Antibiotic exposure in early infancy and risk for childhood atopy

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Background: The increase in pediatric allergy and asthma parallels the increase in use of antibiotics. Antibiotics disturb the flora of the gastrointestinal tract, possibly perturbing the developing immune system.

Objective: We evaluated whether antibiotic use during early infancy increased the risk for atopy.

Methods: Antibiotic prescriptions documented in medical records were collected from a birth cohort born from 1987 through 1989 (n = 725). At 6 to 7 years of age, 448 were followed by means of examination, including skin prick tests and serum IgE measurements to common allergens.

Results: Adjusted odds ratios (aORs) and 95% CIs were calculated comparing children with any versus those with no antibiotic use in the first 6 months and the outcomes of atopy (any positive skin test response), seroatopy (any positive specific IgE test result), either atopy or seroatopy, and both atopy and seroatopy. Atopy increased with antibiotic use approaching statistical significance (aOR, 1.48; 95% CI, 0.94-2.34; *P* = .09); however, the risk was concentrated among children with less than 2 pets in the home (aOR, 1.73; 95% CI, 1.07-2.80; *P* = .024) and children breast-fed for 4 or more months (aOR, 3.02; 95% CI, 1.27-7.17; *P* = .013). The aORs were generally in the same direction for seroatopy and the combined categories.

Conclusion: Antibiotic use in early life appears to contribute to increased risk for atopy in certain subgroups of children.

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Key words: Allergy, *antibiotics, atopy, children, IgE, skin testing*

Abbreviation used
aOR: Adjusted odds ratio

Sequential cross-sectional surveys in numerous locations suggest that the prevalence of pediatric allergy and asthma is increasing worldwide.[1] Strachan[2] proposed the hygiene hypothesis, which suggests that early exposure to infections decreases the risk for allergy and asthma. Holt et al[3] proposed an immunologic model for the hygiene hypothesis, theorizing that early-life exposure to bacterial infections and bacterial products naturally present in the gut protects against atopy and asthma by favoring the development of a T_H1-predominant versus T_H2-predominant (allergic) cytokine profile in the maturing immune system.

Many lifestyle and medical care characteristics, including the use of antibiotics, have changed the patterns of infectious disease and bacterial exposure in infancy in the past 3 decades. Antibiotic use, in addition to the effect on the natural history of infection, is well known to alter gut flora.[4] Although recent surveys in the United States suggest that antibiotic use among children might now be decreasing,[5] the previous increase in antibiotic use among young children is coincident with the increasing prevalence of pediatric allergy and asthma.

The consideration of whether early antibiotic use is associated with increased risk for atopic disease has generated a surge of epidemiologic studies with conflicting results. From 1998 through 2002, a number of European studies examined whether antibiotic use increased the risks for allergy and asthma.[6-13] These studies were cross-sectional,[7-11] relied on parental recall of antibiotic use,[12] or were based solely on record review.[6,13] Although the studies included widely varying periods of antibiotic exposure and ages of children at measurement of disease outcome, all but one[12] suggested that antibiotic exposure increased the risk of pediatric atopy or asthma.[6-11,13] Other studies have not supported this hypothesis.[14-17]

It has been demonstrated in allergy and asthma epidemiology that associations between a risk factor and an allergic outcome can be limited to particular subgroups of a population.[18-20] Generally, previous studies have considered the overall relationship between antibiotic use and atopy among all children combined, adjusting for, rather than stratifying by, other important risk factors. It is a well-known phenomenon that overall risk estimates implying no association can mask important relationships if other

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factors are modifying the effect (interaction). The Detroit Childhood Allergy Study provides a large, prospectively followed, health maintenance organization–based birth cohort in which antibiotic prescriptions were documented by using comprehensive and complete unified group practice medical records, accompanied by data on numerous personal and environmental risk factors collected prospectively by personal interview. Atopic indicators were assessed by means of skin prick testing, serum IgE measurement, and a history and physical examination conducted by a pediatric allergist in a research setting when the cohort children were 6 to 7 years of age. We evaluated the influence of antibiotics during the first 6 months of life in relationship to these indicators of atopy and examined the effect of other important risk factors.

METHODS

Study population and follow-up

The recruitment of the Childhood Allergy Study population has been described elsewhere.[21] All pregnant women enrolled in the medical group component of the largest Michigan health maintenance organization and living in a defined middle-class suburban area north of Detroit were potentially eligible. Women had to be 18 years of age or older, with a due date between April 15, 1987, and August 31, 1989, and were interviewed by study nurses during appointments in their obstetricians' offices after their first trimester. Children born at 36 weeks or later without the need for intensive care and a valid cord IgE measurement were continued in the study. The children were followed by means of telephone questionnaire at their first and third birthdays and by means of home visit at their second and fourth birthdays. At 6 to 7 years of age, the children underwent a clinical evaluation by a board-certified allergist (DRO). All aspects of the study were approved by the Henry Ford Hospital Human Rights Committee, and written informed consent was obtained from the subjects' families.

Exposure measurement–antibiotic use

Paper and electronic medical records of clinical encounters (ie, clinic visits, emergency department visits, and hospitalizations) were abstracted. Only children with a complete clinical record for at least the first 12 months, including evidence that medical group physicians served as the child's source of care, were included.

Information was collected regarding all prescribed antibiotics. Those prescribed within 7 days of each other were considered as a single course. Topical antibiotics and antifungal medications were excluded. Antibiotics were further grouped into those considered to have a relatively broad (penicillin combinations and second- and third-generation cephalosporins) versus narrow antibacterial spectrum.

Data were abstracted regarding respiratory illnesses, febrile episodes, and all conditions requiring antibiotics. Clinical encounters within 3 days of each other were considered part of the same event.

Outcomes measurement–atopic indicators

The clinical evaluation completed at age 6 to 7 years included a standardized history and physical, blood sample, and skin prick testing with the inhalant allergens *Dermatophagoides farinae, Dermatophagoides pteronyssinus*, short ragweed, cat, dog, bluegrass, and *Alternaria* species (extracts from Bayer Biologics [now Hollister-Stier], Spokane, Wash). Both positive (histamine, 1 mg/mL) and negative (glycerosaline) controls were used. Tests were applied by using the puncture method with a lancet (Bayer Biologics). Skin test responses were considered positive if the product of perpendicular wheal diameters was 4 mm or larger to any of the allergens tested and there was a flare of 10 mm or more when the negative control showed no reaction. (On the basis of the results of the positive and negative controls in the first 100 children, the value of 4 mm^2 was optimal for differentiating positive from negative results.) Atopy was defined as a positive skin test response to any of the 7 allergens tested. (*Alternaria* species was added after the study was in progress, and thus the first 44 children were not tested for this allergen. Of these 44, 34 results were negative to the other 6 allergens and were classified in the nonatopy category in our final analyses. The risk estimates were virtually the same if these children were excluded.)

Blood samples were measured for concentration of allergen-specific IgE antibodies by using a commercial assay (AlaSTAT; Diagnostic Products Corp, Los Angeles, Calif) for the same allergens used in skin testing, including *Alternaria* species. Specific IgE levels were expressed in international units per milliliter (1 IU/mL corresponds to 2.4 μg/L), and values of 0.35 IU/mL or greater were considered positive in accordance with the manufacturer's recommendation. Seroatopy was defined as any positive test result for allergen-specific IgE.

Statistical approach

χ^2 tests and logistic regression were used to calculate crude and adjusted odds ratios (aORs), as well as 95% CIs and *P* values, related to any versus no use of antibiotics in the first 6 months of life defined *a priori* and the following 4 outcome categories: atopy, seroatopy, atopy or seroatopy, and atopy and seroatopy. *P* values were considered statistically significant at the .05 level, and no adjustments were made to account for multiple comparisons. The aORs were adjusted for potential confounding variables defined before analyses, including child's sex, firstborn status, maternal history (mother reporting a history of asthma, hay fever, or allergies or allergen immunotherapy), breast-fed status (≥4 months of breast-feeding vs less), and pet exposure (2 or more cats and dogs in the home during the first year of life vs less), as well as fever (on the basis of findings from our previous work on this cohort[22,23]) and reported day-care use and lower respiratory infections (croup, bronchitis, bronchiolitis, bronchospasm, influenza, lobe infiltrate, pneumonia, pneumonitis, and respiratory syncytial virus) in the first year of life. We evaluated whether there were any interactions between these potential confounders, antibiotics, and outcomes. Analyses were repeated considering only courses that included a broad-spectrum antibiotic versus no antibiotic to evaluate the *a priori* hypothesis that these drugs would alter gut flora to a greater extent. We also considered antibiotic exposure during the first 12 months of life versus later and first exposure at 0 to 3 months, 4 to 6 months, and 7 to 12 months, all versus after 12 months of age.

RESULTS

A total of 1194 pregnant woman were eligible, and 953 consented to their child's participation. The 835 children with valid cord blood IgE measurements were enrolled. Medical records were not retrievable for 51 children, and 59 children did not have at least 12 months of follow-up in the medical record (because of change of insurance, clinician, or residence), leaving 725 eligible children. Of these, 448 (61.8%) children underwent the clinical