaluation of the START study was conducted primarily from the health care payer perspective (direct costs) and secondarily from the societal perspective (indirect costs). The primary outcome measure for effectiveness was the number of symptom-free days. This parameter was defined as a complete 24-hour period with no asthma symptoms and has been recognized as a clinical outcome with relevance to patients, providers, and other decision-makers. Unit costs in US dollars were based on reimbursed amounts for each of the health care–resource items such as hospital days, emergency department visits, physician and nurse visits, and telephone contacts. These costs were derived from a large medical- and pharmacy-claims database. The costs for school and work losses were estimated by using standard methods.

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

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

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

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


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

Study Population. Fifty-one patients (mean age: 54.4 ± 13.8 years) with persistent asthma and 28 healthy controls (mean age: 48.1 ± 15.9 years).

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

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

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

Reviewer's Comments. This study raises questions. Is the reduction in airway wall thickness indicative of reductions in airway inflammation? Additional studies (eg, with airway biopsy specimens) are needed to confirm this. Would earlier intervention with ICSs result in normalization of airway wall thickness? This is a particularly important question for those who treat children with asthma.
records. Safety end points included measurement of growth, serum insulin-like growth factor–binding protein 3, cortisol, osteocalcin, and alkaline phosphatase. Clinical and safety outcomes were assessed before and after 6 months of treatment in both treatment and placebo groups.

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

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

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

**EFFECT OF INHALED STEROIDS ON LUNG FUNCTION IN YOUNG CHILDREN: A COHORT STUDY**


**Purpose of the Study.** To determine the use of inhaled corticosteroids (ICSs) for treating recurrent bronchial obstruction in young children up to 2 years of age and to assess possible modifying effects of ICSs on lung function in young children with recurrent bronchial obstruction.

**Study Population.** Observational, noninterventional birth cohort of 3754 newborn children (3697 with complete questionnaire data by 2 years of age); 306 children with documented recurrent bronchial obstruction by 2 years old were identified along with 306 matched controls.

**Methods.** Two tidal-flow/volume measurements were taken (1 at presentation of disease [children were steroid naive] and 1 at 2 years of age [mean ages: 11.2 and 25.6 months, respectively]) from 21 subjects who subsequently received ICS (ICS+), 33 who did not receive ICS (ICS−), and 15 controls. The mean ± SD duration of ICS treatment was 10.3 ± 6.5 months. The main outcomes were treatment with ICS and baseline ratio of time to peak expiratory flow/total expiratory time (tPTEF/TE).

**Results.** From the entire cohort, 77 children (2.1%) and 64 of 306 children (21%) with recurrent bronchial obstruction had received ICS by 2 years of age. Baseline tPTEF/TE was significantly lower at the first visit in ICS+ subjects, as

**INHALED CORTICOSTEROIDS AND GROWTH OF AIRWAY FUNCTION IN ASTHMATIC CHILDREN**


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

**Study Population.** Patients with moderate to severe persistent asthma who participated in a clinical trial recruited between 1988 and 1992 from outpatient clinics for respiratory medicine of Juliana Children’s Hospital (The Hague, Netherlands) and Rotterdam University Hospital/Sophia Children’s Hospital (Rotterdam, Netherlands).

**Methods.** Every 4 months for up to 3 years, lung function was assessed in 54 asthmatic children (initial age: 7–16 years) who inhaled 0.2 mg of salbutamol three times daily and 0.25 mg of budesonide three times daily (β2-agonist [BA] + inhaled corticosteroid [ICS]) or placebo (PL) three times daily (BA + PL) in a randomized, double-blind design. Measurements were conducted before and after maximal bronchodilation. Airway growth was assessed from the change of forced expiratory volume in 1 second and of maximal expiratory flows at 60% and 40% of total lung capacity (TLC) relative to TLC as measures of central, intermediate, and more peripheral airways. Growth patterns were compared with the longitudinal findings in 376 healthy children.

**Results.** Airway patency after maximal bronchodilation in patients on BA + PL remained reduced compared with healthy subjects, whereas in patients on BA + ICS a marked improvement was observed. No differences between patients and controls could be demonstrated for growth patterns of central and intermediate airway function. Compliance with BA + ICS was 75% of the prescribed dose, resulting in significant, sustained improvement of symptoms and postbronchodilator caliber of central and intermediate airways to subnormal within 2 months, but postbronchodilator small-airway patency remained reduced but improved compared with patients on BA + PL.

**Conclusions.** Anti-inflammatory treatment of asthmatic children is associated with normal functional development of central and intermediate airways. The reduced postbronchodilator patency of peripheral airways may reflect remodeling or insufficient anti-inflammatory treatment.

KRICIA P. PALMER, MD  
TODD D. GREEN, MD  
LARRY W. WILLIAMS, MD  
Durham, NC

WANDA PHIPATANAKUL, MD, MS  
Boston, MA
compared with ICS− subjects, as well as in ICS+ and ICS− subjects as compared with controls. The mean difference in baseline IPT/E from the first to second visit was borderline statistically significant in the ICS+ group only and correlated significantly with the duration of ICS treatment.

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

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

WANDA PHIPATANAKUL, MD, MS
Boston, MA

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


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

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

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

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

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

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

MARK H. MOSS, MD
Madison, WI

INHALED CORTICOSTEROIDS AND THE RISK OF FRACTURES IN CHILDREN AND ADOLESCENTS


Purpose of the Study. To determine if children or adolescents who are exposed to inhaled corticosteroids (ICS) (ie, beclomethasone, budesonide, fluticasone) are at a higher risk of having bone fractures compared with nonexposed individuals.

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

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

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

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

Reviewer’s Comments. This excellent study verifies general consensus in the literature that ICS used in recommended doses do not increase fracture risk in children or adolescents when compared with controls. There are some
immunologic effects of interferon (IFN)-γ. The purpose of this study was to evaluate the clinical and immunologic effects of recombinant IFN-α in patients with corticosteroid-resistant asthma with and without Churg-Strauss syndrome.

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

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

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

**Reviewers’ Comments.** Although this study involved only a few patients and additional elucidation of the underlying mechanisms is needed, this study suggests that IFN-α treatment has potential steroid-sparing medication for use in children who may also prove beneficial, especially given the potential for significant toxicity. The use of IFN-α, however, would have to outweigh its inherent potential adverse effects including influenza-like symptoms, nausea, and liver toxicity, to name a few. This preliminary study, however, does make a case for the need for additional, longer-term clinical trials.
Study Population. Thirteen patients from 6 families having AR-HIES and 68 of their relatives.

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

Results. All families were consanguineous. Five are from Turkey and 1 is from Mexico. According to a previously developed scoring system (>20, HIES possible; >40, HIES highly likely), all 13 patients had scores ranging from 19 to >50. All relatives had scores of <20, supporting an autosomal recessive mode of inheritance. Eight of the 13 patients died between the ages of 6 months and 12 years. Features that are common to both forms of HIES include a chronic eczematous skin eruption with staphylococcal superinfection and upper and lower respiratory tract bacterial infections caused by common pathogens as well as unusual organisms (Proteus mirabilis, Pseudomonas aeruginosa, Cryptococcus neoformans) and chronic mucocutaneous candidiasis. Features that are found in AD-HIES that are not shared in AR-HIES include failure to shed primary dentition, bone fragility, coarse asymmetric facies, and pneumatocele formation. Features found only in AR-HIES include susceptibility to severe infection with molluscum contagiosum and herpesviruses. Patients with AR-HIES also have a high rate of life-threatening inflammatory cerebrovascular complications leading to stroke and/or hemorrhage. Serum IgE in patients with AR-HIES ranged from 4500 to 45 000 IU/mL (similar to AD-HIES). In general, serum immunoglobulin levels were elevated because of general stimulation resulting from infectious burden; specific antibody formation appeared normal. Eosinophil counts in patients with AR-HIES were from 2500 to 18 000 cells per mm², somewhat higher than in patients with AD-HIES. There were no major abnormalities of lymphocyte subpopulations, although in vitro T-cell responses to recall antigens and to a B-cell mitogen were depressed. Some patients with AD-HIES have impaired neutrophil chemotaxis and killing; this was not observed in those with AR-HIES. AD-HIES has been linked to a region on chromosome 4q. This linkage has not been observed in patients with AR-HIES.

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

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

Francisco A. Bonilla, MD, PhD
Boston, MA

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


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

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

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

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

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

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

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

SUPPLEMENT 569
GASTROINTESTINAL INVOLVEMENT IN CHRONIC GRANULOMATOUS DISEASE


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

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

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

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

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

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

MARK H. MOSS, MD
Madison, WI

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


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

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

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

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

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

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

FRANCISCO A. BONILLA, MD, PhD
Boston, MA

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


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

**Study Population.** Fifty-eight patients between the ages of 2 and 75 years (17 patients <14 years old [“children” for the purposes of this study]; 41 patients ≥14 years old [“adults”]) with primary antibody deficiency. Thirty-seven patients were receiving IVIG, and 10 were receiving SCIG.
HIV-RNA measurements with PCR may also be valuable means of a DNA polymerase chain reaction (PCR). Plasma DNA sequences in peripheral blood mononuclear cells by to confirm that a child was not HIV-infected. HIV infection decline of HIV antibody levels for up to 2 years after birth a newborn exposed to HIV in utero is a challenge. In the Defic Syndr. Lambert JS, Harris R, Stiehm R, et al. OF PERINATAL HIV-1 INFECTION CULTURE AND HIV-1 DNA AND RNA PERFORMANCE CHARACTERISTICS OF HIV-1 DEFICIENCY DISEASES. may replace IVIG for many patients with immunodeficiency. For a variety of reasons, SCIG is gaining in popularity and the major mode of immunoglobulin delivery in some countries. Many primary care providers have 1 or a few patients who receive this therapy. Less widely recognized, SCIG has also been used with safety and efficacy equivalent to IVIG and has been the major mode of immunoglobulin delivery in some countries (although this is an off-label use in the United States). For a variety of reasons, SCIG is gaining in popularity and may replace IVIG for many patients with immunodeficiency diseases.

FRANCISCO A. BONILLA, MD, PhD Boston, MA

HUMAN IMMUNODEFICIENCY VIRUS

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


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

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

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

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

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

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

JOSEPH A. CHURCH, MD Los Angeles, CA

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


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

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

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

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


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

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

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

Conclusions. HIV induces an immunodeficiency by depleting CD4+ T cells. However, demonstrable immunodeficiency occurs before the onset of severe peripheral T-cell depletion. A variety of mechanisms have been invoked to explain this process. The present study demonstrates an additional potential mechanism by which HIV subverts immune responses to both HIV-specific antigens and to those of other infectious agents. The expansion of HIV-induced Tregs suggests a mechanism by which HIV induces partial tolerance to its own antigens. Therapeutic strategies aimed at reducing HIV-specific Tregs might allow more effective control of HIV replication. Alternatively, species-specific simian immunodeficiency viruses seem to induce little disease caused by immune silence. Perhaps enhancement of HIV-specific Tregs rather than suppression of them might result in similar tolerance and lack of disease progression in HIV-infected humans.

Joseph A. Church, MD
Los Angeles, CA

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


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

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

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

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

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

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

Joseph A. Church, MD
Los Angeles, CA

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


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

Methods. The chemokine RANTES is a specific ligand for CCR5. The investigators generated an analog of RANTES, PSC-RANTES, that has an N-terminal modification. In vitro PSC-RANTES inhibited propagation of SHIV, a chimeric simian/human immunodeficiency virus. Thirty adult female rhesus macaques were pretreated with varying concentrations of PSC-RANTES intravaginally. The animals were subsequently challenged with high-multiplicity (300 median tissue culture infectious doses) SHIV intravaginally. The serum of children immunized with commercial Hib conjugate vaccine. sPRP conjugated to tetanus toxoid (sPRP-TT) from 3 different lots was used for immunization experiments in animals and phase I and II clinical trials in humans. The vaccination dose given was 10 μg of sPRP (sPRP/T ratio 1:2.6 by weight) via intramuscular injection. All clinical trials were double blind and randomized. Single-dose phase I trials of adults (n = 40) and unimmunized children (4–5 y; n = 133) followed by single-dose phase II trials of 1041 children. PRP-specific IgG and bactericidal activity were measured from subject sera samples 4 weeks after immunization. A total of 139 infants were then enrolled in a multiple-dose phase I trial and received vaccine at 2, 4, and 6 months. Infants (1141) then were enrolled in a double-blind phase II trial and randomized to receive either sPRP-TT, sPRP-TT with aluminum phosphate, or commercial conjugate vaccine (Vaxem-Hib) at 2, 4, 6, and 18 months. PRP-specific IgG was measured by enzyme-linked immunosorbent assay at 7, 18, and 19 months.

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

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

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

Wayne G. Shreffler, MD, PhD
New York, NY
Echinacea purpurea therapy for the treatment of the common cold: A randomized, double-blind, placebo-controlled clinical trial


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

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

Results. One hundred twenty-eight patients were enrolled within 24 hours of cold-symptom onset. Group demographic distribution was comparable for gender, age, time from symptom onset to enrollment in the study, average number of colds per year, and smoking history. No statistically significant difference was observed between treatment groups for either total symptom scores (P = .29–.90) or mean individual symptom scores (P = .09–.93). The time to resolution of symptoms was not statistically different (P = .73).

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

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

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


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

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

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

Results. Data were analyzed on 707 URIs that occurred in 407 study patients. Median duration of URIs was 9 days. There was no difference in duration between URIs treated with echinacea or placebo (P = .89). There was also no difference in the overall severity of URI symptoms between the 2 treatment groups (P = .69). There were no statistically significant differences between the 2 groups for peak severity of symptoms, number of days of peak symptoms, number of days of fever, or parental global assessment of severity of the URI. There was no difference in the rate of adverse events reported in the 2 treatment groups; however, rash occurred during 7.1% of the URIs treated with echinacea and 2.7% of URIs treated with placebo (P = .008).

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

Reviewer’s Comments. Echinacea, derived from wildflowers from the daisy family (family Compositae), is one of the most commonly used herbal preparations in the United States, with reported sales of more than $300 million annually despite limited evidence of clinically beneficial effects in the treatment of viral respiratory infections.

This study is one of the largest randomized, controlled trials of echinacea treatment in patients of any age. In addition to the large sample size, the validity of the results is strengthened because enrolled patients had sought care from both traditional and alternative providers in an attempt to negate the effects of preconceived biases about echinacea. These data provide additional information regarding lack of efficacy of echinacea in treating the 6 to 8 colds an average child has each year.
Lymphoid Nodular Hyperplasia and Cow's Milk Hypersensitivity in Children With Chronic Constipation
John E. Duplantier
Pediatrics 2005;116;547
DOI: 10.1542/peds.2005-0698Y

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