Association between early life antibiotic exposure and development of early childhood atopic dermatitis

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Background: Atopic dermatitis (AD) is a chronic, inflammatory skin disease commonly onset during infancy.

Objective: We examine the association between pre-and postnatal antibiotic exposure and the development of AD.

Methods: A retrospective, observational study analyzed 4106 infants at the University of Florida from June 2011 to April 2017.

Results: Antibiotic exposure during the first year of life was associated with a lower risk of AD. The association was strongest for exposure during the first month of life. There were no significant differences in the rates of AD in infants with or without exposure to antibiotics in months 2 through 12, when examined by month. Antibiotic exposure during week 2 of life was associated with lower risk of AD, with weeks 1, 3, and 4 demonstrating a similar trend.

Limitations: Retrospective data collection from a single center, use of electronic medical record, patient compliance with prescribed medication, and variable follow-up.

Conclusions: Early life exposures, such as antibiotics, may lead to long-term changes in immunity. Murine models of atopic dermatitis demonstrate a "critical window" for the development of immune tolerance to cutaneous microbes. Our findings suggest that there may also be a "critical window" for immune tolerance in human infants, influenced by antibiotic exposure. (JAAD Int 2023;10:68-74.)

Key words: antibiotics; atopic dermatitis; pediatric dermatology.

INTRODUCTION

Atopic dermatitis (AD, eczema) is a chronic, inflammatory skin disease affecting approximately 11% of children in the United States.[1] Disease onset is most common during infancy and early childhood. During infancy, there is parallel, interconnected

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maturation of the skin barrier and the cutaneous immune system.[2] Both are critical to the pathogenesis of AD and easily influenced by outside factors, such as antibiotics and topical emollients.[3,4] Thus, this impressionable period is uniquely poised as both a source of knowledge and target of intervention in AD.

The hygiene hypothesis supports a link between early exposure to microbes and immune system development.[5,6] As infants are colonized by microbes in the world outside the womb, the early immune system promotes immune tolerance to both self and foreign antigens, generating long-term tolerance to microbes.[2,7] Within the skin, murine studies have identified early infancy as the critical time to develop immune tolerance. If cutaneous microbes are present during the neonatal period, mice accumulate regulatory T cells and demonstrate tolerance upon reexposure later in life. Without early exposure, an inflammatory response develops when exposed for the first time later in life.[8] Antibiotic exposure may interfere with this acquisition of tolerance, as antibiotics alter cutaneous flora by decreasing microbial diversity.[4] Reduced cutaneous microbial diversity or shifts in cutaneous microbial components, particularly during this newly identified critical window, may lead to the future development of AD through decreased immune tolerance.[9] The critical window of acquired cutaneous immune tolerance in human infants has not been identified; however, a better understanding of the timing of this critical window may guide decisions regarding antibiotic exposure.

The literature exploring population-level antibiotic exposure in the development of AD is inconclusive. Several studies found a positive association between antibiotic exposures in utero or during the early years of life and the subsequent development of AD.[10-18] Others reported no association,[19,20] and few studies reported a negative association.[18] Variation in study design and recall bias likely contribute to the inconsistent findings. Several studies relied on parental report of AD and antibiotic exposure through telephone encounters and questionnaires.[10,14,18,19] In addition to recall bias, this employs parents as diagnosticians, inferring a diagnosis of AD based on reported symptoms such as an "itchy rash."[10] Kusel et al and Metzler et al used skin examinations and physician diagnoses to identify AD, yet, both studies relied solely on parental report of antibiotic exposure.[12,20] Few studies have utilized medical record review to identify both AD diagnoses and antibiotic exposure.[11,13]

Previous studies evaluated antibiotic exposure over broad time intervals, tracking cumulative exposure over 6-month, 1-year, or 2-year increments, in relation to subsequent development of AD.[10,12,13,18,20] Longer time intervals have been studied as well, with Kim at al[11] investigating cumulative exposure to antibiotics over 7 years in relation to development of AD. Studies of smaller time increments to pinpoint a critical window of exposure in children are lacking, with only 1 study tracking antibiotic exposure over the first 7 days of life, representing the shortest interval of time studied to date.[19] Prior studies often focus on in utero or early life antibiotic exposure, with few studies evaluating both in utero and infancy/early childhood antibiotic exposure and AD.[12,14,16,18] Exploring antibiotic exposure in smaller intervals of time is necessary to identify a possible critical window of exposure that results in long-lasting effects on the cutaneous immune system.

This study seeks to fill these knowledge gaps by first examining the association between antibiotic exposure and subsequent development of AD utilizing electronic medical records. By examining exposure starting in utero at small intervals (1 week and 1 month time increments), we explored the possibility of a critical window of microbial exposure that may result in changes to cutaneous immunity. A better understanding of this time period will provide clues to AD prevention.

CAPSULE SUMMARY

- Studies examining the association between antibiotic exposure and subsequent development of atopic dermatitis have reported conflicting results, with almost all tracking cumulative exposure over months to years.
- Early life exposure to antibiotics, particularly during week 2, 3, and 4 of life, may decrease subsequent development of atopic dermatitis.

MATERIALS AND METHODS

This study was approved by the University of Florida Institutional Review Board as an exempt study due to use of deidentified retrospective data. Infants who received their primary care at UF Health Shands Hospital were recruited from June 1, 2011, to April 30, 2017. To achieve this, a cohort of infants were selected who had 2 or more well-child visits after birth, with at least one visit at 300 days of life or later. Maternal charts were paired to infant charts in

Abbreviations used:

AD: atopic dermatitis
NICU: neonatal intensive care unit

the cohort. A total of 4016 mother-infant dyads met the criteria for inclusion in the study cohort. Subjects demonstrated racial and socioeconomic diversity (Table I). The electronic health record (EHR) was reviewed retrospectively for demographic, birth, and medication data. Children were followed until the end of the study period to assess for the development of AD.

Antibiotic exposures were counted only if they occurred before the diagnosis of AD, as the intent of the study was to explore the relationship between antibiotic exposure and subsequent development of eczema. Only first antibiotic exposures were included, as once a patient received an antibiotic, they were then considered exposed and included in the antibiotic-exposed group for analysis. All medications coded as antibiotics were reviewed by the authors, and non-antibacterial medications were excluded from the study. Antibiotic exposures were counted utilizing the EHR to identify outpatient antibiotic prescriptions and inpatient medication orders. Inpatient antibiotic orders were only counted if the medication was received by the patient. Topical antibiotics were excluded from analysis. AD was diagnosed based on International Classification of Diseases (ICD) codes entered as clinical diagnoses by a medical provider. A child was classified as having AD if ICD codes for AD were recorded in the EHR, including ICD-9 (691.8) and ICD-10 (L20.83, L20.84, L20.89, L20.9, L30.8, and L30.9) codes.

Statistical analysis

Data were inspected for implausible values, missingness, and distributional form. Summary statistics (ie, means, standard deviations, and frequencies) were computed for study variables. Independent samples t-tests or chi-square tests were used to compare groups with/without antibiotic exposure in the first year of life on continuous variables and categorical variables, respectively. We used logistic regression to examine the association of antibiotic exposure in the first year of life with AD after adjusting for the sex, delivery mode, race, gestational age, and length of stay in the neonatal intensive care unit (NICU). The level of significance was set at 0.05, and all hypothesis testing was two-sided. SAS version 9.4 was used for all analyses. R software was used to produce graphical displays (https://www.r-project.org/).

Table I. Cohort demographics*

Feature	*N* (%) or mean (SD)
Sex	
Female	1954 (48.8%)
Male	2052 (51.2%)
Race	
Black	1574 (39.2%)
White, non-Hispanic	1543 (38.5%)
Hispanic	286 (7.1%)
Asian	213 (5.3%)
Multiracial	135 (3.4%)
Other	262 (6.5%)
Delivery mode	
Vaginal	2425 (65.0%)
Caesarean section	1309 (35.1%)
Mean maternal age at delivery (y)	27.8 (5.8)
NICU stay	
No	3457 (86.1%)
Yes	559 (13.9%)
Mean NICU length of stay (d)	3.9 (18.1)
Gestational age	
Early preterm (<28 wk)	119 (3.1%)
Very preterm (28 to <32 wk)	121 (3.2%)
Moderate to late preterm (32 to <37 wk)	448 (11.7%)
Early term (37 to <39 wk)	1089 (28.3%)
Full term (39 to <41 wk)	1765 (46.0%)
Late/post term (41 wk or greater)	301 (7.8%)
Mean gestational age (wk)	38.1 (3.3)
Birth weight (grams)	
Extremely low birth weight (<1000 g)	131 (3.3%)
Very low birth weight (1000 to <1500 g)	102 (2.5%)
Low birth weight (1500 to <2500 g)	451 (11.2%)
Normal birth weight (2500 to <4000 g)	3124 (77.8%)
Macrosomia (>4000 g)	208 (5.2%)
Mean birth weight (grams)	3036.0 (757.5)

NICU, Neonatal intensive care unit; *SD*, standard deviation.
*Categorical responses may not sum to total sample size of 4016 due to missing data.

RESULTS

Half (50.4%) of the children received antibiotics at any time during the study period, and 29.7% received antibiotics in the first year of life. Approximately 18% of infants were born preterm (defined as gestational age less than 37 weeks, see also Table I), and 14% of infants were admitted to the NICU. AD was diagnosed in 26.5% of the cohort (95% confidence interval = 25.2%, 27.9%). The mean (standard deviation) age of diagnosis of AD was 9.45 (9.53) months.

Exposure to antibiotics in the first year of life

In children who did not receive antibiotics, 28.0% developed AD in the first year of life, while in children who did receive antibiotics, 22.3% developed AD in the first year of life (P = .0002).

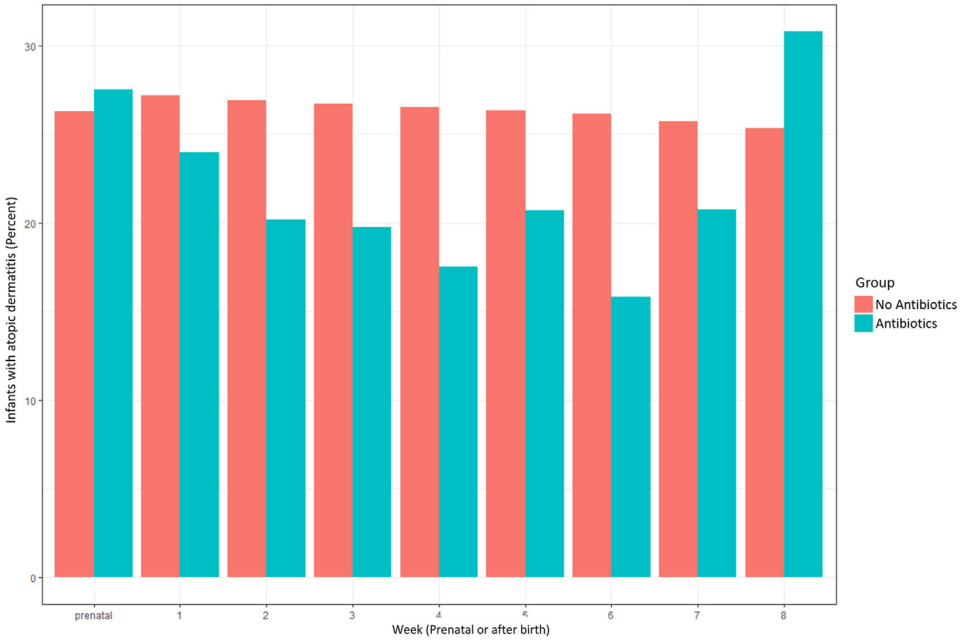

Fig 1. Rate of atopic dermatitis, expressed as a percent of all infants, by week of antibiotic exposure.

Timing of antibiotic exposure

For antibiotic exposure in the prenatal period, we found no difference in rates of AD in children who had been exposed to antibiotics in utero versus children who had not been exposed to antibiotics in utero (P = .485). Prenatal antibiotic exposure was examined by weekly intervals preceding birth and monthly intervals, with similar results. In the period after birth, the data were examined by infant antibiotic exposure in 1-week time increments in the first month of life, then by monthly increments after the first month of life. In children who received antibiotics in week 2 of life, there was a significant difference between the groups of children who received antibiotics. Of infants who received antibiotics in week 2 of life, 20.2% developed eczema, compared to 26.9% in infants who did not receive antibiotics (P = .016). For antibiotic exposure in Week 3 of life, 19.8% of infants who received antibiotics developed eczema; comparatively, 26.7% of infants who did not receive antibiotics developed eczema (P = .052). In week 4, 17.5% of infants who had received antibiotics developed eczema compared to 26.5% in infants who had not received antibiotics (P = .069). Fig 1 depicts the rates of AD by timing of antibiotic exposure. In examining antibiotic exposure by month, we found no difference in the rates of AD in infants who had or had not received antibiotics in months 2, 3, 4, 5, or 6 to 12 months of life.

Exposure to antibiotics in first year of life by infant/maternal characteristics

To further explore if antibiotic exposure was related to AD, we performed a post-hoc analysis of the association between infant/maternal exposures and antibiotic exposure. Of the infants who were admitted to the NICU, 67.6% received antibiotics during the first 2 weeks of life; comparatively, 13.9% of infants who were not admitted to the NICU received antibiotics during the first 2 weeks after birth. Gender, race/ethnicity, delivery mode, NICU admission, NICU length of stay, and gestational age were all significantly associated with antibiotic exposure during the first year of life (see Table II).

Results of logistic regression modeling

To explore the relationship between antibiotic exposure and development of AD in the first year of life, we used logistic regression modeling and included as covariates of the infant/maternal characteristics which were associated with antibiotic exposure (ie, gender, race/ethnicity, delivery mode, NICU admission, NICU length of stay, and gestational age). We found that exposure to antibiotics remained significantly associated with development of AD even with adjustment for NICU stay, gestational age, race/ethnicity (black race), and delivery mode (C-section) (see Table III).

Table II. Exposure to antibiotics in first year of life by infant/maternal characteristics

Characteristic	No antibiotic exposure *N* (%) or mean (SD)	First year antibiotic exposure *N* (%) or mean (SD)	*P*-value
Sex			
Female	70.6%	29.4%	.0034
Male	66.3%	33.7%	
Race			
Black	63.7%	36.3%	<.0001
White, non-Hispanic	70.3%	29.7%	
Hispanic	70.6%	29.4%	
Asian	71.4%	28.6%	
Multiracial	78.5%	21.5%	
Other	74.8%	25.2%	
Delivery mode			
Vaginal	72.3%	27.7%	<.0001
Caesarean section	61.3%	38.7%	
Mean maternal age at delivery (y)	27.9 (5.8)	27.7 (6.0)	.2693
NICU stay			
No	75.3%	24.7%	<.0001
Yes	25.2%	74.8%	
Mean NICU length of stay (d)	0.3 (3.1)	11.6 (30.5)	<.0001
Gestational age (wk)			
Early preterm (<28 wk)	2.5%	97.5%	<.0001
Very preterm (28 to <32)	17.4%	82.6%	
Moderate to late preterm (32 to <37)	56.7%	43.3%	
Early term (37 to <39)	71.9%	28.1%	
Full term (39 to <41)	75.0%	25.0%	
Late/post term (41 wk or greater)	77.1%	22.9%	
Mean gestational age (wk)	38.9 (1.9)	36.5 (4.7)	<.0001

NICU, Neonatal intensive care unit; *SD*, standard deviation.

Table III. Logistic regression, development of atopic dermatitis

Parameter	Logistic regression coefficient estimate	Standard error	*P*-value
Cesarean delivery (reference = vaginal)	−0.1459	0.0850	.086
Sex (reference = female)	0.0396	0.0781	.613
Asian race (reference = White)	0.4382	0.1813	**.016**
Black race (reference = White)	1.0008	0.0910	**<.0001**
Hispanic race (reference = White)	0.3615	0.1639	**.028**
Multiracial (reference = White)	0.2677	0.2350	.255
Other race (reference = White)	−0.0278	0.1849	.881
Days in NICU	−0.00694	0.00393	.077
Gestational age	0.0122	0.0180	.498
First year	0.2939	0.0941	**.002**
Antibiotic exposure (reference = exposed)			

Bolded values meet predetermined level of statistical significance.
NICU, Neonatal intensive care unit.

DISCUSSION

Our findings suggest that antibiotic exposure during the first year of life, particularly the first weeks, may be associated with lower risk of AD later in early childhood. We found a clinically significant difference in AD prevalence (approximately 6%) between the groups who did versus did not receive antibiotics in the first year of life (22.3% vs 28.0%, respectively). The complex pathogenesis of AD is multifactorial, with both race and NICU stay associated with development of AD in prior studies.[21] When adjusting for both NICU length of stay and race, antibiotic exposure during the first year of life was inversely associated with AD. Prenatal antibiotic exposure was not associated with AD. When the first month of life was examined

by weeks, to explore the idea of a "critical window," there was a significant decrease in AD for infants who received antibiotics during week 2 of life. To our knowledge, this is the first study to specifically evaluate weekly intervals of antibiotic exposure and the subsequent development of AD. However, given the retrospective design of this study, this concept is nevertheless speculative.

Murine models support the idea of a "critical window" for antigen exposure during immune development. Exposure during week 2 of life specifically leads to tolerance for these antigens rather than an inflammatory response upon subsequent exposure. Regulatory T-cell migration into the skin in response to cutaneous organisms mediates this tolerance.[8] Our findings suggest that the first month of life may also be a "critical window" for human infants, particularly week 2, as was seen in murine models.

Possibly counterintuitive, exposure to antibiotics during infancy decreased risk of AD. Neonatal antibiotic exposure has been shown to reduce cutaneous microbial diversity.[4] Decreased diversity hinders the breadth of foreign antigens to which the body develops tolerance. The protective effect in our study and in Dom et al[18] may be mediated by the focused development of immune tolerance. Perhaps only tolerance to specific bacteria is needed to prevent AD. In one study,[22] infants with AD lacked cutaneous *Staphylococci* early in infancy, which supports the hypothesis that lack of early exposure to *Staphylococci* contributes to later development of eczema.[21] An alternative hypothesis is that infants receiving antibiotics for infection were exposed to a greater microbial burden, thereby increasing immune tolerance, compared to those who did not have infections and received antibiotics.

When modeling AD with NICU stay and antibiotic exposure by week, both early antibiotic exposure and time spent in the NICU were protective from the development of AD. Although NICU length of stay is associated with the development of AD,[21] this association does not explain the relationship between antibiotics and AD highlighted in this study.

Limitations of this study include the use of ICD-9 and ICD-10 diagnostic codes as a surrogate for the diagnosis of AD. Diagnoses were not confirmed by a dermatologist or other pediatric subspecialist unless the patient was followed in a subspecialty clinic. There are additional possible confounding variables impacting the development of AD which were not included in this study, including exposure to animals and environmental pollutants. The study population was identified from a single tertiary medical center and did not include patients who received care by community pediatricians or outside health systems, which limits generalization of the findings. The duration and frequency of patient follow-up varied. Those who moved away, changed health care systems, or died prior to follow-up at 300 days of life were excluded, which could affect results. Additionally, antibiotic prescriptions outside of the studied health system would not be captured through this model, thus introducing potential bias by misclassifying patients as unexposed. Patients may not reliably use antibiotic medications as prescribed in the outpatient setting. Finally, children who received antibiotics early in life may have parents who more readily seek health care compared to parents of children who did not receive antibiotics.

This study focused on AD diagnoses in infancy, which excluded patients who were diagnosed after age 1. However, including all AD diagnoses would potentially increase bias, as well-child visits are less frequent after age 1, thereby potentially capturing AD diagnoses disproportionately in the population that seeks frequent health care. Despite these limitations, the primary purpose of this study was to generate hypotheses to guide future prospective studies, which will be able to better limit these biases.

In this retrospective study, we found that antibiotic exposure during the second week of life is associated with lower risk of subsequent AD. Our findings suggest that, as in murine models, there may be a "critical window" for immune tolerance in human infants. We did not find an association between prenatal antibiotic exposure and the subsequent development of AD. These results are greatly limited by the retrospective design. Prospective studies are needed to better understand the association and potential causality between neonatal antibiotic exposure, cutaneous immunity, and the development of AD.

Conflicts of interest

None disclosed.

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