The Impact of Maternal Antibiotics on Neonatal Disease

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Objectives We examined the impact of prenatal exposure to maternal antibiotics on risk of necrotizing enterocolitis (NEC), late onset sepsis (LOS), and death in infants born preterm.

Study design Secondary data analysis was conducted via an extant cohort of 580 infants born <32 weeks of gestation and enrolled in 3 level III neonatal intensive care units. Prenatal antibiotic exposure was defined as antibiotics received by the mother within 72 hours before delivery. Postnatal empiric antibiotic exposure was defined as antibiotic initiated within the first day of life without documented infection, categorized as low (<5 days) or high (>5 days) duration.

Results Two-thirds of mothers received antibiotics within 72 hours before delivery, of whom 59.8% received >1 antibiotic. Ampicillin (37.6%) and azithromycin (26.4%) were the most common antibiotics given. NEC occurred in 7.5%, LOS in 11.1%, death in 9.6%, and the combined outcome of NEC, LOS, or death in 21.3% of study infants. In multiple logistic regression models adjusted for gestational age, postnatal empiric antibiotic exposure, and other factors, prenatal antibiotic exposure was associated with reduced risk of NEC (OR 0.28; 95% CI 0.14-0.56; $P < .001$), death (OR 0.29; 95% CI 0.14-0.60; $P = .001$), but not LOS (OR 1.59; 95% CI 0.84-2.99; $P = .15$), although protection was significant for the combined outcome (OR 0.52, $P < .001$). High postnatal empiric antibiotic exposure was associated with greater risk of death but not other outcomes in multiple regression models (OR 3.18, $P = .002$).

Conclusions Prenatal antibiotic exposure was associated with lower rates of NEC or death of infants born preterm, and its impact on infant outcomes warrants further study. *(J Pediatr 2018;■■:■■-■■).*

Necrotizing enterocolitis (NEC) and late-onset sepsis (LOS) cause significant morbidity and mortality among infants born premature in neonatal intensive care units (NICUs). Among infants born <32 weeks of gestational age, 7% develop NEC, in whom case fatality is ~30%.[1,2] LOS occurs in up to one-third of infants <32 weeks of gestational age, with most infants born preterm experiencing the greatest risk.[3] High postnatal empiric antibiotic use is an epidemiologic correlate of both NEC and LOS.[4] Cotten et al studied a national cohort of 5693 infants of extremely low birth weight and found that infants receiving prolonged initial antibiotic therapy had an increased risk for developing NEC or death.[5] Subsequently, Kuppala et al studied 365 infants born premature in Cincinnati, Ohio, and reported that prolonged initial empiric antibiotics were associated with increased risk for NEC, LOS, or death.[6] In a cohort of 328 infants born premature in Saudi Arabia, Abdel Ghany and Ali also reported that each treatment day with empiric antibiotics was associated with an increased risk of death and the combined outcome of NEC or death.[7] Greenwood et al examined the impact of high antibiotic use on the microbiome and found that infants receiving early antibiotics experienced a surge in Enterobacteriaceae as well as greater risk of NEC, sepsis, or death.[8]

However, infant antibiotic exposure may begin prenatally as a result of maternal exposure to antibiotics, and this prenatal exposure could potentially influence neonatal disease. Bizzarro et al noted an increase in ampicillin-resistant *Escherichia coli* infections in mothers exposed to ampicillin.[9] Similarly, Didier et al found that maternal exposure led to an increase in amoxicillin-resistant organisms.[10] However, the effects of maternal antibiotic exposure before delivery on neonatal outcomes have not been well defined. With this concern in mind, we analyzed an extant cohort of infants born preterm to test the hypothesis that infant antibiotic exposure prenatally is associated with increased incidence of NEC, LOS, or death.

Methods

We conducted a secondary analysis of an extant cohort of 580 infants <32 weeks of gestational age. All infants in this study were part of a prospective, National Institutes of Health–funded study of the preterm microbiome and risk of NEC,

GBS	Group B streptococci
LOS	Late-onset sepsis
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NSD	NEC, sepsis or death

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sepsis, and death.[11] Study infants were enrolled from 2 level III NICUs in Cincinnati, Ohio, and 1 level III NICU in Birmingham, Alabama, from 2009 to 2012. Enrollment criteria included delivery <32 weeks of gestation, being free of congenital anomalies, and survival free of NEC in the first week of life. One patient was excluded because of unknown maternal antibiotic status. Data collection followed the protocol of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network registry. Infants were enrolled immediately after delivery and were followed up until discharge, transfer, 120 days postpartum, or death. Maternal and infant data were abstracted from medical records. The institutional review boards at the 3 participating hospitals approved the study.

Maternal antibiotic exposure was defined as antibiotic treatment within 72 hours before delivery. Indications for maternal antibiotic exposure included cesarean delivery, group B streptococci (GBS) prophylaxis, premature rupture of membranes, chorioamnionitis, and to prolong pregnancy (latency). Maternal antibiotic exposure did not include antibiotics given after the time of delivery or antibiotic initiated by surgeons during (but not before) cesarean delivery. Early empirical neonatal antibiotic exposure was defined as antibiotic treatment initiated within the first postnatal day without culture-identified infection. The duration of early antibiotic therapy was defined as the total number of continuous days of administration of antibiotics with sterile culture results. Empiric infant antibiotics used in this cohort were ampicillin and gentamicin, with empiric infant antibiotic exposure defined as either low (<5 days) or high (>5 days).[3,5,6,8] NEC was defined via Bell stage II or III criteria.[12] Spontaneous intestinal perforation was excluded by including only cases of NEC that occurred after 7 days of life. LOS was defined as a positive blood, cerebrospinal fluid, urine, or sterile site culture after the third postnatal day. If patients were diagnosed with NEC or LOS or died after day 7 of their NICU course, they were considered positive for the combined outcome, NEC, sepsis or death (termed NSD).

Statistical Analyses

Differences in clinical characteristics were tested via the Fisher exact test for categorical variables and ANOVA, and *t* tests or Kruskal–Wallis for continuous variables, as appropriate. Maternal and neonatal baseline characteristics were compared across groups based on maternal antibiotic exposure alone and infant antibiotic exposure alone, and across the 4 combined maternal and infant antibiotic exposure groups. The individual outcomes of NEC, LOS, and death and the occurrence of any of these outcomes also were compared across the groups as noted previously. Multivariable logistic regression models were used to evaluate independent associations between maternal and infant antibiotic exposure and these outcomes. A set of clinical predictors of NEC, LOS, and death were defined a priori and examined in the models. Gestational age, sex, race, mode of delivery, high human milk exposure, maternal chorioamnionitis, cesarean delivery, premature rupture of membranes, maternal pre-eclampsia, prenatal steroids, parity, multiple birth, and hospital location were all included in the initial analysis. We defined high human milk exposure as feeding with human milk for more than 75% of the days from birth to 30 days of life or the onset of NEC or death, whichever occurred first.

Modeling was performed by the use of backward elimination, with factors systematically eliminated in order of the highest (nonsignificant) *P* values. Factors not included as potential confounders were postnatal infant health status measures that were considered to be on the same causal chain as (or potential biomarkers of) the study outcomes (eg, Apgar scores or respiratory status, which may be indicators of infant health). Factors that were eliminated from models did not appreciably affect the observed association between maternal or infant antibiotic use and study outcomes; the ORs of maternal antibiotic impact on study outcomes changed <4% after elimination of potential covariates (at most a single digit change at the second decimal point). Multiple logistic regression models reported here were standardized across outcomes by including a set of independent variables, including prenatal and postnatal antibiotic use and all factors with a *P* value <.10 in any of the outcome-specific final models.

Results

Clinical and demographic characteristics of study infants and their mothers are presented in **Table I**, compared by the number of maternal antibiotics used. Of the 580 infants included in the study, 362 (62.4%) were delivered to mothers who had received antibiotics in the 72 hours before delivery. Infant birth weight was similar across maternal antibiotic exposure groups, as was gestational age, infant sex, and race. The median gestational age at the time of delivery in both maternal exposure groups was 28 weeks. Pre-eclampsia was more common among mothers without antibiotic exposure (46.3% and 24.5% respectively, $P < .001$). Three hundred sixty-three infants (62.5%) were born via cesarean delivery, which was more common among mothers who were not exposed to antibiotics ($P < .001$). Antenatal corticosteroids were more regularly used in mothers who had antibiotic exposure ($P < .001$). Clinical chorioamnionitis was greater among mothers who received antibiotics ($P < .001$). Human milk feeding did not differ by maternal antibiotic exposure.

Overall, 135 (23.2%) study infants received ≥5 days of postnatal empiric antibiotic. Infants who were born with prenatal antibiotic exposure were more likely to experience high postnatal empiric antibiotic exposure than infants without prenatal antibiotic exposure ($P = .002$). Among the 362 infants exposed to prenatal antibiotic, 100 (27.5%) had high postnatal antibiotic exposure, whereas among the 218 infants with no prenatal antibiotic exposure, 35 (16.0%) had high postnatal antibiotic exposure.

Of the 580 infants in the study, there were 106 twin deliveries and 10 triplet deliveries. There was no difference in prenatal antibiotic exposure between multiple and singleton births. Nevertheless, analysis of maternal antibiotic use was based on the 309 individual mothers who were provided antibiotics prenatally (rather than the 362 study infants who also received

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