tively. There was no significant adverse association between exclusive breastfeeding and physician-diagnosed AD in infants with a family history of AD (odds ratio [OR]: 0.92), in those without a family history of AD (OR: 0.97), or in those with itchy rash (OR: 1.2 and 0.92, respectively). In group I, exclusive breastfeeding was protective for AD, compared with feeding with a conventional cow's milk formula (OR: 0.64). If stratified by family history of AD, there was no difference in effect of breastfeeding on physician-diagnosed AD and itchy rash in group I. The difference in the NI group was not determined because of the small number of participants.

Conclusions. Exclusive breastfeeding for the first 4 months of infancy was not shown to increase the risk of developing AD in infants with or without a family history of AD.

Reviewers' Comments. A number of studies have shown that breastfeeding could be a risk factor for atopic dermatitis and even suggest a detrimental effect of continuing to breastfeed infants with severe AD and food allergy. The role of breastfeeding in allergic diseases has been controversial, but the weight of the evidence in meta-analyses and in this study support a protective effect in regard to prevention.

Sheila Bonilla, MD
Michael S. Kaplan, MD
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THREE-YEAR OUTCOMES OF DIETARY FATTY ACID MODIFICATION AND HOUSE DUST MITE REDUCTION IN THE CHILDHOOD ASTHMA PREVENTION STUDY

Peat JK, Mihrshahi S, Kemp AS, et al. *J Allergy Clin Immunol*. 2004;114:807–813

Purpose of the Study. To measure the effects of dietary supplementation with ω-3 fatty acids and house d-e (HDM) allergen avoidance in children with a family history of asthma.

Study Population. Children at high risk for asthma, defined by having at least 1 parent or sibling with current asthma or frequent wheeze.

Methods. A total of 616 children at high risk for asthma were enrolled antenatally, and 526 children remained in the trial when they were 3 years old. HDM allergen avoidance involved the use of both physical and chemical methods for the reduction of allergen concentrations. Dietary intervention included supplementation of the infant's/child's diet with tuna fish oil and use by the family of canola-based oils and spreads. Participants were randomized to 1 of the 4 study groups: placebo diet and active HDM controls, active diet supplements and active HDM controls, placebo diet and no HDM controls, and active diet supplements and no HDM controls. The outcomes were symptoms of allergic disease and HDM allergen sensitization at 3 years.

Results. There was a significant 10.0% (95% confidence interval [CI]: 3.7, 16.4) reduction in the prevalence of cough in atopic children in the active-diet group ($P = .003$; number needed to treat: 10) but a negligible 1.1% (95% CI: −7.1, 9.5) reduction in cough among nonatopic children. There was a 7.2% (95% CI: 10.11, 14.3) reduction in sensitization to HDM in the active allergen-avoidance group ($P = .05$; number needed to treat: 14). No significant differences in wheeze were found with either intervention.

Conclusions. These results suggest that HDM allergen avoidance and dietary supplementation with foods rich in ω-3 fatty acids may have a role in preventing the development of allergic sensitization and airways disease in early childhood, which offers the prospect of reducing allergic disease in later life.

Reviewer's Comments. Although the reported risk reduction in the active-intervention groups was modest, this study suggests that a relatively simple intervention may be used in public health to modulate the development of allergic sensitization and airways disease at an early age. Hopefully, a follow-up study will determine the long-term effect of combined dietary ω-3 fatty acid supplementation and environmental HDM allergen avoidance.

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EARLY INFANT MULTIVITAMIN SUPPLEMENTATION IS ASSOCIATED WITH INCREASED RISK FOR FOOD ALLERGY IN ASTHMA

Milner JD, Stein DM, McCarter R, Moon RY. *Pediatrics*. 2004;114:27–32

Purpose of the Study. Dietary vitamins have immunomodulating effects in vitro, and individual vitamins have been shown to skew T cells toward either T-helper 1 or T-helper 2 phenotypic classes, suggesting that they may participate in inflammatory or allergic disease. The objective of the study was to determine if early vitamin supplementation during infancy affects the risk for asthma and allergic disease during early childhood.

Study Population. Cohort data were analyzed from the National Center for Health Statistics 1988 National Maternal-Infant Health Survey, which followed pregnant women and their newborns, and the 1991 longitudinal follow-up of the same patients, which measured health and disease outcomes. There were >8000 patients in this study.

Methods. Patients were stratified by race and breastfeeding status. Factors that are known to be associated with alteration of risk for asthma or food allergies were identified by using univariate logistic regression. Those factors were then analyzed in multivariate logistic-regression models. Early vitamin supplementation was defined as vitamin use within the first 6 months.

Results. The overall incidence of asthma was 10.5% and of food allergy was 4.9%. In univariate analysis, being male gender, having a smoker in the household, being in child care, being premature (<37 weeks' gestation), being black, having no history of breastfeeding, and having lower income and lower education were associated with higher risk for asthma. Being in child care, having higher levels of education and income, and having a history of breastfeeding were associated with a higher risk for food allergies. In multivariate logistic analyses, a history of vitamin use within the first 6 months of life was associated with a higher risk for asthma in black infants (odds ratio [OR]: 1.27; 95% confidence interval [CI]: 1.04, 1.56). Early vitamin use was also associated with a higher risk for food allergies in the exclusively formula-fed population (OR: 1.63; 95% CI: 1.21, 2.20). Vitamin use at 3 years of age was associated with increased risk for food allergies but not asthma in both breastfed (OR: 1.62; 95% CI: 1.19, 2.21) and exclusively formula-fed (OR: 1.39; 95% CI: 1.03, 1.88) infants.

Conclusions. The conclusions of the authors were that early vitamin introduction is related to increased likelihood for asthma in black children and food allergies in exclusively formula-fed children.

Reviewer's Comments. Although there are some laboratory data to support the potential for some vitamins to

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 to parents of children with asthma.

James R. Banks, MD
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Arnold, MD

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

Niimi A, Matsumoto H, Amitami R, et al. *Am J Med*. 2004;116:725–731

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, cromomes, 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% ($P < .001$) but remained high ($P < .0001$ vs control). Serum ECP levels decreased significantly after treatment ($P < .001$). Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/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 FEV_1 ($r = 0.45$; $P = .003$) 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.

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EFFECTS OF INHALED FLUTICASONE PROPIONATE IN CHILDREN LESS THAN 2 YEARS OLD WITH RECURRENT WHEEZING

Teper AM, Colom AJ, Kofman CD, Maffey AF, Vidaurreta SM, Bergada I. *Pediatr Pulmonol*. 2004;37:111–115

Purpose of the Study. To evaluate the efficacy and safety of inhaled fluticasone propionate in children <2 years old with a history of recurrent wheezing and risk factors for asthma persisting into late childhood.

Study Population. Subjects were 30 children, aged 7 to 24 months, with ≥3 episodes of wheeze responsive to bronchodilators and a family history of asthma, allergic rhinitis, or eczema.

Methods. In this double-blind study, subjects were randomized to receive either inhaled 50 μg of fluticasone twice daily, 125 μg of fluticasone twice daily, or placebo for 6 months. Medication was administered with a metered-dose inhaler using an Aerochamber and mask. Efficacy end points included number of wheezing episodes and number of days on which albuterol was required. Parents were trained to record these clinical symptoms and medication use on a chart. Subjects were seen monthly to assess proper use of the medication device and evaluate daily symptom

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 ± 1.9, 1.9 ± 1.9, and 2.8 ± 1.2 per patient for placebo, 100-μg fluticasone, and 250-μg fluticasone groups, respectively. Mean days of albuterol use were 24.3 ± 1.3, 6.5 ± 0.8, and 9.1 ± 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.

Reviewers' 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.

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INHALED CORTICOSTEROIDS AND GROWTH OF AIRWAY FUNCTION IN ASTHMATIC CHILDREN

Merkus PJFM, van Pelt W, van Houwelingen JC, et al. *Eur Respir J.* 2004;23:861–868

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 (β_2-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.

Reviewer's Comments. This study shows that treatment with ICS can improve several measures of lung function and promote normal lung growth in asthma but also demonstrates that residual functional abnormalities may present in asymptomatic children with asthma even with daily doses of ICSs. This suggests that anti-inflammatory treatment of children with asthma based on symptoms alone may not be enough to result in normalization of postbronchodilator airway function. There may be some ethical and practical considerations in treatment of asthmatic children in the absence of respiratory symptoms, and additional study is required to determine what is best for long-term optimal prognosis.

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

Devulapalli CS, Haaland G, Pettersen M, Carlsen KH, Lodrup Carlsen KC. *Eur Respir J.* 2004;23:869–875

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

compared with ICS$^-$ subjects, as well as in ICS$^+$ and ICS$^-$ subjects as compared with controls. The mean difference in baseline *tPTEF/tE* 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.

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

Bacharier LB, Raissy HH, Wilson L, McWilliams B, Strunk RC, Kelly HW. *Pediatrics*. 2004;113:1693–1699

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 adrenocorticotrophic 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 $\mu g/m^2$ 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.

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INHALED CORTICOSTEROIDS AND THE RISK OF FRACTURES IN CHILDREN AND ADOLESCENTS

Schlienger RG, Jick SS, Meier CR. *Pediatrics*. 2004;114:469–473

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

limitations to this study admitted by the authors in their discussion. For example, there is a small sample size in the individual strata, and as a result there are wide confidence intervals. Therefore, the authors could not exclude with certainty that long-term exposure to ICS might be associated with slightly increased fracture risk. More studies would be needed to better assess the impact of longer-term treatment and the use of concomitant oral steroids on fracture risks.

Christopher Randolph, MD
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CLINICAL AND IMMUNOLOGICAL EFFECT OF LOW-DOSE IFN-α TREATMENT IN PATIENTS WITH CORTICOSTEROID-RESISTANT ASTHMA

Simon HU, Seelbach H, Ehmann R, Schmitz M. *Allergy.* 2003;58:1250–1255

Purpose of the Study. To evaluate the clinical and immunologic effects of interferon (IFN)-α in patients with corticosteroid-resistant asthma with and without Churg-Strauss syndrome.

Study Population. Ten patients with severe steroid-resistant asthma, 3 of whom had Churg-Strauss syndrome, were studied.

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 decreased leukocyte numbers, decreased numbers of eosinophils in patients with prior eosinophilia, 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, these patients with steroid-resistant asthma improved with IFN-α treatment. Although this study involved only adults, the use of IFN-α as a potential steroid-sparing medication for use in children may also prove beneficial, especially given justified patient, parental, and physician concerns about using long-term oral corticosteroids in children because of 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.

David Fleischer, MD
Robert A. Wood, MD
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Immunodeficiency

PRIMARY IMMUNODEFICIENCY

IMMUNODEFICIENCY AND INFECTIONS IN ATAXIA-TELANGIECTASIA

Nowak-Wegrzyn A, Crawford TO, Winkelstein JA, Carson KA, Lederman HM. *J Pediatr.* 2004;144:505–511

Purpose of the Study. To describe immunodeficiency in ataxia-telangiectasia (A-T) and its clinical manifestations and course.

Study Population. Patients with A-T who underwent multidisciplinary assessment at Johns Hopkins Hospital (Baltimore, MD).

Methods. Charts from the first 100 consecutive patients with A-T who were assessed at Johns Hopkins Ataxia-Telangiectasia Clinical Center were reviewed. Specific criteria for the diagnosis of A-T had to be met. Immunologic data were obtained by reviewing laboratory assessments of patients' immune systems. Infections were determined by patient and family interviews and chart review.

Results. A large percentage of patients had immunoglobulin deficiencies at the time of first immunologic assessment: 65% had IgG4 deficiency, 63% had IgA deficiency, 48% had IgG2 deficiency, and 23% had IgE deficiency. Deficiencies did not correlate or progress with age. Lymphopenia occurred in 71% of patients. CD19 B lymphocytes were reduced in 75% of patients. CD4 T cells were decreased in 69% of the patients, and CD8 T cells were decreased in 51% of the patients. Patients had no untoward effects from live viral vaccines. Recurrent upper respiratory infections occurred in one third of the patients regardless of age. Lower respiratory tract infections increased with age. Viral and opportunistic infections were not common.

Conclusions. Patients with A-T have a wide array of laboratory-based immunodeficiencies. However, there seems to be no correlation between laboratory values and clinical manifestation of immunodeficiency in this population.

Reviewers' Comments. This study confirms previously characterized immunodeficiencies in A-T patients. However, the large number of patients involved in this study allowed for a more extensive review of immunodeficiencies as well as clinical correlation of laboratory values. At this time it seems that clinical immunodeficiency is not common in A-T. Rather, the high rate of respiratory infections may be attributable to other factors of A-T such as neurologic deficits leading to aspiration.

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AUTOSOMAL RECESSIVE HYPERIMMUNOGLOBULIN E SYNDROME: A DISTINCT DISEASE ENTITY

Renner ED, Puck JM, Holland SM, et al. *J Pediatr.* 2004; 144:93–99

Purpose of the Study. To describe the clinical and immunologic features of a distinct subgroup of patients with hyper-IgE syndrome (HIES) having autosomal recessive inheritance (AR-HIES) as distinct from the form having autosomal dominant inheritance (AD-HIES).

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 2 500 to 18 000 cells per mm^3, 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.

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

Orange JS, Jain A, Ballas ZK, Schneider LC, Geha RS, Bonilla FA. *J Allergy Clin Immunol*. 2004;113:725–733

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.

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GASTROINTESTINAL INVOLVEMENT IN CHRONIC GRANULOMATOUS DISEASE

Marciano BE, Rosenzweig SD, Kleiner DE, et al. *Pediatrics*. 2004;114:462–468

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 kindred, 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.

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

Zebracki K, Palermo TM, Hostoffer R, Duff K, Drotar D. *Ann Allergy Asthma Immunol.* 2004;93:557–561

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.

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

Gardulf A, Nicolay U, Math D, et al. *J Allergy Clin Immunol.* 2004;114:936–942

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

(a control group to compare for effects specifically related to the switch from IVIG to SCIG); prior therapy for 1 patient was not stated.

Methods. Patients received weekly SCIG infusions at home over a period of 10 months (43 infusions). Questionnaires were administered at baseline and at 6 and 10 months. For assessment of HRQOL in children, parents completed the Child Health Questionnaire-Parental Form 50; adults used the Short Form 36. For assessment of treatment satisfaction, the authors adapted a Life Quality Index instrument previously developed in a study of antibody-deficient patients receiving IVIG.

Results. On the Child Health Questionnaire-Parental Form 50, the children demonstrated significant improvement in 6 of 14 concepts analyzed: "role/social-emotional, behavioral," "general health perceptions," "parental impact-emotional," "parental impact-time," "family activities," and "global health." On the Short Form 36, adults had improvements in vitality, mental health, and social functioning. These differences were found only in those adults who switched from IVIG to SCIG, not in those who were already receiving SCIG, suggesting that the improvement resulted from the change in therapy. Both children and adults had significant improvements in Life Quality Index. Again, in the adults, no change was seen in the group that was already receiving SCIG at enrollment. At study end, all children/parents, the 10 adults on SCIG at enrollment, and 73% of the adults who switched preferred to continue SCIG at home. Two expressed a preference for SCIG regardless of setting, 1 expressed a preference for home regardless of method, 1 expressed no preference for anything, and only 1 expressed a preference for IVIG in the hospital.

Conclusions. Home therapy with SCIG in children and adults with antibody deficiency is generally self-perceived as superior to in-hospital therapy with IVIG with respect to several validated measures of HRQOL.

Reviewer's Comments. IVIG has been a major mode of therapy for immunodeficiency for 30 years. 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.

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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

Lambert JS, Harris R, Stiehm R, et al. *J Acquir Immune Defic Syndr.* 2003;34:512–519

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.

Study Population. Infants participating in the Pediatric AIDS Clinical Trials Group protocol 185.

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.

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

Vigano A, Saresella M, Trabattoni D, et al. *J Pediatr.* 2004;145:542–548

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

volumes. "Naive" $CD4^+$ T cells were lower in the GH-deficient children, as were central memory T cells. In contrast, effector memory $CD4^+$ T cells and effector $CD8^+$ T cells were increased in the GH-deficient children.

Conclusions. Thymic and postthymic lymphocyte pathways are impaired in HIV-infected children, and antiretroviral therapy–associated immune reconstitution is often incomplete. GH might be useful in the management of HIV-infected children with GH deficiency and incomplete immune reconstitution with antiretroviral therapy.

Reviewer's Comments. The reasons why some patients respond to antiretroviral therapy more effectively than others is generally unknown. However, this study suggests that some of this variation may be related to the GH axis of the infected patients. Whether GH-replacement therapy will improve the immune reconstitution in GH-deficient subjects awaits clinical trials. Of interest, also, would be the effect of GH treatment on subjects with incomplete immune reconstitution but normal GH-stimulation studies.

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HUMAN IMMUNODEFICIENCY VIRUS-DRIVEN EXPANSION OF CD4+CD25+ REGULATORY T CELLS, WHICH SUPPRESS HIV-SPECIFIC CD4 T-CELL RESPONSES IN HIV-INFECTED PATIENTS

Weiss L, Donkova-Petrini V, Caccavelli L, et al. *Blood.* 2004;104:3249–3256

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 $>500/mm^3$ 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 viral 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 derives expansion of $CD4^+CD25$ regulatory T cells. This regulatory T-cell subset in turn suppresses HIV-specific $CD4^+$ T-cell responses in HIV-infected patients.

Reviewer's Comments. 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.

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

Brenchley JM, Schacker TW, Ruff, LE, et al. *J Exp Med.* 2004;200:749–759

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 diseases 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.

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

Laderman MM, Veazey RS, Offord R, et al. *Science*. 2004; 306:485–487

Purpose of the Study. Topical agents that prevent transmission of HIV across mucosae 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 and monitored for up to 24 weeks.

Results. All 5 animals treated with the highest dose of PSC-RANTES were protected from SHIV infection. Lower doses also proved protective to a lesser extent. Plasma levels of PSC-RANTES were not detectable, suggesting specific local protection against viral infection.

Conclusions. PSC-RANTES, a selective blocker of CCR5, protected rhesus macaques from intervaginal exposure to a highly infectious dose of SHIV, although the topical concentration of PSC-RANTES that was shown to be protective was many times higher than the concentration required to neutralize the same virus in vitro.

Reviewer's Comments. A safe, simple, and affordable topical microbicide that would effectively prevent vaginal transmission of HIV is desperately needed, particularly in the developing world. This study provides proof of the concept that targeting the coreceptor for HIV entry into target cells, CCR5, is a viable strategy for the prevention of vaginal transmission of HIV. Cost, however, would be a major obstacle to the implementation of this strategy, but it is now clear that HIV can be stopped before it infects the vaginal mucosa.

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Infectious Disease

A SYNTHETIC CONJUGATE POLYSACCHARIDE VACCINE AGAINST *HAEMOPHILUS INFLUENZAE* TYPE B

Verez-Bencomo V, Fernandez-Santana V, Hardy E, et al. *Science*. 2004;305:522–525

Purpose of the Study. To demonstrate the safety and immunogenicity of synthetic glycoconjugate vaccine against *Haemophilus influenzae* type b (Hib).

Study Population. Adults, children, and infants in Camaguey, Cuba.

Methods. The authors established a large-scale good manufacturing protocol for the production of ~100-g batches of polyribosylribitol phosphate (PRP), the Hib capsular polysaccharide. Synthetic PRP (sPRP) conjugated to protein was shown to be capable of binding antibody from 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/TT 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) were 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.

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ECHINACEA PURPUREA THERAPY FOR THE TREATMENT OF THE COMMON COLD: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL

Yale SH, Liu K. *Arch Intern Med*. 2004;164:1237–1241

Pupose of the study. *Echinacea purpurea* stimulates the immune response and is promoted to reduce symptom 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.

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EFFICACY AND SAFETY OF ECHINACEA IN TREATING UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN: A RANDOMIZED CONTROLLED TRIAL

Taylor J, Weber W, Standish L, et al. *JAMA*. 2003;290: 2824–2830

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.

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Three-Year Outcomes of Dietary Fatty Acid Modification and House Dust Mite Reduction in the Childhood Asthma Prevention Study

Anna Nowak-Wegrzyn

Pediatrics 2005;116;540
DOI: 10.1542/peds.2005-0698J

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