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Intrapartum Antibiotics and Childhood Atopic Dermatitis

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Abstract

Introduction—Atopic dermatitis (AD) in children significantly impacts families due to medical costs, “lost” hours, and secondary characteristics like asthma and ancillary infections. We investigate whether children delivered vaginally to women receiving intrapartum antibiotics have a greater risk of AD under 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 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 2 years (RR 1.03 [0.75-1.41], p=0.854). Factors with greatest risks of diagnosis with AD by 2 years were intrapartum antibiotic exposure for >24hrs (RR 1.99 [1.13-3.49], p=0.0173), first born (RR 1.78 [1.33-2.38], p<0.0001) and higher maternal education (RR 1.43[0.99-2.06], p=0.039). No statistical difference in prevalence of AD related to parental eczema, maternal Group B Streptococcus status, or gestational age existed.

Conclusions—Exposure to antibiotics for <24hrs during a vaginal delivery does not increase the risk of AD. Studies are needed to understand if exposures >24hrs during the intrapartum period increase the risk of AD.

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Keywords

intrapartum antibiotics; eczema; atopic dermatitis; childbirth

Introduction

Atopic dermatitis (AD) has been growing in prevalence in industrialized countries over the last 40 years.[1-2] Each year, AD results in significant medical cost, lost hours of schooling and employment, and increased mortality risk associated from secondary characteristics such as asthma, ancillary infections, and smallpox vaccination complications.[3] Susceptibility genes, immunological factors, 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, however, by disrupting the host's microbiota either directly or indirectly. Microorganisms have key roles in the host's metabolic function (i.e., vitamin, 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 that of non-atopic counterparts.[7-10] Therefore, antibiotic exposure causing disruption of the colonizing microbiota during the birthing process may lead to AD.

The risk of AD in children less than 2 years of age with antibiotic exposure in utero during the second and/or third trimester of pregnancy is elevated.[11-12] Antibiotic exposures in the first months of life significantly increase the odds of later diagnosis of allergic disease.[13-15] Negele et al (2004) examined data of 2500 healthy full-term infants of which 435 were born by caesarean and 2065 by vaginal delivery.[16] Infants born by caesarean show an elevated risk of developing asthma, atopic dermatitis, or allergic rhinoconjunctivitis compared to their counterparts.[17] Others report similar findings.[15, 17-18] Since 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 & Kallen (2003) also showed cesarean delivery increased the relative risk for asthma and gastroenteritis in children, but did not explore AD.[19] The rise in 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 of Group B Streptococcus and premature rupture of membranes. Antibiotics administered to the mother have been shown to disrupt maternal microflora.[20]

Our primary study objective was to determine whether children delivered vaginally with intrapartum antibiotics have a greater risk of developing AD by the age of 2 years than their non-antibiotic exposed counterparts. Given the growing prevalence of AD, we wanted to determine whether or not 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 under the age of 2 years. In our retrospective study, we analyzed medical records of women who gave birth vaginally either with or without intrapartum antibiotics and the medical records of their children.

Methods

Women of a child(ren) that had been delivered vaginally without complications and was now between 2 and 10 years of age 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 (IRB Protocol No. 28656EP) and Elizabethtown College's Institutional Review Board (IRB Protocol No. 200846). Hospital billing records from the Milton S. Hershey Medical Center in south central Pennsylvania, USA 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, 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 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.

For each mother-child pair, data were abstracted from labor and delivery inpatient records, as well as the child's inpatient and outpatient-records. Additionally participants were required to complete an electronic questionnaire (developed with Franklin and Marshall College's Center for Opinion Research (COR)). For those participants unable to complete the questionnaire on-line, 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 (e.g., smoker versus non-smoker, breast feeding of baby and duration, pets). Information pertaining to family history of atopic dermatitis, asthma, or allergies and whether the child has siblings with or without atopic dermatitis, asthma, or allergies was collected. After completion of the survey, participants were remunerated.

Participants were dichotomized as to those who received intrapartum antibiotics and those who did not. Participants retained for the study included women who were greater than 18 years of age at the time of invitation, uncomplicated vaginal deliveries resulting in the delivery of a child whose birth weight was between 2268 g and 4753 g, and children not diagnosed with complications or congenital malformations during the perinatal or post-delivery period. Inpatient medical records of the mother were used to identify results of the Group B Streptococcus test, other pregnancy complications, the amount of time she spent at the hospital in labor, 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. Medical records of the child were also used to identify the severity of

AD and other measures of health based on records from baby well 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 due to the presence of a pruritic rash.

Based on the conservative measure of prevalence of atopic dermatitis at 15% among those not exposed to intrapartum antibiotics and 28% for those exposed to intrapartum antibiotics and 80% power with an odds ratio of 1.6, we estimated a need to enroll 594 women of which 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 that are categorical. Relative risks and their 95% confidence intervals 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 were also explored. Secondary analyses explored other specific aspects of the delivery and pregnancy including positive test for Streptococcus B during pregnancy, type of antibiotic administered during labor and delivery, intrapartum antibiotic exposure at the hospital (classified as ≤4 hours, 4-12 hrs, 12-24 hrs, >24 hrs), and receipt of antibiotics by the neonate. For analyses, antibiotics were grouped as penicillins, cephalosporins, macrolides, and aminoglycosides. Additionally, some of the women who participated in the study had given birth to more than one 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 due to their shared environmental conditions and genetic makeup. The proportion of sibling children (i.e., single pregnancy multiples or maternal siblings from separate pregnancies) who were included in the study was 26%. Relative risks and associated confidence intervals were estimated using log-linear models and the generalized estimating equations (GEE) approach was used to account for the lack of independence between siblings. All analyses were performed using SAS 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. Twelve percent (n=137) of the invitations were returned by the US Postal Service. Respondents totaled 525 women, 3.5% of them 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. The women enrolled in the study self-identified as 8 Hispanic or Latino, 11 Asian, 11 Black or African American, 1 American Indian/Alaska Native, 1 Native Hawaiian or other Pacific Islander, 435 white, and 2 of more than one race. 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 (US Census Records, http://www.census.gov/popfinder/).

We analyzed data of 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, mean weight of 3507.0±473.7 g, and 228 (46.3%) were females. Intrapartum antibiotics were administered during 128 births (Table I). 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=0.0881). Of those women receiving intravenous antibiotics during delivery, 16 received more than one class of antibiotic. Intrapartum antibiotic exposure and diagnosis of AD by 2 years of age was observed in 28.9% of the children (RR 1.03 [0.75-1.41], p=0.854).

As shown in Tables I and II, the greatest risks of being diagnosed with AD by 2 years of age were associated with intrapartum antibiotic exposure for greater than 24 hrs (RR 1.99 [1.13-3.49], p=0.0173), first born (RR 1.78 [1.33-2.38], p<0.0001) and higher maternal education (RR 1.43 [0.99-2.06], p=0.039). The relative risk was not statistically significant between childhood eczema and familial history of eczema (mother: RR 1.16 [0.77-1.74], p=0.495; father: RR 1.55 [0.96-2.51], p=0.146; siblings: RR 1.26 [0.85-1.86], p=0.344). It was also not statistically significant between childhood eczema and familial history of asthma (mother: RR 0.99 [0.65-1.54], p=0.958; father: RR 1.20 [0.75-1.93], p=0.477; siblings: RR 1.07 [0.67-1.75], p=0.760) or allergies (mother: RR 0.93[0.68-1.25], p=0.600; father: RR 1.23 [0.92-1.64], p=0.170; siblings: RR 0.85 [0.60-1.22], p=0.390). There was also no significant relationship with gender, pets, or maternal cigarette use (Table I). Women who tested positive for Group B Streptococcus (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 [0.48-1.20], p=0.200; Table I).

Exposure to antibiotics as a neonate did not increase the relative risk of developing AD (Table III). Within the first 24hrs 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 one dose of antibiotics; 103 (23.6%) of the children were diagnosed with AD (RR 1.26 [0.90-1.77], p=0.163). 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 while 85 of 286 infants receiving breast milk in the first three months developed AD (Table I).

Discussion

We found intrapartum antibiotic exposure greater than 24hrs may increase the likelihood that children under the age of two will develop atopic dermatitis (AD). In our study, 11 children were exposed to intrapartum antibiotics for greater than 24hours of which none of their mothers had tested positive for GBS, yet 6 of them developed atopic dermatitis. While most research has focused on antibiotic exposures during the prenatal or postpartum periods, and mode of delivery, antibiotics during the intrapartum period alter the mother's microbiome.[21, 22] An extended intrapartum period with antibiotics may increase the risk of AD be due to disruption of the microbial colonization, or other factors such as environmental exposures or genetic predisposition and merits additional study. Intrapartum

antibiotic exposures <24hrs were not significant (Table II). We also found a significant relative risk of diagnosis of AD in children under the age of 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 a child would be diagnosed with AD (Table I).

The extensive use of antibiotics in general medicine, and particularly during the critical time of birth highlights the need for examination of medical practices that may contribute to unintended consequences. While use of antibiotics are 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 due solely to the administration of intrapartum antibiotics. Examination of pediatric records and elective questionnaires were used to confirm AD. Earlier studies have shown disruption of microbial colonization of the neonate may lead to the development of the atopies, asthma, and allergies.[12, 21-24] However, few, if any, studies have controlled for both birthing method (i.e., vaginal or caesarean) 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 relative risks, as the limited number of significant relationships did not warrant a logistic regression analysis. Variables that were self-reported such as familial history, pets, smoking, and sibling outcomes, rely on recall and carry less significance than data from medical records. However, self-reported data are important when examining a multi-faceted 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 which should be examined to ensure short-term gains do not have unintended long-term consequences.

Penicillins were administered 84.4% of the time women received intrapartum antibiotics; there was no difference in AD risk when analyzing penicillins versus other antibiotics. Exposure to intravenously delivered antibiotics for more than 4 hrs can decrease vertical transmission of Group B Streptococcus (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 more than 24 hrs. None of the 11 women receiving intrapartum antibiotics for >24hours in our study had tested positive for GBS, suggesting other factors may be important. Our hypothesis stating that intrapartum antibiotics and the subsequent disruption of colonizing microbiota of the neonate lead to increased risk of AD is supported. Direct exposure to antibiotics of the child between birth and 2 years of age did not increase the risk of developing AD. Interestingly, birth order and maternal education are also both positively related with the likelihood a child is diagnosed with AD before the age of 2 years (Table I). Others have found that first-born children have a greater likelihood of AD.[29-30] Researchers have suggested the finding of firstborn and increased risk of AD occurs as explained by the hygiene hypothesis, which assumes a lack of microbial antigen exposure results in underproduction of the 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. Firstborn children typically have the undivided attention of the care-giver and the symptomatic rash may lead

to clinician visits.[32] To fully explain firstborn and AD as explained by the hygiene hypothesis, we would expect elevated RRs associated with absence of pets and primarily being fed formula during the first three months of life thus reducing microbial exposures. These were not observed (Table I). Furthermore, reporting bias may also account for the significant relationship of mother's education and diagnosis of AD. Mothers of greater maternal age or with additional years of schooling beyond high school may be more likely to take the child to a clinician due to the 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 atopic dermatitis 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, since in our study it may have been masked by the fact that all family history data were self-reported recall data and 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 would anticipate no clinical change in administering intrapartum antibiotics. However, we encourage clinicians to reevaluate possible short-term versus long-term risks to the neonate for intrapartum antibiotic exposure for >24 hrs, as it possibly increases the risk of AD. Although limited in size and power, our study reveals no unintended long-term atopic consequence associated with short-term use of intrapartum antibiotics. Intrapartum antibiotic use which directly benefits the neonate, such as prophylaxis use for limiting the possible spread of Group B Streptococcus or sexually transmitted diseases, should continue as they outweigh long-term risk.

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 physician's documentation reporting of atopies and historical reporting by parents could have led to under-reporting 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 prevalence of AD has not been achieved 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 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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Table I

Relative risk of atopic dermatitis associated with infant characteristics.

	Eczema, % (n)	RR (95% CI)	p Value
Gender			
Male	30.3 (80/264)	1.19 (0.9, 1.56)	0.229
Female	25.0 (57/228)		
Intrapartum Antibiotics			
Yes	28.9 (37/128)	1.03 (0.75, 1.41)	0.854
No	27.5 (100/364)		
Birth Order			
First Born	36.9 (80/217)	1.78 (1.33, 2.38)	0.0001
Second Born or later	20.7 (57/275)		
Maternal Eczema (ever)*			
Yes	32.3 (21/65)	1.16 (0.77, 1.74)	0.495
No	32.2 (98/350)		
Paternal Eczema (ever)*			
Yes	41.4 (12/29)	1.55 (0.96, 2.51)	0.146
No	27.7 (106/382)		
Sibling Eczema (ever)*			
Yes	31.4 (28/80)	1.26 (0.85, 1.86)	0.344
No	27.3 (81/311)		
Maternal Asthma (ever)*			
Yes	27.9 (19/68)	0.99 (0.65, 1.49)	0.958
No	28.6 (99/346)		
Paternal Asthma (ever)*			
Yes	34.1 (14/41)	1.20 (0.75, 1.93)	0.477
No	28.1 (104/370)		
Pets (cats/dogs)*			
Yes	29.0 (80/276)	1.10 (0.73, 1.66)	0.652
No	27.4 (26/95)		
GBS Status			
Negative	63 (63/229)	1.32 (0.83, 2.09)	0.200
Positive	21.0 (17/81)		
Smoking*			
No	29.5 (120/407)	1.65 (0.66, 4.13)	0.207
Yes	17.4 (4/23)		
Infant Feeding, first 3 months*			

	Eczema, % (n)	RR (95% CI)	p Value
Primarily breastfed	29.7 (85/286)	1.10 (0.79, 1.53)	0.579
Primarily formula fed	26.9 (39/145)		
Gestational Age (weeks)			
≤40 weeks	27.2 (94/346)		
>40 weeks	30.1 (43/143)	1.07 (0.78, 1.46)	0.678
Birth Weight (grams)			
<2500	57.1 (4/7)	4.23 (0.9, 19.92)	0.068
2500-4500	27.7 (132/477)	1.92 (0.96, 3.83)	0.064
>4500	12.5 (1/8)		
Maternal education (years)*			
Did not attend college	22.5 (32/142)	0.70 (0.48, 1.01)	0.039
College degree or beyond	32.0 (97/303)		

* self-reported

Table II

Intrapartum antibiotic exposure by time and atopic dermatitis (n=118). Relative risks were calculated when compared to no intrapartum exposure (n=364), atopic dermatitis (n=100). Atopic dermatitis was diagnosed in 10 children not included in analyses because intrapartum antibiotic exposure time could not be determined.

Exposure time (hrs)	Eczema, % (n)	RR (95% CI)	p value
0-4	32.1 (9/28)	1.17 (0.66-2.06)	0.59
4-12	20.8 (11/53)	0.76 (0.44-1.31)	0.319
12-24	26.9 (7/26)	0.98 (0.51-1.89)	0.952
>24	54.5 (6/11)	1.99 (1.13-3.49)	0.017

Table III

Relative risk of atopic dermatitis associated with infant exposure to antibiotics.

	Eczema, % (n)	RR (95% CI)	p
Exposure <24 hours			
Yes	38.7 (12/32)	1.43 (0.92, 2.24)	0.186
No	27.1 (125/461)		
Exposure <7 days			
Yes	35.9 (14/39)	1.32 (0.88, 1.99)	0.245
No	27.2 (123/453)		
Exposure <30 days			
Yes	30.5 (18/59)	1.11 (0.74, 1.67)	0.627
No	27.5 (119/433)		
Exposure <1 year			
Yes	30.2 (80/265)	1.19 (0.89, 1.59)	0.235
No	25.1 (57/227)		
Exposure by 2 years			
Yes	23.6 (103/348)	1.26 (0.9, 1.77)	0.163
No	23.6 (34/144)		