Allergy

RISK FACTOR, PREVENTION, AND THE HYGIENE HYPOTHESIS

Antibiotic Exposure in the First Two Years of Life and Development of Asthma and Other Allergic Diseases by 7.5 yr: A Dose-Dependent Relationship


PURPOSE OF THE STUDY. The goal of this study was to investigate the associations of antibiotic use in the first 2 years of life with the development of asthma, eczema, and hay fever by age 7.5 years in a longitudinal birth cohort.

STUDY POPULATION. Subjects were 4952 children from ALSPAC (Avon Longitudinal Study of Parents and Children), a population-based cohort that recruited 14,541 expectant mothers with due dates between April 1, 1991, and December 31, 1992, in Avon, United Kingdom.

METHODS. Child antibiotic use and asthma, eczema, and hay fever symptoms were maternally reported through questionnaires collected annually when subjects were ≥6 months of age. In 3 questionnaires covering the periods 0 to 6, 6 to 15, and 15 to 24 months, mothers reported whether their child had taken any antibiotics, the number of courses, and when the courses were taken. The primary outcome was asthma at 7.5 years, defined as maternal report of a physician’s diagnosis of asthma and symptoms of wheezing during the previous 12 months. Two secondary outcomes (eczema and hay fever) were maternally reported at the same time. Atopy was assessed by skin prick tests at age 7.5 years and defined as a positive response (≥2 mm wheal) to Dermatophagoides pteronyssinus, grass, or cat allergen. Headache reported at 7.5 years, which has no plausible link with antibiotic use, was used as a positive control to test for reporting bias. Data were analyzed by using multivariate logistic regression.

RESULTS. Children reported to have taken antibiotics during infancy (0–2 years) were more likely to have asthma at 7.5 years (odds ratio: 1.75 [95% confidence interval: 1.40–2.17]), and the odds increased with greater numbers of courses. When accounting for reverse causation, the association was weakened but still evident. In addition, the association was evident but weaker for eczema and hay fever compared with asthma. The effect seemed to be associated with cumulative dose rather than a critical period of exposure during the first 2 years of life. There was no association between infant antibiotic use and atopy on skin prick testing at 7.5 years or reported headaches at the same age.

CONCLUSIONS. The authors found a strong, dose-dependent correlation between increased antibiotic exposure during the first 2 years of life and the development of asthma at 7.5 years, which did not seem to be mediated through an association with atopy.

REVIEWER COMMENTS. The worldwide prevalence of atopic diseases, including asthma, has increased considerably over the last 30 years in developed, Westernized countries. Possible explanations for such a rise include recent trends in vitamin D deficiency, the hygiene hypothesis, and an increase in antibiotic prescriptions. Antibiotic exposure in infancy causes disruption to the developing gut microbiota, which could predispose subjects to asthma and allergic diseases because this period is critical in immune development. Although the authors have found a strong, dose-dependent association between antibiotic use in infancy and later asthma, the lack of association with objectively measured atopy contradicts this proposed mechanism. The authors interestingly suggest that there may be other mechanisms involved in mediating effects of alterations in the gut microbiota, such as nonatopic inflammation.

Enterovirus Infections in Early Childhood and the Risk of Atopic Disease—A Nested Case-Control Study


PURPOSE OF THE STUDY. The goal of this study was to assess the relationship between enterovirus infections in the first 2 years of life and atopic diseases. It also studied the importance of different enterovirus serotypes in atopic diseases.

STUDY POPULATION. The study population was derived from the Finnish DIPP (Diabetes Prediction and Prevention) Study. Newborn infants with HLA-DQB1 risk alleles had clinic visits every 3 to 6 months for the first 2 years of life and at subsequent intervals of 6 to 12 months. At each visit, children had a comprehensive history and physical examination performed and a venous blood sample obtained. For the present study, 71 subjects were identified as case children if they had the following: a diagnosis of asthma, atopic dermatitis, or allergic rhinitis; who had stored serum obtained at 1, 2, and 5 years available; and had serum-specific immunoglobulin E antibodies against a mixture of aeroallergens (birch, timothy, mugwort, cat, dog, horse, mite, and Cladosporium). There were 142 control subjects matched for HLA-DQB1 genotype, age, and gender.

METHODS. This study had a nested case-control design. Serum samples obtained at 1 year were analyzed for the presence of neutralizing antibodies against 5 echovirus serotypes. Serum samples obtained at 2 years were analyzed for the
presence of neutralizing antibodies against 12 enterovirus serotypes. Conditional logistic regression analysis was used to determine the association between enterovirus infections and atopic diseases. Categorized variables were used for confounding factors of pets at home, maternal education, paternal education, maternal tobacco use during pregnancy, older siblings, and day care attendance.

RESULTS. Cumulative exposure to different enterovirus serotypes by measured neutralizing antibodies was inversely associated with atopy (odds ratio: 0.73 [95% confidence interval: 0.56–0.96]; \( P = .025 \)). The most pronounced protection was seen when echoviruses were analyzed as a separate group from coxsackieviruses (odds ratio: 0.63 [95% confidence interval: 0.46–0.88]; \( P = .006 \)). The number of neutralizing antibodies against different coxsackievirus serotypes did not differ between case and control children.

CONCLUSIONS. An inverse association was found between cumulative exposure to echoviruses and atopic diseases with immunoglobulin E sensitization. Exposure to a high number of different echoviruses during the first years of life may protect from atopic diseases.

REVIEWER COMMENTS. The prospective nature and use of serologic assays to detect viral infections in this study are unique. Measurement of virus neutralizing antibodies at 2 time points yields reliable information about accumulation of antibodies over time. Viruses induce a strong T helper 1 response, which may suppress the excessive T helper 2 response typically seen in atopic disease. The present study supports the previously reported theory that atopic diseases develop less frequently in children with early microbial contacts. The gut is an important organ in the development of immunologic tolerance. The study of enteroviruses is particularly interesting because they are transmitted orofecally and replicate primarily in the gut. As acknowledged by the authors, further studies are needed to determine whether enteroviruses are surrogate markers for environmental factors or total infection burden.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2014–1817F

Karla L. Davis, MD
Stephen N. Marks, MD
Honolulu, HI

Pacifier Cleaning Practices and Risk of Allergy Development


PURPOSE OF THE STUDY. The study examined the effect of how parents clean their infant’s pacifier on the risk of developing eczema, asthma, or allergic sensitization.

STUDY POPULATION. Subjects were from a cohort of 187 term infants recruited into the AllergyFlora study in Gothenburg, Sweden. Mainly, families with at least 1 parent with allergic disease were approached. A total of 184 children were followed up until 18 months of age, and 174 were followed up to 36 months of age. Fourteen percent were delivered by cesarean delivery, 80% had at least 1 parent with a history of allergic disease, and 74% used a pacifier in the first year of life.

METHODS. When the children were 6 months old, parents were asked: “Does the child use a pacifier?” and “Is it cleaned by boiling, rinsing in tap water, or by the parents sucking on it?” with >1 option possible. A pediatric allergist examined the children and reviewed the medical record at 18 months, 36 months, and when symptoms suggested a diagnosis of eczema or asthma.

RESULTS. Of those who used pacifiers, nearly one-half of the parents (48%) reported they had sucked on the pacifier. By the age of 18 months, 25% of the children had developed eczema and 5% had developed asthma. Sucking the pacifier strongly lowered the risk of eczema (odds ratio: 0.37 [95% confidence interval: 0.15–0.91]; \( P = .02 \)) and asthma (odds ratio: 0.12 [95% confidence interval: 0.01–0.99]; \( P = .03 \)). Parents of vaginally delivered infants were more likely to suck the child’s pacifier. The group exposed to both maternal vaginal microbiota and parental oral microbiota via the pacifier had the lowest prevalence of eczema (20%), whereas infants exposed to neither maternal vaginal microbiota nor parental oral microbiota had the highest prevalence (54%). Children who were either vaginally delivered or whose parents sucked on their pacifiers had an intermediate prevalence of eczema (31%). Evaluation of the microbiota present in saliva at 4 months of age according to molecular genetics (terminal-restriction fragment length polymorphism) distinguished patterns of microbes in the saliva depending on pacifier cleaning practices.

CONCLUSIONS. Sucking on the infant’s pacifier before it is given to the infant may protect against early development of eczema and asthma. This practice may influence the infant’s oral microbiota composition. At 18 months of age, the prevalence of eczema was ~2.5 times lower among vaginally delivered children whose parents sucked on their pacifiers than among children born via cesarean delivery whose parents did not suck on their pacifiers (20% vs 54%). Evidence for the transfer of respiratory pathogens according to this practice was not apparent. Dental caries seemed unrelated to close salivary contact.

REVIEWER COMMENTS. Although this association does not prove causation, this surprising finding supports the “hygiene hypothesis” and the role of initial (birth) and subsequent (oral) exposures to microbes in modulating immune responses in a favorable manner. In this situation, the sharing of maternal saliva may replicate saliva and oral microbes likely shared by premastication of food by the mother for feeding to the infant, a practice that is now only rarely
Nested Case-Control Study

Karla L. Davis and Stephen N. Marks

Pediatrics 2014;134;S135

DOI: 10.1542/peds.2014-1817F

Updated Information & Services

including high resolution figures, can be found at:

http://pediatrics.aappublications.org/content/134/Supplement_3/S135.2

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints

Information about ordering reprints can be found online:

http://www.aappublications.org/site/misc/reprints.xhtml
Enterovirus Infections in Early Childhood and the Risk of Atopic Disease—A Nested Case-Control Study
Karla L. Davis and Stephen N. Marks
*Pediatrics* 2014;134;S135
DOI: 10.1542/peds.2014-1817F

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/134/Supplement_3/S135.2