

The Childhood Origins of Asthma (COAST) study

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Although asthma is probably a heterogeneous disease or syndrome, three factors and/or events consistently emerge for their ability to significantly influence asthma inception in the first decade of life: immune response aberrations, which appear to be defined best by the concept of cytokine dysregulation; lower respiratory tract infections, in particular respiratory syncytial virus (RSV); and some form of gene–environment interaction that needs to occur at a critical time-period in the development of the immune system or the lung. It remains to be firmly established, however, how any one or all of these factors, either independently or interactively, influence the development of childhood asthma. For example, cytokine dysregulation (T helper 1/T helper 2 imbalance) appears to track best epidemiologically with allergic diseases. As not everyone who undergoes allergic sensitization develops asthma, some other host–environment interaction must need to occur to target this chronic allergic inflammatory response to the lower airway. Some evidence suggests that this event might be an environmental insult in the form of a virus infection, particularly with RSV, which has a predilection for infecting, destroying, and/or in some way biologically altering lower airway epithelium. However, only a fraction of children develop recurrent wheezing following RSV infections, despite the fact that nearly all children have been infected at least once by 2 years of age. Thus, although RSV infections may have the potential of targeting the inflammatory response to the lower airway, they may only be able to do so during a vulnerable time-period during development of the immune system or lung. This developmental component may further reflect important gene–environment interactions that regulate both short- and long-term airway physiological alterations that manifest themselves clinically as childhood asthma. Efforts to determine and define the importance of these three factors to asthma pathogenesis are the focus and goal of the COAST (Childhood Origins of Asthma) project.

Robert F. Lemanske

University of Wisconsin Medical School, Madison,
 WI, USA

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Robert F. Lemanske, Jr, Division of Pediatric Allergy, Immunology, and Rheumatology, University of Wisconsin Hospital, 600 Highland Avenue K4-916, Madison, WI 53792, USA
 Tel.: +1 608 263 6184
 Fax: +1 608 265 2207
 E-mail: rfl@medicine.wisc.edu

From prospective epidemiological evaluations, for many individuals the asthmatic phenotype had its roots in the first few years of life. In infants and children, wheezing illnesses associated with lower respiratory tract infections have been noted in ≈50% of patients by 6 years of age (1). Based on the time of onset and pattern of wheezing symptoms, these children have been grouped into at least three phenotypes: transient wheezers (present in the first 3 years, gone by 3 years of age);

persistent wheezers (present in the first 3 years and still present beyond 3 years of age); and late-onset wheezers (not present in the first 3 years, but symptoms begin between 3 and 6 years of age) (1). Both virus-specific and host-specific factors may contribute to the clinical expression of these phenotypes. Virus-specific factors include the ability to induce virus-specific immunoglobulin E (IgE) antibody [e.g. respiratory syncytial virus (RSV) (2,3) and parainfluenza virus (4)], and the

type of cytokine response to various viral peptides (e.g. G vs. F proteins of RSV) (5) or viruses [interleukin (IL)-11 responses to asthma-associated viruses] (6). Host-specific factors which appear to be important in the transient wheezing phenotype are primarily lung size (7), while in the persistent wheezing phenotype, risk factors include exposure to passive smoke, a maternal history of asthma, and an elevated serum IgE level obtained at 9–12 months of age (1,8–11). Interestingly, the prevalence, at age 6 years, of allergic sensitization, is increased in both the persistent and late-onset wheezing phenotypes, but serum levels of IgE are only increased in the persistent wheezing phenotype when evaluated at 9 months of age (1). These latter relationships suggest that gene–environment interactions may be contributing to the expression of these two phenotypes.

Of the various risk factors which may influence the development of persistent wheezing and asthma, two are most often implicated: first, the presence of atopy in the host (genetic); and second, the development of lower respiratory tract infections (environmental) (12–14). At present, however, the relative importance of these two factors is uncertain owing to a paucity of prospective longitudinal analyses. From the available information, however, interactions between these two factors appear to be bi-directional and dynamic in that the atopic state can influence the lower airway response to viral infections (1,15), viral infections can influence the development of allergy (16–18), and interactions can occur when individuals are exposed simultaneously to both allergens and viruses (19–21). Some (16), but not all (14), investigators have noted that infantile RSV infections increase the risk of allergic sensitization later in childhood. These divergent findings in terms of clinical outcomes may be related to the severity, etiology (i.e. RSV vs. other respiratory tract viruses) and/or timing (developmental component) of the initial infection in relationship to allergen exposures (22). Prospective studies designed to address the contribution of each of these factors to childhood asthma pathogenesis are obviously needed.

What is the relationship between viral infections and asthma?

Acute viral infections have been demonstrated to be temporally associated with a number of important clinical consequences (23), including: the development of wheezing-associated illnesses in infants and small children (24–31); initiating acute exacerbations of asthma, in both children and

adults (24,28,32,33); and inducing short- and long-term alterations in airway physiology, such as increasing airway responsiveness (34) and creating abnormalities in airflow (35), lung volumes (36,37) and gas exchange (38). Recent prospective observations have demonstrated that certain viral infections, especially RSV, may also contribute to the inception of childhood asthma in the first decade of life (14,39).

Do RSV infections contribute to asthma inception?

In infants, infection with RSV has received much attention because of its predilection to produce a pattern of symptoms termed ‘bronchiolitis’, which parallel many of the features of childhood and adult asthma (12). During 1980–96 in the USA, rates of hospitalization of infants with bronchiolitis increased substantially, as did the proportion of total and lower respiratory tract hospitalizations associated with bronchiolitis (40); RSV caused $\approx 70\%$ of these episodes. However, RSV bronchiolitis represents only the most severe fraction of cases, in that by 1 year of age, 50–65% of children will have been infected with this virus and, by 2 years of age, nearly 100% (41). Children 3–6 months of age are most prone to develop lower respiratory tract symptoms, suggesting that a developmental component (e.g. lung and/or immunological maturation) may also be involved (41). Although controversy exists regarding the relevance of antecedent RSV infections and the development of recurrent wheezing (42), a recent long-term prospective study of large numbers of children has demonstrated that RSV infections are a significant, independent risk factor for subsequent frequent wheezing, at least within the first decade of life (14,16). It remains to be established, however, how RSV infections produce these outcomes, owing to the fact that virtually all children have been infected with this virus before their second birthday.

Are cytokine responses dysregulated in children with allergies and/or asthma?

Recent observations have stimulated research efforts to further define the relative importance and pathophysiological contributions of cytokine dysregulation [the so-called T helper 1/T helper 2 (Th1/Th2) imbalance] to the development of various atopic phenotypes, including asthma (43). Although questions remain as to the full impact of a Th1/Th2 dysregulation in established asthma, the contribution of cytokine polarization to the inception and evolution of various atopic diseases, including asthma, has received more uni-

form support. At birth, largely as a result of placentally derived Th2 trophic factors, cytokine profiling of cord blood indicates that the newborn infant's mononuclear cell response is skewed towards a Th2-like phenotype (production of IL-4, IL-5, IL-6, and IL-10) (44). The relative nature of this Th1/Th2 imbalance [as reflected by diminished interferon- γ (IFN- γ) production] may be a predictor of the subsequent development of allergic disease and/or asthma (44–47).

In children who are destined to be at increased risk of developing allergic diseases and/or asthma, a further diminution in cord blood mononuclear cell generation of IFN- γ (46,48) and IL-13 (49) has been noted, and the capacity of these children to generate normal IFN- γ responses lags behind a non-atopic control population (44,50,51). Although in the first decade of life these differences eventually become less evident, the IFN- γ response curve is shifted to the right in the first few years of life for atopic children (lymphocytes from atopic children produce significantly less of this cytokine in comparison to lymphocytes from non-atopic children). These observations indicate that there may be a critical time-period in the development of the atopic child in which target organs, such as the lung, may be particularly vulnerable to environmental stress factors such as viral respiratory tract infections. While these observations have generated intense interest in the intrauterine/neonatal, genetic, and environmental influences, conflicting results have prevented the establishment of any firm conclusions (52). Therefore, well-designed prospective studies are needed to address these various factors and their interactions.

The COAST (Childhood Origins of Asthma) study

To study the contribution of, and the interactions among, age, patterns of cytokine secretion and virus infections, with respect to the subsequent development of childhood asthma, a cohort of children ($n=287$) who are at increased risk of developing asthma (at least one parent has allergies and/or asthma) were enrolled at birth to participate in a prospective study designed to address these issues. The following research hypothesis is the primary focus of the COAST study (Fig. 1), namely that the development of the persistent wheezing phenotype in children, or childhood asthma, requires the presence of at least two factors at a critical time-point in the development of the immune system or lung. These two factors are as follows:

1 dysregulation of cytokine responses at birth (genetic factor); and

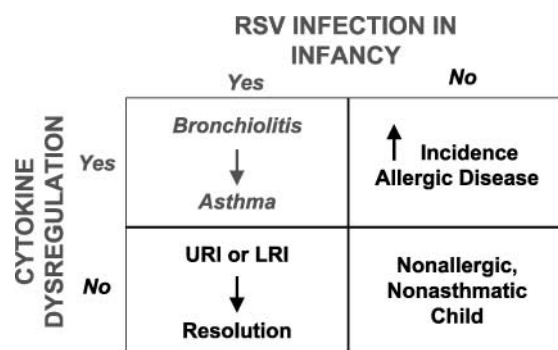


Fig. 1.

[Q8]

2 development of a clinically significant lower respiratory tract viral infection (primarily RSV bronchiolitis) (environmental factor).

The COAST study was funded by the National Heart Lung and Blood Institute (National Institutes of Health, Bethesda, MD) in September 1998 and launched in November of that same year. The COAST hypothesis evolved from data generated in a rat model of virus-induced airway dysfunction developed in collaboration with Dr William Castleman and presently used within our laboratories (53–56), as well as from data reported in humans. Taken together, these findings led to the ‘two-hit’ hypothesis (a restatement of the research hypothesis stated already) Cow’s milk protein allergy/intolerance (Fig. 2) pertaining to the inception of childhood asthma. Cytokine dysregulation, potentially present at birth, is influential in determining the host response to viral infections. For example, if an infection occurs with a particular virus (i.e. RSV) at a critical time-period (i.e. infancy), the combination of cytokine dysregulation and RSV infection has a

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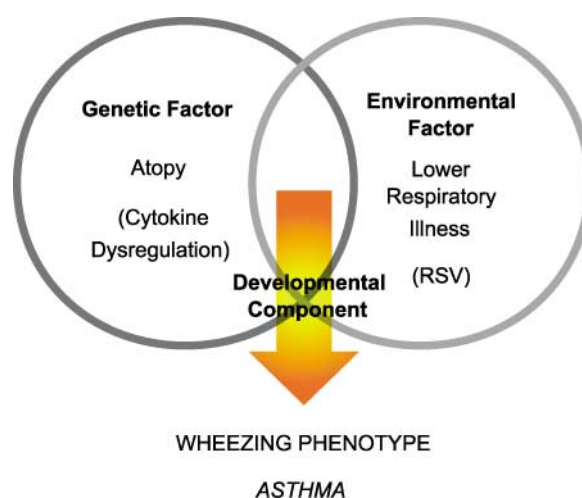


Fig. 2.

[Q9]

significant probability of producing the clinical syndrome of bronchiolitis and, over time, the development of a persistent wheezing phenotype or asthma. In contrast, infants and children who have demonstrable cytokine dysregulation, but do not develop an infantile RSV infection, have an increased probability of developing allergic sensitization, including asthma, which may have its initial presentation in later childhood or adolescence. In children with normal cytokine regulatory patterns, RSV infections can produce both upper and lower respiratory tract illnesses (the latter being more common in premature infants or in term infants with diminished pulmonary function at birth), but the wheezing and coughing which may be associated with these infections resolve over time.

Based on sample-size calculations to address this hypothesis, a total of 146 children at high risk of developing allergies and/or asthma needed to complete the study in order to obtain 70% power to detect a log-odds ratio of 2.2 (odds ratio = 9.0) in favor of development of the persistent wheezing phenotype for the double-factor group (cytokine dysregulation and RSV infection), relative to the other groups, with a one-sided test statistic having a 5% Type I error rate. The test statistic is the interaction test for a logistic regression model, and sample size and power formulas were derived using the formula for the variance of the associated logistic-regression parameter estimate (57). Community interest in the project far exceeded initial expectations and enrolment was expanded to 312 consenting families. Of these 312 babies, 287 children are still actively enrolled. The remaining 25 were excluded for the following reasons: 14 cord blood failures; four withdrawals; two genetic abnormalities; one respiratory distress syndrome; and four non-allergic parents (the mothers were not skin tested until after delivery).

[Q5]

To be eligible for study participation, either the expectant mother (31.3 ± 4.8 years) or father (32.9 ± 5.3 years) had to be allergic (defined as one or more positive aeroallergen skin tests), asthmatic (defined initially historically), or both. The distribution of these parental phenotypes was as follows: 44.5% allergy only; 1.8% asthma only; 37.7% allergy and asthma; and 16% neither (the other parent qualified the child for participation). Infants needed to be born at term (mean birth weight = 3.51 ± 0.5 kg; head circumference = 34.7 ± 2.3 cm; 56.4% male and 43.6% female gender; 86.8% Caucasian and 13.2% ethnic minority) (month of birth amortized evenly over a 1-year cycle), have APGAR scores of at least 7 at 5 min (8.9 ± 0.49), and not have any significant neonatal respiratory difficulties or anomalies that

would preclude them from participating fully in the study.

To address the experimental hypothesis, we are in the process of performing *in vitro* evaluations of cytokine response patterns in the children at birth and at 1, 2, and 3 years of age, and also in their parents, and defining viral respiratory pathogens responsible for significant lower respiratory tract illnesses throughout the first 3 years of life. Thus far, >3000 nasal mucus specimens have been obtained in protocol-initiated visits and during respiratory illnesses of sufficient severity to dictate specimen collection, according to a predefined symptom-severity scoring system. We further plan to evaluate these variables over time (developmental aspect), and to determine the relative contribution of these factors in influencing the development of various wheezing phenotypes during early childhood. In the past 2.5 years, we have made considerable progress in evaluating this hypothesis (58–68). However, because the development of the persistent wheezing phenotype cannot be ascertained until children enrolled in the COAST project reach at least 3 years of age, the major outcome measure cannot be evaluated prior to November 2001. Once the cohort reaches this landmark, we will be in a strong position to evaluate comprehensively and prospectively the contribution(s) of cytokine dysregulation, viral infections, and the timing of these events with regard to immune system and lung development with the development of various wheezing (asthmatic) phenotypes in childhood.

[Q6]

Acknowledgments

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References

- MARTINEZ FD, WRIGHT AL, TAUSSIG LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; 332: 133–8.
- WELLIVER RC, SUN M, RINALDO D, OGRA PL. Predictive value of respiratory syncytial virus-specific IgE responses for recurrent wheezing following bronchiolitis. *J Pediatr* 1986; 109: 776–80.
- WELLIVER RC, WONG DT, SUN M, MIDDLETON E JR, VAUGHAN RS, OGRA PL. The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. *N Engl J Med* 1981; 305: 841–6.
- WELLIVER RC, WONG DT, SUN M, MCCARTHY N. Parainfluenza virus bronchiolitis. Epidemiology and pathogenesis. *Am J Dis Child* 1986; 140: 34–40.
- ALWAN WH, KOZLOWSKA WJ, OPENSHAW PJM. Distinct types of lung disease caused by functional subsets of antiviral T cells. *J Exp Med* 1994; 179: 81–9.

6. EINARSSON O, GEBA GP, PANUSKA JR, ZHU Z, LANDRY M, ELIAS JA. Asthma-associated viruses specifically induce lung stromal cells to produce interleukin-11, a mediator of airways hyperreactivity. *Chest* 1995; 107: 132S-3S.
7. MARTINEZ FD, MORGAN WJ, WRIGHT AL, HOLBERG C, TAUSSIG LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988; 319: 1112-7.
8. MARTINEZ F, CLINE M, BURROWS B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 1992; 89: 21-6.
9. MORGAN WJ, MARTINEZ FD. Risk factors for developing wheezing and asthma in childhood. In: STEMPER DA, SZEFLER SJ, eds. *Pediatric Clinics of North America*. Philadelphia, PA: W. B. Saunders Co., 1992: 1185-203.
10. HALONEN M, STERN D, TAUSSIG LM, WRIGHT A, RAY CG, MARTINEZ FD. The predictive relationship between serum IgE levels at birth and subsequent incidences of lower respiratory illnesses and eczema in infants. *Am Rev Respir Dis* 1992; 146: 866-70.
11. HOLBERG CJ, WRIGHT AL, MARTINEZ FD, RAY CG, TAUSSIG LM, LEBOWITZ MD. Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. *Am J Epidemiol* 1991; 133: 1135-51.
12. LANDAU LI. Bronchiolitis and asthma: Are they related? *Thorax* 1994; 49: 293-6.
13. SEARS MR. Epidemiology of childhood asthma. *Lancet* 1997; 350: 1015-20.
14. STEIN RT, SHERRILL D, MORGAN WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999; 354: 541-5.
15. BARDIN PG, FRAENKEL DJ, SANDERSON G, et al. Amplified rhinovirus colds in atopic subjects. *Clin Exp Allergy* 1994; 24: 457-64.
16. SIGURS N, BJARNASON R, SIGURBERGSSON F, KJELLMAN B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 2000; 161: 1501-7.
17. FRICK OL, GERMAN DF, MILLS J. Development of allergen in children. I. Association with virus infections. *J Allergy Clin Immunol* 1979; 63: 228-41.
18. FRICK OL. Effect of respiratory and other virus infections on IgE immunoregulation. *J Allergy Clin Immunol* 1986; 78: 1013-8.
19. LEMANSKE RF JR, DICK EC, SWENSON CA, VRTIS RF, BUSSE WW. Rhinovirus upper respiratory infection increases airway hyperreactivity and late asthmatic reactions. *J Clin Invest* 1989; 83: 1-10.
20. CALHOUN WJ, DICK EC, SCHWARTZ LB, BUSSE WW. A common cold virus, rhinovirus 16, potentiates airway inflammation after segmental antigen bronchoprovocation in allergic subjects. *J Clin Invest* 1994; 94: 2200-8.
21. SKONER DP, WHITESIDE TL, WILSON JW, DOYLE WJ, HERBERMAN RB, FIREMAN P. Effect of rhinovirus 39 infection on cellular immune parameters in allergic and nonallergic subjects. *J Allergy Clin Immunol* 1993; 92: 732-43.
22. TSITOURA DC, KIM S, DABBAGH K, BERRY G, LEWIS DB, UMETSU DT. Respiratory infection with influenza A virus interferes with the induction of tolerance to aeroallergens. *J Immunol* 2000; 165: 3484-91.
23. CYP CAR D, STARK J, LEMANSKE RF JR. The impact of respiratory infections on asthma. In: STEMPER DA, SZEFLER SJ, eds. *Pediatric Clinics of North America*. Philadelphia: W. B. Saunders Co., 1992: 1259-76.
24. JOHNSTON SL, PATTEMORE PK, SANDERSON G, et al. Role of virus infections in children with recurrent wheeze or cough. *Thorax* 1993; 48: 1055-60.
25. MINOR TE, BAKER JW, DICK EC, et al. Greater frequency of viral respiratory infections in asthmatic children as compared with their nonasthmatic siblings. *J Pediatr* 1974; 85: 472-7.
26. MINOR TE, DICK EC, DEMENT AN, OUELLETTE JJ, COHEN M, REED CE. Viruses as precipitants of asthmatic attacks in children. *JAMA* 1974; 227: 292-8.
27. HENDERSON FW, CLYDE WA, COLLIER AM, et al. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. *J Pediatr* 1979; 95: 183-90.
28. JOHNSTON SL, PATTEMORE PK, SANDERSON G, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *Br Med J* 1995; 310: 1225-8.
29. HENDERSON FW, CLYDE WA JR, COLLIER AM, et al. The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. *J Pediatr* 1979; 95: 183-90.
30. CARLSEN KH, ORSTAVIK I, LEEGAARD J, HOEG H. Respiratory virus infections and aeroallergens in acute bronchial asthma. *Arch Dis Child* 1984; 59: 310-5.
31. MERTSOLA J, ZIEGLER T, RUUSKANEN O, VANTO T, KOIVIKKO A, HALONEN P. Recurrent wheezy bronchitis and viral respiratory infections. *Arch Dis Child* 1991; 66: 124-9.
32. NICHOLSON KG, KENT J, HAMMERSLEY V, CANCIO E. Risk factors for lower respiratory complications of rhinovirus infections in elderly people living in the community: Prospective cohort study. *BMJ* 1996; 313: 1119-23.
33. RYLANDER E, ERIKSSON M, PERSHAGEN G, NORDVALL L, EHRNST A, ZIEGLER T. Wheezing bronchitis in children. Incidence, viral infections, and other risk factors in a defined population. *Pediatr Allergy Immunol* 1996; 7: 6-11.
34. EMPEY DW, LAITINEN LA, JACOBS L, GOLD WM, NADEL JA. Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. *Am Rev Respir Dis* 1976; 113: 131-9.
35. GRÜNBERG K, TIMMERS MC, DE KLERK EPA, DICK EC, STERK PJ. Experimental rhinovirus 16 infection causes variable airway obstruction in subjects with atopic asthma. *Am J Respir Crit Care Med* 1999; 160: 1375-80.
36. WOHL MEB, STIGOL L, MEAD J. Resistance of the total respiratory system in healthy infants with bronchiolitis. *Pediatrics* 1969; 43: 495-509.
37. STOKES GM, MILNER AD, HODGES IGC, GROGGINS RC. Lung function abnormalities after acute bronchiolitis. *J Pediatr* 1981; 98: 871-4.
38. HALL CB, HALL WJ, GALA CL, MAGILL FB, LEDDY JP. Long-term prospective study of children after respiratory syncytial virus infection. *J Pediatr* 1984; 105: 358-64.
39. CASTRO-RODRÍGUEZ JA, HOLBERG CJ, WRIGHT AL, et al. Association of radiologically ascertained pneumonia before age 3 yr with asthmatic symptoms and pulmonary function during childhood. A prospective study. *Am J Respir Crit Care Med* 1999; 159: 1891-7.
40. SHAY DK, HOLMAN RC, NEWMAN RD, LIU LL, STOUT JW, ANDERSON LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA* 1999; 282: 1440-6.

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41. OPENSHAW PJM. Immunological mechanisms in respiratory syncytial virus disease. *Springer Semin Immunopathol* 1995; 17: 187–201.
42. REIJONEN TM, KOTANIEMI-SYRJÄNEN A, KORHONEN K, KORPPI M. Predictors of asthma three years after hospital admission for wheezing in infancy. *Pediatrics* 2000; 106: 1406–12.
43. GERN JE, LEMANSKE RF JR, BUSSE WW. Early life origins of asthma. *J Clin Invest* 1999; 104: 837–43.
44. PRESCOTT SL, MACAUBAS C, HOLT BJ, et al. Transplacental priming of the human immune system to environmental allergens: Universal skewing of initial T cell responses toward the Th2 cytokine profile. *J Immunol* 1998; 160: 4730–7.
45. PRESCOTT SL, HOLT PG. Abnormalities in cord blood mononuclear cytokine production as a predictor of later atopic disease in childhood. *Clin Exp Allergy* 1998; 28: 1313–6.
46. TANG MLK, KEMP AS, THORBURN J, HILL DJ. Reduced interferon-gamma secretion in neonates and subsequent atopy. *Lancet* 1994; 344: 983–5.
47. HALONEN M, MARTINEZ FD. A deficient capacity to produce interferon-gamma: Is it a risk for asthma and allergies? *Clin Exp Allergy* 1997; 27: 1234–6.
48. MATSUI E, KANEKO H, TERAMOTO T, et al. Reduced IFN-gamma production in response to IL-12 stimulation and/or reduced IL-12 production in atopic patients. *Clin Exp Allergy* 2000; 30: 1250–6.
49. WILLIAMS TJ, JONES CA, MILES EA, WARNER JO, WARNER JA. Fetal and neonatal IL-13 production during pregnancy and at birth and subsequent development of atopic symptoms. *J Allergy Clin Immunol* 2000; 105: 951–9.
50. MARTINEZ FD, STERN DA, WRIGHT AL, HOLBERG CJ, TAUSSIG LM, HALONEN M. Association of interleukin-2 and interferon-gamma production by blood mononuclear cells in infancy with parental allergy skin tests and with subsequent development of atopy. *J Allergy Clin Immunol* 1995; 96: 652–60.
51. HOEKSTRA MO, HOEKSTRA Y, DE REUS D, RUTGER B, GERRITSEN J, KAUFFMAN HF. Interleukin-4, interferon-gamma and interleukin-5 in peripheral blood of children with moderate asthma. *Clin Exp Allergy* 1997; 27: 1254–60.
52. BODNER CH, ROSS S, LITTLE J, et al. Risk factors for adult onset wheeze. A case control study. *Am J Respir Crit Care Med* 1998; 157: 35–42.
53. MIKUS LD, ROSENTHAL LA, SORKNESS RL, LEMANSKE RF JR. Reduced interferon- γ secretion by natural killer cells from rats susceptible to postviral chronic airway dysfunction. *Am J Respir Cell Mol Biol* 2001; 24: 74–82.
54. SORKNESS RL, CASTLEMAN WL, KUMAR A, KAPLAN MR, LEMANSKE RF JR. Prevention of chronic post-bronchiolitis airway sequelae with interferon- γ treatment in rats. *Am J Respir Crit Care Med* 1999; 160: 705–10.
55. KUMAR A, SORKNESS R, KAPLAN MR, CASTLEMAN WL, LEMANSKE RF JR. Chronic, episodic, reversible airway obstruction after viral bronchiolitis in rats. *Am J Respir Crit Care Med* 1997; 155: 130–4.
56. UHL EW, CASTLEMAN WL, SORKNESS RL, BUSSE WW, LEMANSKE RF JR, McALLISTER PK. Parainfluenza virus-induced persistence of airway inflammation, fibrosis, and dysfunction associated with TGF- β_1 expression in Brown Norway rats. *Am J Respir Crit Care Med* 1996; 154: 1834–42.
57. AGRETI A. *Categorical Data Analysis*. New York: Wiley, 1990.
58. MEYER PA, ROBERG KA, ANKLAM KS, et al. Association of neonatal cord blood Th1/Th2 cytokine response profiles with respiratory syncytial virus infections in the first year of life. *Am J Respir Crit Care Med* 2001; 163: A972.
59. ROBERG KA, ADLER KJ, BROOKS GD, et al. Relationship among viral respiratory infections, attendance at daycare, and wheezing illnesses in the first year of life. *Am J Respir Crit Care Med* 2001; 163: A970.
60. MARTIN MS, ANKLAM KS, ROBERG KA, et al. Relationship of specific viral etiologic agents versus virus-induced nasal IL-8 to respiratory symptoms in infancy. *J Allergy Clin Immunol* 2001; 107: S93.
61. NEAVILLE WA, ANKLAM KS, MOSS MH, et al. Children with decreased production of IFN- γ from cord blood mononuclear cells have an increased risk of developing atopic dermatitis. *J Allergy Clin Immunol* 2001; 107: S79.
62. ANKLAM KS, ROSENTHAL LA, MIKUS LD, ROBERG KA, GERN JE, LEMANSKE RF JR. Do newborn Th1/Th2 cytokine responses predict IgE levels at 1 year of age? *J Allergy Clin Immunol* 2001; 107: S77.
63. BROOKS GD, ANKLAM KS, ROBERG KA, et al. Reduced newborn mononuclear cell production of IL-5 and IL-13 is associated with wheezing in the first year of life. *J Allergy Clin Immunol* 2001; 107: S77.
64. MOSS MH, ANKLAM KS, ROSENTHAL LA, et al. Reduced IFN- γ /IL-5 ratio in response to mitogens in atopic asthmatic adults. *J Allergy Clin Immunol* 2001; 107: S41.
65. ADLER KJ, ROBERG KA, CARLSON-DAKES KT, et al. Frequency and etiology of respiratory tract illnesses in infants at high risk for childhood asthma. *Am J Respir Crit Care Med* 2000; 161: A917.
66. MOSS MH, ANKLAM KS, ROSENTHAL LA, et al. Reduced IFN- γ production in response to respiratory viruses in atopic asthmatic adults. *J Allergy Clin Immunol* 2000; 105: S279.
67. ROBERG KA, CARLSON-DAKES KT, ANKLAM KS, et al. Frequency and etiology of respiratory tract illnesses in infants with a maternal history of allergies and/or asthma. *J Allergy Clin Immunol* 2000; 105: S213.
68. ANKLAM KS, MOSS MH, ROSENTHAL LA, et al. Comparison of mononuclear cell IFN- γ production in atopic/asthmatic parents with their newborn infants. *J Allergy Clin Immunol* 2000; 105: S150.

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