# Prolonged Initial Empirical Antibiotic Treatment is Associated with Adverse Outcomes in Premature Infants

Venkata S. Kuppala, MD, Jareen Meinzen-Derr, PhD, Ardythe L. Morrow, PhD, and Kurt R. Schibler, MD

**Objective** To investigate the outcomes after prolonged empirical antibiotic administration to premature infants in the first week of life, and concluding subsequent late onset sepsis (LOS), necrotizing enterocolitis (NEC), and death.

**Study design** Study infants were ≤32 weeks gestational age and ≤1500 g birth weight who survived free of sepsis and NEC for 7 days. Multivariable logistic regression was conducted to determine independent relationships between prolonged initial empirical antibiotic therapy (≥5 days) and study outcomes that control for birth weight, gestational age, race, prolonged premature rupture of membranes, days on high-frequency ventilation in 7 days, and the amount of breast milk received in the first 14 days of life.

**Results** Of the 365 premature infants who survived 7 days free of sepsis or NEC, 36% received prolonged initial empirical antibiotics, which was independently associated with subsequent outcomes: LOS (OR, 2.45 [95% CI, 1.28-4.67]) and the combination of LOS, NEC, or death (OR, 2.66 [95% CI, 1.12-6.3]).

**Conclusions** Prolonged administration of empirical antibiotics to premature infants with sterile cultures in the first week of life is associated with subsequent severe outcomes. Judicious restriction of antibiotic use should be investigated as a strategy to reduce severe outcomes for premature infants. *(J Pediatr 2011;159:720-5)*.

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Antibiotics are the most commonly prescribed medications for newborns in intensive care nurseries.[1] In the United States, the majority of the very premature infants receive empirical antibiotic treatment during the first days of life even though the incidence of early-onset sepsis (EOS) is low.[2,3] Concerns about occult intrauterine infection that precipitates premature labor, premature rupture of membranes, and chorioamnionitis often prompt initiation of empirical antibiotic treatment.[4] Although antibiotic treatment of premature infants may be prudent given these considerations, the duration of treatment is often arbitrary, based not on positive culture results but on the clinician's perceived risk of infection.[5] Intensive broad-spectrum antibiotic use can have serious, unintended consequences in premature infants, including rapidly increasing drug resistance in sepsis cases[6] and increased risk of invasive fungal infection.[7]

Antibiotic therapy may have significant adverse consequences in early postnatal weeks,[8,9] which coincides with the time of initial gastrointestinal colonization.[10,11] Although it is not known to what extent antibiotic exposure disrupts colonization of the developing infant gastrointestinal tract, preterm infants have intestinal microflora distinct from that of healthy, full-term infants.[12,13] Moreover, several observations suggest the importance of gastrointestinal colonization to the health of premature infants. Results of randomized controlled trials that provided probiotic organisms to preterm infants have reported decreased adverse outcomes, including late-onset sepsis (LOS), necrotizing enterocolitis (NEC), and death.[14,15] Human milk contains prebiotic oligosaccharides that stimulate beneficial colonization of the gastrointestinal tract,[16] and provision of human milk reduces the incidence of LOS and NEC among premature infants.[17-19]

We tested the hypothesis that prolonged initial empirical antibiotic use in preterm infants is an independent risk factor for development of the combination of outcomes that appear related to aberrant colonization: LOS, NEC, or death. Human milk feeding and other clinical factors were examined and controlled for as potential confounders.

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| ELBW | Extremely low birth weight |
| EOS | Early-onset sepsis |
| LOS | Late-onset sepsis |
| NEC | Necrotizing enterocolitis |
| NICHD NRN | *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network |

From the Perinatal Institute (V.K., J.M-D., A.M., K.S.), Biostatistics and Epidemiology (J.M-D., A.M.), Cincinnati Children's Hospital Medical Center; and Department of Pediatrics, University of Cincinnati College of Medicine (J.M-D., A.M., K.S.), Cincinnati, OH

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## Methods

We conducted a retrospective cohort study of 365 very low birth weight infants (≤32 weeks gestational age and ≤1500 g birth weight) who survived the first week of life without sepsis and NEC. All the infants were part of a cohort originally identified at 3 neonatal intensive care units in Cincinnati, from April 2000 through December 2004, to examine epidermal growth factor in relation to NEC.[20] Infants in the original cohort excluded from this study included 8 infants who died, 11 infants with culture-proven sepsis, and 2 infants with NEC in the first week of life. Nineteen other infants in the original cohort who did not receive empirical antibiotic treatment on day of life one but who underwent an evaluation for sepsis and received antibiotic treatment within the first week of life were excluded. Study infants were participants in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) registry. As part of the NICHD NRN system, infants were enrolled immediately after delivery and were followed up until discharge, transfer, 120 days postpartum, or death. In addition to the standard NRN data, supplemental maternal and infant data were abstracted from medical records. Institutional review boards at Cincinnati Children's Hospital Medical Center, Good Samaritan Hospital, and University Hospital approved this study.

We defined initial empirical antibiotic treatment as the antibiotic treatment initiated within the first postnatal day. The duration of initial empirical antibiotic therapy was defined as the total number of continuous days of administration of antibiotics with sterile culture results. The infants were categorized into 3 groups: 0 days of initial antibiotic therapy, 1-4 days of initial antibiotic therapy (limited antibiotics), and ≥5 days of initial antibiotic therapy (prolonged antibiotics). The cumulative days of antibiotic treatment also were collected for the hospital course. EOS was defined as in the NICHD NRN registry on the basis of positive blood culture results obtained within the first 3 postnatal days and treated for ≥5 days.[2,3] Infants diagnosed with EOS were excluded from the analysis of empirical antibiotic treatment. LOS was defined as a positive blood, cerebrospinal fluid, urine, or sterile site culture after 3 postnatal days. Coagulase-negative staphylococci and polymicrobial cultures were included as LOS if the clinical team indicated it was a true infection in the medical record and that they treated the infection accordingly. NEC was defined by using modified Bell stage II or III criteria.[21] "Full enteral feeds" was defined as successful intake of at least 120 mL/kg/d.

### Analysis

Given the fixed sample size of 365 very low birth weight infants, the combined outcomes of LOS, NEC or death (91 cases), and LOS alone (76 cases) were used as the primary outcome variables to assure 80% power to detect at least a 2-fold association between prolonged and shorter duration antibiotic use groups. The number of deaths (20 cases) and NEC alone (17 cases) was too few to provide sufficient power to analyze independently. Factors associated with the median duration of antimicrobial treatment and the frequency of prolonged antibiotic treatment in the first week of life were examined for all infants. Maternal and neonatal baseline characteristics collected in the first 7 postnatal days were compared across these 3 groups. Differences among the 3 antibiotic groups were tested by using the $\chi^2$ test of proportions for categorical variables and analysis of variance for continuous variables. When further comparisons were made between the 2 groups, a multiple comparison correction was made. The Wilcoxon rank sum test was used when comparisons of median values were tested. Median values for continuous variables were reported when the data did not follow a normal distribution.

Multivariable logistic regression models were used to evaluate independent associations between prolonged initial empirical antibiotic treatment and the primary outcomes of LOS, NEC, or death, and LOS alone, and secondary outcomes of NEC alone and death alone. LOS, NEC, or death outcomes that occurred on or after day of life 7 were used in the analyses. In addition to prolonged initial empirical antibiotic treatment, a comprehensive set of clinical predictors of mortality identified from a previous national study were examined in the models.[22] Final regression models were parsimonious and included only covariates significant at the .10 level. The Hosmer-Lemeshow test statistic and other model diagnostics were used to select the final models based on the best fit.

## Results

Clinical and demographic characteristics of study infants and their mothers segregated by initial empirical antibiotic treatment group are presented in **Table I**. Ampicillin and gentamicin were the universally prescribed antibiotic combination for initial empirical treatment. Other antibiotics also prescribed during the first 7 days of life included clindamycin (1.4%), amphotericin B (1%), nafcillin (0.8%), and cefotaxime (0.8%). One infant received erythromycin secondary to isolation of Ureaplasma from amniotic fluid. Infants in the prolonged antibiotic group were significantly more likely to have lower birth weight, younger gestational age, an Apgar score at 5 minutes of age less than 6, endotracheal intubation, and surfactant treatment for clinical features of respiratory distress syndrome, more conventional ventilation days, high-frequency ventilation days, and highest oxygen (fraction of inspired oxygen) concentration at 7 days of life compared with infants in the limited antibiotic groups. Infants in the prolonged antibiotic group were more likely to have a mother diagnosed with chorioamnionitis and a mother who received antepartum antibiotics compared with infants in the limited antibiotic groups. However, infants in the prolonged antibiotic group were less likely to have a mother with hypertension or eclampsia, to have been the product of a multiple gestation, or to have been delivered by cesarean section.