main outcome measure was maternal report of a provider’s diagnosis of eczema or atopic dermatitis in the first 6 months of life.

**Methods.** The authors used a prospective birth cohort study design and multiple logistic-regression models to assess the associations between potential predictors and incidence of atopic dermatitis.

**Results.** The incidence of atopic dermatitis in the first 6 months of life was 17.1%. The risk of atopic dermatitis was increased among infants born to black or Asian mothers (adjusted odds ratio [OR]: 2.41 and 2.58, respectively) and among infants whose mothers had eczema (OR: 2.67). Other predictors included increased gestational age at birth (OR: 1.14; 95% confidence interval: 1.02, 1.27, for each 1-week increment) and male gender (OR: 1.76).

**Conclusions.** These findings suggest that genetic and prenatal and perinatal influences are important in the early presentation of atopic dermatitis.

**Reviewer’s Comments.** There are relatively little data about risk factors for atopic dermatitis in the United States, and the strengths of this study are the prospective evaluation of risk factors in a large population with data collection beginning in the prenatal period. The results of the study point to a number of risk factors related to heredity and potentially genetics as being important in early onset of wheeze. The preponderance of affected males is interesting given that infant boys are also more likely to wheeze. Although this may be due in part to changes in airway mechanics, the results of this study, together with data demonstrating higher total serum IgE levels in boys, suggest that immune development is also related to gender. Environmental factors were not prominent as risk factors and variation in the maturation of the immune system seem to have a role in the development of asthma. These findings suggest that genetic and potentially genetics as being important in early onset of atopic dermatitis.

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**Conclusions.** The authors concluded that reduced plasma sCD14 at birth and impaired IFNγ production at 3 months of age increase the risk of recurrent wheezing in the first year of life. Because of the interrelationship of CD14 and IFNγ, a CD14-mediated response to endotoxin may play an important role in enhancing the maturation of IFNγ production and preventing the inception of recurrent wheezing.

**Reviewers’ Comments.** The relation of CD14 and IFN with endotoxin exposure lends support for the “hygiene hypothesis,” which postulates that decreased exposure to infectious agents in infancy increases the risk for atopy. From this study, it is impossible to assess whether sCD14 levels at birth and IFNγ production at 3 months of age are simply independent markers that correlate with recurrent wheeze or whether they are truly in the same causal pathway to recurrent wheezing. Additional studies will need to be done to confirm causality. Unfortunately, the design of the study did not allow the investigators to explore whether IFNγ production and sCD14 levels were important in atopic versus nonatopic recurrent wheezing.

**REDUCED INTERFERON γ PRODUCTION AND SOLUBLE CD14 LEVELS IN EARLY LIFE PREDICT RECURRENT WHEEZING BY 1 YEAR OF AGE**


**Purpose of the Study.** To determine if interferon γ (IFNγ) production and soluble CD14 (sCD14) levels correlate longitudinally with the risk of developing recurrent wheezing in the first year of life. Both environmental risk factors and variation in the maturation of the immune system seem to have a role in the development of asthma. Previous studies have demonstrated reduced IFNγ production in atopic and nonatopic wheezers. IFNγ production correlates positively with endotoxin exposure and with sCD14 levels, and CD14 functions as a receptor for endotoxin. Thus, the investigators reasoned that a CD14-mediated response to endotoxin might play a role in the maturation of IFNγ production, possibly preventing the onset of recurrent wheezing.

**Study Population.** Subjects were 238 infants followed prospectively from birth to 12 months as part of the Infant Immune Study in Arizona.

**Methods.** Mothers of enrolled infants completed questionnaires about known environmental risk factors for wheezing before birth and throughout the infant’s first 12 months of life. At 12 months, the mothers were also asked how often their infant’s chest had ever sounded “wheezy” or “whistling” and the age of the first wheezing episode. Frequency of wheezing was quantified, and any response more than “very rarely” was classified as recurrent wheezing. Blood was obtained at birth and 3 months of age for the measurement of sCD14 levels in plasma and IFNγ production from stimulated peripheral blood mononuclear cells.

**Results.** Wheezing episodes during the first year of life were experienced by 94 infants (39.5%), and 41 experienced recurrent episodes. The mean IFNγ production and sCD14 levels increased from birth to 3 months. Infants in the lowest quartile of IFNγ production at 3 months and of sCD14 levels at birth had up to 4.5 and 3.2 increased odds, respectively, of developing recurrent wheezing compared with children in the medium and high quartiles for these parameters. These relationships persisted after adjusting for demographic and environmental asthma risk factors.

**Conclusions.** The authors concluded that reduced plasma sCD14 at birth and impaired IFNγ production at 3 months of age increase the risk of recurrent wheezing in the first year of life. Because of the interrelationship of CD14 and IFNγ, a CD14-mediated response to endotoxin may play an important role in enhancing the maturation of IFNγ production and preventing the inception of recurrent wheezing.

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**SOLUBLE CD14 AS A PREDICTOR OF SUBSEQUENT DEVELOPMENT OF RECURRENT WHEEZING IN HOSPITALIZED YOUNG CHILDREN WITH RESPIRATORY SYNCYTIAL VIRUS-INDUCED BRONCHIOLITIS**


**Purpose of the Study.** To investigate the relationship between the serum level of soluble CD14 (sCD14) in children hospitalized because of respiratory syncytial virus (RSV)-induced bronchiolitis and the subsequent development of recurrent wheezing.

**Study Population.** Twenty-one infants aged 2 to 14 months who were hospitalized because of RSV bronchiolitis in the winter of 2001–2002. All were at least 37 weeks’ gestation without any neonatal complications or prior illness.

**Methods.** sCD14 was measured on admission to the hospital. RSV infection was documented by direct immunofluorescence. Children were assessed every 2 months for 1 year after discharge for the development of recurrent wheezing.

**Results.** Nineteen patients completed the study. Six children did not have recurrent wheezing in the 12-month
follow-up period (group A), and 13 had recurrent wheezing (group B). There was no significant difference in birth weight, male-to-female ratio (1:1), or age at hospitalization (group A: 6.3 ± 5.3 months; group B: 4.2 ± 3.3 months) between groups. There was a trend for children in group A to have been breastfed more than those in group B (83% vs 46%; P = .18). Similarly, children in group A tended to have higher birth weight than those in group B (3303 ± 647 vs 2864 ± 486 g; P = .15). Children in group A (non-wheezers) had significantly higher sCD14 levels on hospital admission than those in group B (wheezers) (14521 ± 1773 vs 11243 ± 3264 pg/mL; P < .05). sCD14 levels correlated with age at hospitalization (P < .01). The sCD14 level was >11,000 pg/mL in 5 of 6 (83%) children in group A and 6 of 13 (46%) children in group B. This level was chosen as it is available in the best predictor for subsequent recurrent wheezing.

Conclusions. In infants hospitalized for RSV bronchiolitis, high serum sCD14 levels correlate with protection from subsequent recurrent wheezing and may modulate the influence of RSV development of lower airway disease.

Reviewers’ Comments. Membrane-bound CD14 on monocytes and macrophages binds lipopolysaccharide (LPS) and transfers it from LPS-binding protein to Toll-like receptors (TLRs). CD14/TLR activation by LPS enhances interleukin 12 and interleukin 18 synthesis, T(H)1 differentiation, and inhibition of the atopic phenotype. It is not clear from this study if increased sCD14 levels are the result of a differential responsiveness to RSV in group A or if sCD14 levels predated acquisition of the RSV infection. Nonetheless, this study adds another layer to our understanding of the early role of innate immune responsiveness and the subsequent risk of development of atopic disease.

MITCHELL R. LESTER, MD
Norwalk, CT

THE INTRODUCTION OF SOLIDS IN RELATION TO ASTHMA AND ECZEMA


Purpose of the Study. Some feeding guidelines recommend delayed introduction of solids for the prevention of asthma and allergy. This study sought to explore whether late introduction of solids is protective against the development of asthma, eczema, and atopy.

Study Population. A total of 642 unselected children recruited before birth and followed to the age of 5.5 years.

Methods. A questionnaire was administered yearly. Food exposure was derived from the first-year questionnaire: “When did you start feeding your son/daughter the following foods?: fruits, vegetables, infant rice, cereal products, meat, fish, milk products, egg.” Median age at which each solid food was introduced and length of time the infant was breastfed were determined. Wheezing was defined as wheezing in the absence of a cold or infection in the preceding 12 months, and eczema was defined as a positive response to “has a doctor ever told you that your son/daughter has eczema?” Skin-prick tests to grass, cats, and dust mites were performed at age 5.5 years, and atopy was defined as at least 1 positive skin test. Clinical outcomes were compared for early (before the median age) or late (after the median age) introduction of foods and how long the infants were breastfed.

Results. No effect of the early or late introduction of solid foods in relation to any of the outcomes was observed. No association between exclusive breastfeeding at the age of 8 weeks and any of the outcomes was found.

Conclusion. The results do not support the recommendations given by present feeding guidelines, which state that a delayed introduction of solids is protective against the development of asthma and allergy.

Reviewer’s Comments. Published feeding guidelines on the delayed introduction of solid foods to prevent allergy state that “conclusive studies are not yet available to permit definitive recommendations.” Nonetheless, recommendations are made regarding delaying the introduction of certain foods until certain ages. Some meta-analyses have favored breastfeeding for prevention of eczema (and other atopic diseases), but individual studies on both sides continue to be published. This study suggests that delayed introduction of solid foods does not prevent asthma, eczema, or atopy. The most obvious type of allergy that such a delay might prevent is allergy to the food itself, but this “prevention” is somewhat self-fulfilling, because you cannot become allergic to a food to which you have not been exposed. This is complicated further by exposure to foods in breast milk. Additionally, many toddlers who become allergic to foods, particularly milk and egg, routinely outgrow the allergy. Although this study is helpful in examining the relationship (or lack thereof) between the introduction of solid foods and asthma, eczema, and atopy, we need more research to tell us if delayed introduction of solid foods will prevent or merely delay the development of food allergy.

JOHN M. KELSO, MD
San Diego, CA

EFFECTS OF BREAST-FEEDING OF THE FIRST 3 YEARS OF LIFE—RESULTS FROM THE GINI-BIRTH COHORT STUDY


Purpose of the Study. Most studies have shown a protective effect of breastfeeding on atopic disease, but some have shown an increased risk. This study examined the impact of exclusive breastfeeding for the first 4 months of infancy on the prevalence of atopic dermatitis (AD) during the first 3 years of life.

Study Population. A large birth cohort of healthy term neonates in Germany enrolled between 1995 and 1998 for a study designed to investigate risk factors for and course and prevention of allergic disease.

Methods. Group I (interventional) consisted of infants with a family history of allergy who were either exclusively breastfed for the first 4 months or were not breastfed or supplemented (by randomization) with hydrolyzed formula (study formula) or conventional cow’s milk formula. Group NI (noninterventional) consisted of infants whose parents did not wish to participate in the intervention trial or who did not have a family history of allergy. Both groups received a yearly self-administered questionnaire on health, nutrition, and living conditions. Parents in group I also received dietary recommendations to avoid allergenic food and participated in structured interviews at the study centers.

Results. Of the 5538 infants recruited at birth, 4194 (75.7%) completed the 3-year questionnaires. Of these, 3903 (93.1%) completed data on feeding regimen and physician-diagnosed AD. Fifty-two percent of these infants were breastfed exclusively and 522 (13.4%) were bottle-fed exclusively during the first 4 months of life. The overall prevalence of physician-diagnosed AD and intermittent itchy rash for at least 6 months was 20% and 9.1%, respec-
Soluble CD14 as a Predictor of Subsequent Development of Recurrent Wheezing in Hospitalized Young Children With Respiratory Syncytial Virus-Induced Bronchiolitis

Mitchell R. Lester

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