wheezing in African American infants who are pre-maturely born.

STUDY POPULATION. The study population consisted of 300 African American infants born between 28 and 36 weeks’ gestation (mean gestational age: 33 weeks; median birth weight: 1.9 kg) at 4 sites in the United States over a 3-year period. The subjects were then managed for the first year of life for the development of parent-reported recurrent wheezing defined as ≥2 episodes of wheezing with or without an infection (primary outcome).

METHODS. This was a multicenter, double-blind randomized clinical trial. Patients and families were enrolled before discharge from the NICU or newborn nursery. There was no standardization of the feeding protocol (formula or breast milk) in enrolled subjects. Initially, all infants received an open-label multivitamin providing 400 IU of vitamin D per day. When the infants achieved a daily intake of 200 IU of vitamin D from formula or fortified human milk, they were randomly assigned to either the sustained supplementation group (continuing to receive 400 IU/day of vitamin D) or the diet-limited supplementation group (cessation of supplementation [placebo supplement]). Both groups were supplemented with active treatment or placebo until 6 months of age adjusted for prematurity. A total of 153 infants were randomly assigned to the sustained group, and 147 were randomly assigned to the diet-limited group.

RESULTS. A total of 277 infants (92.3%) completed the trial. Recurrent wheezing was reported in 31.1% of the infants in the sustained supplementation group and in 41.8% in the diet-limited group (risk difference = −10.7%; relative risk: 0.66; \( P = .02 \)). Secondary outcomes included medically attended illnesses and markers of allergy, eczema, and bone health. No significant differences between the 2 groups were seen. Serum 25(OH)D levels were measured at baseline and 3 months. There were no statistical differences between treatment and placebo groups, and no levels exceeded 80 ng/mL (the upper limit was accepted as normal). No statistical differences were seen in any adverse event between the 2 groups.

CONCLUSIONS. In this study, we found that in African American infants born prematurely, sustained supplementation with vitamin D resulted in a reduced risk of recurrent wheezing by 12 months adjusted age versus those infants with diet-limited supplementation.

REVIEWER COMMENTS. In an accompanying editorial, it was noted that the authors of a 2011 Institute of Medicine report concluded that the available evidence was insufficient to establish a functional relationship between vitamin D and any health outcome other than the maintenance of bone health across the life span. Authors of a recent review also concluded that there are a few suitable clinical trials to support the beneficial effect of vitamin D supplementation on respiratory disease. In 2 previous studies published in the *Journal of the American Medical Association*, authors examined the effects of prenatal supplementation of vitamin D on recurrent wheezing or asthma among infants managed to 3 years of age (COPSAC2010 [Chawes BL, Bennelykke K, Stokholm J, et al. Effect of vitamin D3 supplementation during pregnancy on risk of persistent wheeze in the offspring: a randomized clinical trial. *JAMA*. 2016;315(4):353–361] and VDAART [Litonjua AA, Carey VJ, Laranjo N, et al. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years: the VDAART randomized clinical trial. *JAMA*. 2016;315(4):362–370]). Both revealed no statistical differences. In the D-Wheeze supplementation trial, a statistically significant decrease was shown in recurrent wheezing in those African American infants who were born prematurely and supplemented with vitamin D. Potential mechanisms for the positive effects of vitamin D include effects on the development of neonatal lung tissue and immune system. The author of the editorial notes that the vitamin D intakes studied in this trial are not relevant to infants who are not African American and premature.

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Prednisolone for the First Rhinovirus-Induced Wheezing and 4-Year Asthma Risk: A Randomized Trial

Koistinen A, Lukkarinen M, Turunen R, et al. *Pediatr Allergy Immunol*. 2017;28(6):557–563

PURPOSE OF THE STUDY. To investigate the effect of rhinovirus load on the effectiveness of oral corticosteroid (OCS) use on the subsequent development of asthma in children with a history of rhinovirus-induced wheezing.

STUDY POPULATION. The study population included Finnish children, ages 3 to 23 months, born ≥36 gestational weeks, with a first acute wheezing episode found to be positive for rhinovirus via PCR test of nasopharyngeal aspirate. A total of 59 (75%) children who had sufficient data about rhinovirus load and follow-up were included in the analysis.

METHODS. This was a prospective, randomized placebo-controlled trial in Finland. At study entry, during the first-time acute wheezing episode, children between 3 and 23 months of age were examined by study physicians, and blood samples and nasopharyngeal aspirates were collected for PCR testing. Children who were rhinovirus positive were randomly assigned to receive a 3-day course of either oral prednisolone or placebo. Children were reexamined by a study physician, and data were captured.
by using a standardized questionnaire at 2 weeks, 2 months, 12 months, and 4 years after the first wheezing episode. The primary outcome was incident asthma, defined as time to initiation of asthma controller medication until the age of 5, on the basis of the 2007 National Asthma Education and Prevention Program guidelines for the diagnosis of asthma. An interaction analysis was performed to determine if the effect of OCS on incident asthma was modified by rhinovirus genome load.

RESULTS. A total of 79 children were randomly assigned to receive prednisolone or placebo, and 59 (75%) children who had sufficient follow-up and data were analyzed. Initiation of asthma controller medication occurred in 40 of 59 (68%) children, in 20 of 29 in the prednisolone group, and in 20 of 30 in the placebo group. The interaction analysis revealed evidence of effect modification by rhinovirus genome load. Rhinovirus genome load modified the effect of OCS use on the time of initiation to asthma controller medication. In children with a rhinovirus load >7000 copies per mL, this risk of initiation of asthma controller medication was lower in the prednisolone group compared with the placebo group (hazard ratio: 0.38 [0.14, 1.01]; P interaction: .05). No differences were found between the prednisolone and placebo groups among children with a rhinovirus genome load <7000 copies per mL.

CONCLUSIONS. Although prednisolone did not affect the time to initiation of asthma controller medication when compared with placebo, children with a high rhinovirus load who received OCS during the first acute wheezing episode had a reduced risk of developing asthma by age 5.

REVIEWER COMMENTS. Although OCS treatment has not been found to be effective for acute treatment or secondary prevention of asthma in children suffering from early wheezing, it is suggested that the small trial that OCS may reduce the risk of developing asthma among a subgroup of children with high rhinovirus load. Limitations include incomplete follow-up, small study size, and the fact that the authors performed multiple analyses to identify a rhinovirus threshold that was statistically significant. Future authors should aim for their research to be larger and more generalizable. Better predictors of asthma are needed not only to be able to provide better asthma anticipatory guidance to parents but also to be able to target appropriate populations for the development of prevention approaches.

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Wheezing and Infantile Colic Are Associated With Neonatal Antibiotic Treatment
Oosterloo BC, van Elburg RM, Rutten NB, et al. Pediatr Allergy Immunol. 2018;29(2):151–158

PURPOSE OF THE STUDY. The authors of the Intestinal Microbiota Composition After Antibiotic Treatment in Early Life study examined the effect of antibiotics given during the first week of life on the development of atopic disease and infantile colic (as well as other nonatopic disease). They also studied whether the development of these conditions depends on the duration of antibiotics.

STUDY POPULATION. An observational birth cohort of term infants (>36 weeks’ gestation) were recruited from 4 Dutch teaching hospitals.

METHODS. AB- infants were healthy untreated controls, whereas AB+ infants received broad-spectrum antibiotics. AB2 received antibiotics for 2 to 3 days (low suspicion for neonatal infection), and AB7 received antibiotics for 7 days (probable or confirmed infection). Parents recorded daily allergic symptoms and filled out monthly questionnaires regarding parent-reported eczema. At 1 year of life, physician diagnosis was recorded, and a serum screening test for atopy was performed with the Phadiatop infant assay. If atopy was found, specific immunoglobulin E for cat, dog, mite, peanut, milk, egg, and grass pollen mix were measured. Factors that were controlled for included the duration of breastfeeding, delivery mode, tobacco exposure, day care attendance, the presence of siblings, familial history of atopy, and household educational level.

RESULTS. A total of 436 infants were included in the study, 151 of whom received antibiotics (AB2: n = 42; AB7: n = 109), with a follow-up time of 1 year. The incidence of wheezing was higher in AB+ (41.0%) than in AB- (35.0%) and was significantly higher in AB7 (42.2%) but not in AB2 (38.1%) compared with AB-. The incidence of both parent-reported and doctor-diagnosed infantile colic was significantly higher in AB+ (21.9% and 4.0%, respectively) than in AB- (14.4% and 0.4%, respectively), and the incidence of parent-reported infantile colic was significantly higher in AB7 (24.8%) versus AB2 (14.3%). Allergic sensitization was found in 11.7% of AB+ and 7.0% of AB-; this trend was not statistically significant. However, sensitization to >1 allergen was found in 7 of 9 AB+ infants versus 0 of 9 AB- infants. No significant difference was found between AB- and AB+ regarding both parent-reported (37.7% vs 34.7%, respectively) and doctor-diagnosed (11.9% vs 14.0%, respectively) eczema. However, the median number of days with parent-reported rash was higher in AB+ (8.0 days) than in AB- (5.0 days).

CONCLUSIONS. Antibiotic administration during the first 7 days of life was positively correlated with the development
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