Letters

RESEARCH LETTER

Association Between Use of Multiple Classes of Antibiotic in Infancy and Allergic Disease in Childhood

Antibiotic administration negatively affects the microbiome by decreasing bacterial diversity, and this has been associated with allergic disease.[1-3] Exposure to multiple classes of antibiotics may lead to even greater perturbations to the gut biome than 1 class alone. The purpose of this study is to determine whether exposure to multiple antibiotic classes in infancy is associated with a higher risk of developing allergic disease in early childhood.

Methods | This retrospective cohort study was conducted with a previously collected cohort of 798 426 children who were Department of Defense Tricare beneficiaries.[1] These children had a birth medical record in the Military Health System database between October 1, 2001, and September 30, 2013, with continued enrollment from 35 days of age or younger until at least 1 year of age. Children with an initial birth stay in the hospital of more than 7 days or a diagnosis with an outcome allergic condition within the first 6 months of life were excluded. Exposures were defined as having any dispensed prescription for penicillin, penicillin with a β-lactamase inhibitor, cephalosporin, sulfonamide, or macrolide in the first 6 months of life.

The main outcomes were the presence of any allergic disease, food allergy, anaphylaxis, asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, or contact dermatitis. Cox proportional hazards modeling was performed. The first model used exposure to specific classes of antibiotics to analyze the development of any allergic disease. The second model used antibiotic classes as an ordinal variable representing the number of antibiotic classes prescribed in the first 6 months. Adjusted hazard ratios represented the association of an increase in the number of classes of antibiotic with each of the outcomes. Models were adjusted for cesarean delivery, prematurity, sex, antacid medication exposure (proton pump inhibitors or histamine-2 receptor antagonists), and total days of supplied antibiotics. The study was reviewed and approved by the institutional review board of the Uniformed Services University, with a waiver of informed consent because data were deidentified. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc), and 2-tailed *P* values less than .05 were considered significant. Data were collected from October 1, 2001, to September 30, 2013. Data analysis occurred from February 2019 to May 2019.

Results | Among the 798 426 children in the cohort (including 400 323 male children [50.1%]), there were 162 605 filled prescriptions for antibiotics (penicillin, 96 793 prescriptions [59.5%]; macrolide, 21 347 prescriptions [13.1%]; cephalosporin, 21 284 prescriptions [13.1%]; penicillin with β-lactamase inhibitor, 15 811 prescriptions [9.7%]; sulfonamides, 6212 prescriptions [3.8%]). There were 664 710 children (83.3%) prescribed no classes of antibiotic, 109 341 children (13.7%) prescribed 1 class, 20 358 (2.5%) prescribed 2 classes, 3543 (0.44%) prescribed 3 classes, and 474 children (0.06%) prescribed 4 or more classes of antibiotics during the first 6 months of life. Data for children in the cohort were available for a median of 4.6 (interquartile range, 2.5-7.9) years.

All types of antibiotic classes assessed were associated with significant increased adjusted hazard ratios (aHRs) for any outcome allergic disease (**Table 1**). The aHRs were lowest for sulfonamides (1.06 [95% CI, 1.03-1.10]) and 1.19 or greater for all the other classes (aHR range, 1.19 [95% CI, 1.17-1.21] for cephalosporin to 1.30 [95% CI, 1.28-1.31] for penicillin). Children prescribed an additional class of antibiotic had increased aHRs for each subtype of allergic disease (any food allergy, 1.08 [95% CI, 1.05-1.11]; anaphylaxis, 1.08 [95% CI, 1.02-1.15]; asthma, 1.47 [95% CI, 1.45-1.49]; atopic dermatitis, 1.13 [95% CI, 1.11-1.15]; allergic rhinitis, 1.33 [95% CI, 1.32-1.34]; allergic conjunctivitis, 1.18 [95% CI, 1.15-1.22]; contact dermatitis, 1.11 [95% CI, 1.10-1.12]; **Table 2**), even after adjusting for the total days of antibiotic prescribed (data not shown).

Discussion | This study found that all commonly prescribed antibiotics during infancy are associated with subsequent diagnosis of allergic disease. Administration of more than 1 class

Table 1. Adjusted Hazard Ratios for Any Parameter Allergic Disease in Children Exposed to a Specific Class of Antibiotic[a]

Antibiotic Class	Adjusted Hazard Ratios (95% CI)
Penicillin	1.30 (1.28-1.31)
Penicillin with β-lactamase inhibitor	1.21 (1.18-1.23)
Cephalosporin	1.19 (1.17-1.21)
Sulfonamide	1.06 (1.03-1.10)
Macrolide	1.28 (1.26-1.30)

[a] Parameter allergic diseases include any food allergy, anaphylaxis, asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and contact dermatitis.

Table 2. Adjusted Hazard Ratios for Allergic Diseases in Children Given 1 Additional Class of Antibiotic During Infancy[a]

Characteristic	Adjusted Hazard Ratio (95% CI)
Any food allergy	1.08 (1.05-1.11)
Anaphylaxis	1.08 (1.02-1.15)
Asthma	1.47 (1.45-1.49)
Atopic dermatitis	1.13 (1.11-1.15)
Allergic rhinitis	1.33 (1.32-1.34)
Allergic conjunctivitis	1.18 (1.15-1.22)
Contact dermatitis	1.11 (1.10-1.12)

[a] Models were adjusted for cesarean delivery, prematurity, sex, antacid medication exposure (proton pump inhibitors or histamine-2 receptor antagonists), and total days of supplied antibiotics.

of antibiotic was associated with increased risk, most notably for asthma and allergic rhinitis. This association persisted even after adjusting for the total days of antibiotics supplied.

A limitation of this study is the potential reverse causality of infants at increased risk of developing allergic disease also being more susceptible to bacterial illness and thus requiring additional classes of antibiotic administration. While this bias may have played a role, it is unlikely because of our model adjustment for cesarean delivery, prematurity, sex, antacid medication exposure, and total days of supplied antibiotics.

Exposure to multiple antibiotic classes may cause broader diversity perturbations to the microbiome.[4] Thus, perturbation of the microbiome may be a risk factor for the development of allergic disease.

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