ORIGINAL RESEARCH

Intrapartum Antibiotics and Childhood Atopic Dermatitis

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Introduction: Atopic dermatitis (AD) in children significantly impacts families because of medical costs, "lost" hours, and secondary characteristics such as asthma and ancillary infections. We investigate whether children delivered vaginally to women receiving intrapartum antibiotics have a greater risk of AD when younger than the age of 2 years than their counterparts.

Methods: We conducted a retrospective analysis of women who delivered child(ren) vaginally between 1996 and 2008. Women were identified as those who received intrapartum antibiotics and those who did not. Pediatric records were used to determine the incidence of AD.

Results: We collected data for 492 mother–child pairs. Intrapartum antibiotics were administered during 128 births; 28.9% of those children were diagnosed with AD by age 2 years (relative risk [RR], 1.03; 95% confidence interval [CI], 0.75–1.41). Factors with the greatest risk of diagnosis of AD by 2 years of age were intrapartum antibiotic exposure for >24 hours (RR, 1.99; 95% CI, 1.13–3.49), first born (RR, 1.78; 95% CI, 1.33–2.38), and higher maternal education (RR, 1.43; 95% CI, 0.99–2.06). No statistical differences in the prevalence of AD related to parental eczema, maternal group B Streptococcus status, or gestational age existed.

Conclusions: Exposure to antibiotics for <24 hours during a vaginal delivery does not increase the risk of AD. Studies are needed to understand whether exposure for >24 hours during the intrapartum period increases the risk of AD. (J Am Board Fam Med 2015;28:82–89.)

Keywords: Antibiotics; Birth; Dermatitis, Atopic; Obstetrics; Pediatrics

The prevalence of atopic dermatitis (AD) has been growing in industrialized countries over the past 40 years.[1,2] Each year, AD results in significant medical costs, lost hours of schooling and employment, and increased mortality risk associated with secondary characteristics such as asthma, ancillary in-

fections, and smallpox vaccination complications.[3] Susceptibility genes, immunologic factors, the host environment, and skin barrier defects are associated with the development of AD but do not explain the increased prevalence. Current medical procedures may contribute by either directly or indirectly disrupting the host's microbiota. Microorganisms have key roles in a host's metabolic function (eg, vitamin and amino acid synthesis, bile and biotransformations), immune system development, pathogen resistance, angiogenesis, and fat storage.[4–6] Intestinal microbiota and, consequently, fecal samples of children who have AD, asthma, or allergies are distinctive from those of their nonatopic counterparts.[7–10] Therefore antibiotic exposure disrupting the colonizing microbiota during the birthing process may lead to AD.

The risk of AD in children younger than 2 years of age with antibiotic exposure in utero during the second and/or third trimester of pregnancy is elevated.[11,12] Exposure to antibiotics during the first

months of life significantly increase the odds of a later diagnosis of allergic disease.[13–15] Negele et al[16] examined data from 2500 healthy, full-term infants, of whom 435 were born by caesarean delivery and 2065 by vaginal delivery. Infants born by caesarean delivery have an elevated risk of developing asthma, AD, or allergic rhinoconjunctivitis compared with their counterparts.[17] Others report similar findings.[15,17,18] Because AD is not characterized by a single marker but is rather a cluster of clinical findings and multiple immunologic abnormalities, it is often excluded from studies examining asthma and allergies. For example, a study by Hakansson and Kallen[19] also showed cesarean delivery increased the relative risk for asthma and gastroenteritis in children, but it did not explore AD. The increase in the prevalence of AD may mirror clinical practices in Western societies, such as cesarean deliveries and antibiotic use. Currently, antibiotics are often prescribed to women during pregnancy for urinary tract infections, community-acquired pneumonia, chorioamnionitis, and sexually transmitted diseases. During labor and delivery women often receive antibiotics intravenously as prophylaxis for group b *Streptococcus* (GBS) and premature rupture of membranes. Antibiotics administered to the mother have been shown to disrupt her microflora.[20]

Our primary study objective was to determine whether children delivered vaginally and exposed to intrapartum antibiotics have a greater risk of developing AD by the age of 2 years than their counterparts not exposed to antibiotics. Given the growing prevalence of AD, we wanted to determine whether the indirect disruption of the colonizing microbiota by the administration of intrapartum antibiotics to the mother has the unintended long-term consequence of AD. We tested the hypothesis that there is a significant positive relationship between the administration of antibiotics during a vaginal delivery and the development of AD in children younger than 2 years old. In our retrospective study we analyzed the medical records of women who gave birth vaginally and either received or did not receive intrapartum antibiotics and the medical records of their children.

Methods

Mothers of a child(ren) who was delivered vaginally without complications and was now between 2 and 10 years old were invited into the study. Potential participants were identified for the study in accordance with the Milton S. Hershey Medical Center's Human Subjects Protection Office Institutional Review Board (protocol no. 28656EP) and Elizabethtown College's Institutional Review Board (protocol no. 200846). Hospital billing records from the Milton S. Hershey Medical Center in south-central Pennsylvania were used to identify potential participants based on coding of a vaginal delivery. Women invited to the study received a short letter from their primary care provider that included an introduction to the study, the study aims, a description of the targeted population, and contact information should they have questions. A link to an electronic questionnaire and record release forms for the child's pediatric records, along with a description of how the data would be used and secured, were also included with the letter of invitation. Interested participants enrolled by completing and returning the medical release forms.

Data for each mother–child pair were abstracted from labor and delivery inpatient records, as well as the child's inpatient and outpatient records. In addition, participants were required to complete an electronic questionnaire (developed with Franklin and Marshall College's Center for Opinion Research). For those participants who were unable to complete the questionnaire online, options to use a computing center or a paper copy of the questionnaire were provided. The questionnaire was used to collect data on the pregnancy; delivery of the child; race/ethnicity; family history, including the presence of chronic illnesses or diseases that run in the family; and lifestyle choices (eg, smoker vs nonsmoker, breastfeeding and duration, pets). Information pertaining to family history of AD, asthma, or allergies and whether the child has siblings with or without AD, asthma, or allergies was collected. Participants were remunerated after completing the survey.

Participants were dichotomized as those who received intrapartum antibiotics and those who did not. Participants retained for the study included women who were older than 18 years of age at the time of invitation, those who had an uncomplicated vaginal delivery resulting in the birth of a child whose birth weight was between 2268 and 4753 g, and children not diagnosed with complications or congenital malformations during the perinatal or postdelivery period. Inpatient medical records of

the mother were used to identify results of the GBS test, other pregnancy complications, the amount of time she spent in labor at the hospital, and information pertaining to the administration of antibiotics during delivery. Children's medical records were used to exclude children who did not meet the birth weight criteria, as well as children with a 5-minute Apgar score <5. Data pertaining to any course of antibiotics the newborn received were recorded, as well as the duration of the child's hospital stay. The child's medical records also were used to identify the severity of AD and other measures of health based on records from well-baby visits. AD was considered present when there was a presumed history from parent with confirmation in the medical records or when a prescription drug classed for the treatment of eczema or AD, such as pimecrolimus, tacrolimus, or topical corticosteroids, had been prescribed because of the presence of a pruritic rash.

Based on the conservative measure of the prevalence of AD at 15% among those not exposed to intrapartum antibiotics and 28% for those exposed to intrapartum antibiotics, as well as an 80% power with an odds ratio of 1.6, we estimated a need to enroll 594 women, of whom half were exposed to intrapartum antibiotics. Descriptive statistics including the mean, median, and standard deviation were used to characterize the study with respect to continuous measures and frequency tables to summarize those measures that are categorical. Relative risks and their 95% confidence intervals (CIs) were used to characterize the associations between AD and exposure to intrapartum antibiotics and the other covariates. Interaction effects between the primary exposure and the other covariates also were explored. Secondary analyses tested other specific aspects of the delivery and pregnancy, including a positive test for GBS during pregnancy, the type of antibiotic administered during labor and delivery, intrapartum antibiotic exposure at the hospital (classified as ≤4, 4–12, 12–24, >24 hours), and receipt of antibiotics by the neonate. For analyses, antibiotics were grouped as penicillins, cephalosporins, macrolides, and aminoglycosides. In addition, some of the women who participated in the study had given birth to more than 1 child meeting the selection criteria. In such circumstances data corresponding to all eligible births was collected. Outcome data from siblings were correlated with each other because of their shared environmental conditions and genetic makeup. The proportion of sibling children (ie, single-pregnancy multiples or maternal siblings from separate pregnancies) who were included in the study was 26%. Relative risks and associated CIs were estimated using log-linear models, and the generalized estimating equation approach was used to account for the lack of independence between siblings. All analyses were performed using SAS software version 9.2 (SAS Inc., Cary, NC).

Results

Invitations to participate in the study were mailed to 1143 women who had vaginal deliveries at Milton S. Hershey Medical Center between 1996 and 2008; 12% (n = 137) of the invitations were returned by the US Postal Service. Respondents totaled 525 women, of whom 3.5% were not enrolled in the study because the medical release was incomplete.

A total of 507 women (and their child[ren]) were enrolled in the study. These women self-identified as Hispanic or Latino (n = 8), Asian (n = 11), black or African American (n = 11), American Indian/Alaska Native (n = 1), Native Hawaiian or other Pacific Islander (n = 1), white (n = 435), and more than one race (n = 2). The ethnicity/race was unknown for 38 women. Based on US Census records from Dauphin and Lancaster counties, the population was representative of the area (http://www.census.gov/popfinder/).

We analyzed data from 492 mother–child pairs for which we were able to link hospital labor and delivery records to the child's pediatric records and the inclusion criteria were met. The mothers' mean age was 29.8 ± 5.1 years. Children enrolled in the study had a mean gestational age of 39.3 ± 1.4 weeks and a mean weight of 3507.0 ± 473.7 g; 228 (46.3%) were girls. Intrapartum antibiotics were administered during 128 births (Table 1). Penicillins were the most frequent class of drugs used (n = 108), followed by macrolides (n = 16), aminoglycosides (n = 3), and cephalosporins (n = 1). No significant differences between the intrapartum drug classes and the occurrence of AD were detected (P = .0881). Of those women receiving intravenous antibiotics during delivery, 16 received more than 1 class of antibiotic. Intrapartum antibiotic exposure and diagnosis of AD by 2 years of age occurred in 28.9% of the children (relative risk [RR], 1.03; 95% CI, 0.75–1.41).

Table 1. Relative Risk of Atopic Dermatitis Associated With Infant Characteristics

	Eczema, % (n/N)	RR (95% CI)	P Value
Sex			
Male	30.3 (80/264)	1.19 (0.9–1.56)	.229
Female	25.0 (57/228)	—	—
Intrapartum antibiotics			
Yes	28.9 (37/128)	1.03 (0.75–1.41)	.854
No	27.5 (100/364)	—	—
Birth order			
First born	36.9 (80/217)	1.78 (1.33–2.38)	.0001
Second born or later	20.7 (57/275)	—	—
Maternal eczema (ever)*			
Yes	32.3 (21/65)	1.16 (0.77–1.74)	.495
No	32.2 (98/350)	—	—
Paternal eczema (ever)*			
Yes	41.4 (12/29)	1.55 (0.96–2.51)	.146
No	27.7 (106/382)	—	—
Sibling eczema (ever)*			
Yes	31.4 (28/80)	1.26 (0.85–1.86)	.344
No	27.3 (81/311)	—	—
Maternal asthma (ever)*			
Yes	27.9 (19/68)	0.99 (0.65–1.49)	.958
No	28.6 (99/346)	—	—
Paternal asthma (ever)*			
Yes	34.1 (14/41)	1.20 (0.75–1.93)	.477
No	28.1 (104/370)	—	—
Pets (cats/dogs)*			
Yes	29.0 (80/276)	1.10 (0.73–1.66)	.652
No	27.4 (26/95)	—	—
GBS status			
Negative	63 (63/229)	1.32 (0.83–2.09)	.200
Positive	21.0 (17/81)	—	—
Smoking*			
No	29.5 (120/407)	1.65 (0.66–4.13)	.207
Yes	17.4 (4/23)	—	—
Infant feeding during first 3 months*			
Primarily breastfed	29.7 (85/286)	1.10 (0.79–1.53)	.579
Primarily formula fed	26.9 (39/145)	—	—
Gestational age (weeks)			
≤40	27.2 (94/346)		
>40	30.1 (43/143)	1.07 (0.78–1.46)	.678
Birth weight (grams)			
<2500	57.1 (4/7)	4.23 (0.9–19.92)	.068
2500–4500	27.7 (132/477)	1.92 (0.96–3.83)	.064
>4500	12.5 (1/8)	—	—
Maternal education (years)*			
Did not attend college	22.5 (32/142)	0.70 (0.48–1.01)	.039
College degree or more	32.0 (97/303)	—	—

*Self-reported.
CI, confidence interval; RR, relative risk.

Table 2. Intrapartum Antibiotic Exposure by Time and Atopic Dermatitis* (n = 118)

Exposure Time (hours)	Eczema, % (n/N)	RR† (95% CI)	P Value
0–4	32.1 (9/28)	1.17 (0.66–2.06)	.59
4–12	20.8 (11/53)	0.76 (0.44–1.31)	.319
12–24	26.9 (7/26)	0.98 (0.51–1.89)	.952
>24	54.5 (6/11)	1.99 (1.13–3.49)	.017

*Atopic dermatitis was diagnosed in 10 children who were not included in the analyses because intrapartum antibiotic exposure time could not be determined.
†Relative risks (RRs) were calculated when compared with no intrapartum exposure (n = 364) and atopic dermatitis (n = 100). CI, confidence interval.

As shown in Tables 1 and 2, the greatest risks of being diagnosed with AD by 2 years of age were associated with intrapartum antibiotic exposure for >24 hours (RR, 1.99; 95% CI, 1.13–3.49), first born (RR, 1.78; 95% CI, 1.33–2.38), and higher maternal education (RR, 1.43; 95% CI, 0.99–2.06). The RR between childhood eczema and familial history of eczema was not statistically significant (mother: RR, 1.16; 95% CI, 0.77–1.74; father: RR, 1.55; 95% CI, 0.96–2.51; siblings: RR, 1.26; 95% CI, 0.85–1.86). It was also not statistically significant between childhood eczema and familial history of asthma (mother: RR, 0.99; 95% CI, 0.65–1.54; father: RR, 1.20; 95% CI, 0.75–1.93; siblings: RR, 1.07; 95% CI, 0.67–1.75) or allergies (mother: RR, 0.93; 95% CI, 0.68–1.25; father: RR, 1.23; 95% CI, 0.92–1.64; siblings: RR, 0.85; 95% CI, 0.60–1.22). There was also no significant relationship with sex, pets, or maternal cigarette use (Table 1). Women who tested positive for GBS comprised a subset of the women who received intrapartum antibiotics (n = 81; 16.4%); no significant risk of AD was associated with testing positive for GBS (RR, 0.76; 95% CI, 0.48–1.20; Table 1).

Exposure to antibiotics as a neonate did not increase the relative risk of developing AD (Table 3). Within the first 24 hours of delivery, 31 of the children in the study had received antibiotics. By 2 years of age, 348 of the 492 children had received at least 1 dose of antibiotics; 103 of the children (23.6%) were diagnosed with AD (RR, 1.26; 95% CI, 0.90–1.77). Breast milk versus formula feedings did not change the risk of AD; 39 of 145 infants fed primarily formula for the first 3 months of life developed AD, whereas 85 of 286 infants receiving breast milk in the first 3 months developed AD (Table 1).

Discussion

We found intrapartum antibiotic exposure for >24 hours may increase the likelihood that children younger than the age of 2 will develop AD. In our study, 11 children were exposed to intrapartum antibiotics for >24 hours, and none of their mothers had tested positive for GBS, yet 6 of them developed AD. While most research has focused on antibiotic exposure during the prenatal or postpartum periods and mode of delivery, antibiotic exposure during the intrapartum period alters the mother's microbiome.[21,22] Although intrapartum exposure to antibiotics for <24 hours was not statistically significant (Table 2), extended exposure to antibiotics >24 hours during the intrapartum period may increase the risk of AD due to disruption of microbial colonization or other factors such as environmental exposures or genetic predisposition and merits additional study. We also found a significant RR of diagnosis of AD in children younger than age 2 associated with birth order and maternal education; first-born children or children of mothers who have a college education or higher both increased the likelihood that a child would be diagnosed with AD (Table 1).

The extensive use of antibiotics in general medicine, and particularly during the critical time of

Table 3. Relative Risk of Atopic Dermatitis Associated With Infant Exposure to Antibiotics

Age at Exposure to Antibiotics	Eczema, % (n/N)	RR (95% CI)	P Value
<24 Hours			
Yes	38.7 (12/32)	1.43 (0.92–2.24)	.186
No	27.1 (125/461)	—	—
<7 Days			
Yes	35.9 (14/39)	1.32 (0.88–1.99)	.245
No	27.2 (123/453)	—	—
<30 Days			
Yes	30.5 (18/59)	1.11 (0.74–1.67)	.627
No	27.5 (119/433)	—	—
<1 Year			
Yes	30.2 (80/265)	1.19 (0.89–1.59)	.235
No	25.1 (57/227)	—	—
By 2 years			
Yes	23.6 (103/348)	1.26 (0.9–1.77)	.163
No	23.6 (34/144)	—	—

CI, confidence interval; RR, relative risk.

birth, highlights the need for examination of medical practices that may contribute to unintended consequences. While the use of antibiotics is certainly associated with significant short-term medical gains, they may have unintended long-term consequences. This study controlled for method of delivery to focus on the disruption of microbial colonization of the neonate solely by the administration of intrapartum antibiotics. Examination of pediatric records and elective questionnaires were used to confirm AD. Earlier studies showed that disruption of microbial colonization in neonates may lead to the development of atopies, asthma, and allergies.[12,21–24] Few, if any, studies, however, have controlled for both birthing method (ie, vaginal or caesarean delivery) and antibiotic exposure. Therefore the cause of early childhood AD remains unclear. Our retrospective examination provided the opportunity to examine vaginal deliveries and a single atopy, childhood eczema. We report RRs because the limited number of significant relationships did not warrant a logistic regression analysis. Self-reported variables such as familial history, pets, smoking, and sibling outcomes rely on recall and carry less significance than data from medical records. Self-reported data are, however, important when examining a multifaceted chronic disease such as AD. Because initial microbial colonization can define successional trajectories[25] and because microbiota are directly involved in the maturation of the immune system,[26] microbial colonization of the neonate is a crucial time in development and should be examined to ensure short-term gains do not have unintended long-term consequences.

When women received intrapartum antibiotics, penicillins were administered 84.4% of the time; there was no difference in AD risk when analyzing penicillins versus other antibiotics. Exposure to antibiotics delivered intravenously for >4 hours can decrease vertical transmission of GBS and other early onset invasive infections.[27,28] In our study the risk of AD was not elevated unless antibiotics had been administered for >24 hours. None of the 11 women receiving intrapartum antibiotics for >24 hours in our study tested positive for GBS, suggesting other factors may be important. Our hypothesis that intrapartum antibiotics and the subsequent disruption of colonizing microbiota in the neonate lead to increased risk of AD is supported. Direct exposure to antibiotics in children between birth and 2 years of age did not increase the risk of developing AD. Interestingly, birth order and maternal education are both positively related with the likelihood a child will be diagnosed with AD before the age of 2 years (Table 1). Others found that first-born children have a greater likelihood of AD.[29,30] Researchers have suggested the finding of first born and increased risk of AD is explained by the hygiene hypothesis, which assumes a lack of microbial antigen exposure results in underproduction of Th_1 and subsequent over production of Th_2 cells.[31] Although our study supports this finding, we believe it may also reflect a reporting bias. First-born children typically have the undivided attention of the caregiver and a symptomatic rash may lead to clinician visits.[32] To fully explain first born and AD using the hygiene hypothesis, we would expect elevated RRs associated with the absence of pets and primarily being fed formula during the first 3 months of life reducing microbial exposures. These were not observed (Table 1). Furthermore, reporting bias may also account for the significant relationship of the mother's education and diagnosis of AD. Older mothers and those with additional years of schooling beyond high school may be more likely to take their child to a clinician because of a symptomatic rash observed with AD and/or have more confidence to mention the condition during an office visit.[32,33]

Heritable mutations in the skin barrier gene filaggrin predispose children to AD and asthma.[34] Our study supports AD as a multifactorial disease, and although genetic inheritance was not significant and does not explain the presence of AD in young children, it may be a contributing factor. Further examination of the role of genetics in AD is needed; in our study it may have been masked by the fact that all family history data were self-reported recall data, as well as the low power of our study.

Based on the finding that there is no significant relationship between the short-term use of intrapartum antibiotics and the development of early childhood eczema, we anticipate no clinical change in the administration of intrapartum antibiotics. However, we encourage clinicians to reevaluate possible short-term versus long-term risks to neonates with intrapartum antibiotic exposure for >24 hours because it possibly increases the risk of AD. Although limited in size and power, our study reveals no unintended long-term atopic consequences associated with the short-term use of in-

trapartum antibiotics. Intrapartum antibiotic use that directly benefits the neonate, such as prophylaxis for limiting the possible spread of GBS or sexually transmitted diseases, should continue because they outweigh long-term risks.

Limitations of our study included the inability to achieve our projected sample size, which reduced the power of the study, increasing the risk of a type II error. The retrospective nature of the study, relying on physicians' documentation reporting atopies and historic reporting by parents, could have led to underreporting of atopic disease, as well. The study was performed in a small area of south-central Pennsylvania and may not be generalizable to other populations. In conjunction, the lack of heterogeneity may also impact generalization.

An understanding of the increase in the prevalence of AD has not been provided by this study. AD, a chronic disease, affects almost one-third of the population.[2,35] Developing clear biomarkers may help reveal how genetics, microbial colonization, immune system development, and the environment factor in to the presence and prevalence of this disease. Further investigation should examine broader demographics, dietary exposures, and other environmental exposures in the first 2 years of life.

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