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

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Abstract

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

Study design—Study infants were ≤32 weeks gestational age and ≤ 1500 grams 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 controlling 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 surviving 7 days free of sepsis or NEC, 36% received prolonged initial empirical antibiotics, which was independently associated with subsequent outcomes: LOS (odds ratio [OR] 2.45, 95% confidence interval [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.

Keywords

prolonged antibiotic treatment; death; human milk; late-onset sepsis; necrotizing enterocolitis; premature infant

Antibiotics are the most commonly prescribed medications in newborn 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 precipitating

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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] coinciding 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. Randomized, controlled trials providing 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[19], and provision of human milk reduces the incidence of LOS and NEC among premature infants [16–18].

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.

METHODS

We conducted a retrospective cohort study of 365 very low birth weight infants (VLBW, ≤32 weeks gestational age and ≤ 1500 grams birth weight) who survived the first week of life without sepsis and NEC. All infants were part of a cohort originally identified at three 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 eight infants who died, 11 infants with culture-proven sepsis, and two 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 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 followed until discharge, transfer, 120 days postpartum, or death. In addition to the standard NRN data, supplemental maternal and infant data was 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. Infants were categorized into three 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 were also 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

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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 they treated the infection accordingly. NEC was defined using modified Bell's stage II or III criteria[21]. 'Full enteral feeds' was defined as successful intake of at least 120 milliliters/kilogram/day.

Analysis

Given the fixed sample size of 365 VLBW 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 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 three groups. Differences among the three antibiotic groups were tested using chi-square test of proportions for categorical variables and analysis of variance for continuous variables. When further comparisons were made between two groups, a multiple comparison correction was made. 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 occurring 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 0.10 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%), Amphoterecin 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 (FiO_2) 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. On the other hand, 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.

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Initiation and Advancement of Enteral Nutrition

Among neonatologists in Cincinnati the consensus practice was to initiate enteral feeding within the first few days of life and to advance feeding volume in a range between 10 ml/kg/day and 20 ml/kg/day, using mother's own breast milk when available. Given the preference for early feeding, delayed initiation or advancement of feeding reflected clinical perception of increased severity of illness. Time to initiation of enteral feeding (median [range]; 3 days [0–18] versus 2 days [0–36], $p<0.001$) and to attaining full enteral feeding (16 days [4–80] versus 11 days [1–65], $p<0.001$) was delayed for infants receiving prolonged initial empirical antibiotic treatment compared with those receiving limited initial antibiotics. About one quarter of infants received no human milk in the first 14 days of life and this proportion did not differ among groups according to early empirical antibiotic treatment duration. The total human milk intake over the first 14 days of life was significantly lower ($p<0.001$) among infants receiving prolonged initial empirical antibiotics (median [range]; 131ml/kg [0–1440]) compared with those receiving limited initial empirical antibiotics (345 ml/kg [0–1600]). Similarly, the number of infants receiving ≥ 500 ml/kg of human milk in the first 14 days of life was significantly lower ($p<0.001$) among infants treated for with prolonged initial empirical antibiotics (22%) compared with infants receiving limited initial empirical antibiotics (40%).

LOS, NEC, or Death Outcomes

A total of 76 (21%) study infants were diagnosed as having LOS, 17 (4.6%) were diagnosed with NEC (Bells stage ≥ 2), and 20 (5.5%) infants died. LOS, NEC, or death occurred more often in the prolonged antibiotic group compared with the limited antibiotic group (Table II). Also, LOS alone and death, but not NEC alone, occurred more often in the prolonged antibiotic group compared with the limited antibiotic group infants. A total of 122 pathogens were isolated from 100 positive cultures (82 gram positive bacteria, 30 gram negative bacteria and 10 Candida isolates) from these 76 infants. Pathogens included *Candida, Citrobacter, Escherichia coli, Enterobacter, Enterococcus,* group β *Streptococcus and other Streptococcal* species, *Klebsiella, Pseudomonas, Serratia, Staphylococus aureus, and* coagulase-negative *Staphylococcus*. Coagulase-negative *Staphylococcus* was isolated in one-half of LOS cases. Case fatality was higher in gram negative (3 deaths in 30 cases, 10%) than gram-positive sepsis (5 deaths in 82 cases, 6.1%). Multivariable analyses (Table III) found that prolonged early antibiotic therapy was independently associated with the composite outcome of LOS, NEC, or death and with LOS after 7 days of life controlling for birth weight, gestational age, race, prolonged premature rupture of membranes, number of days on high frequency ventilation in first week of life, and the amount of breast milk received in first 14 days of life. For each day of initial empirical antibiotic therapy, the odds of LOS, NEC or death and of developing LOS increased significantly. For infants who had received any initial empirical antibiotic exposure (305 infants), the adjusted attributable risk (AR) of LOS, NEC, or death was 32 per 100 infants and the number needed to harm (NNH) was 3.

DISCUSSION

We found that prolonged initial empirical antibiotic therapy is associated with a two-fold higher incidence of LOS, NEC or death and a three-fold higher incidence of LOS alone. Importantly, these associations persisted after adjusting for proxy severity of illness indicators previously identified as predictors for mortality [(22)]. Although administration of empirical antibiotics to preterm infants is common and is regarded to be safe, our study and others suggest that the duration of therapy is often arbitrary and the risk-benefit ratio of prolonged empirical antibiotic use may in fact be unfavorable. Cordero and Ayres reported that in their cohort of 742 extremely low birth weight (ELBW, ≤ 1000 grams birth weight)

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infants with initial sterile blood cultures 60% received empirical antibiotics for > 3 days[5]. They concluded that the decision to extend the duration of empirical antibiotic therapy appeared to be an institutional decision, not one based on severity of illness. Cotten et al reported that 53% of the 4039 ELBW infant enrolled in the NICHD NRN between 1998 and 2001 received initial empirical antibiotic therapy for ≥ 5 days duration despite sterile blood cultures[8]. In their study prolonged initial empirical antibiotic treatment of ELBW infants was associated with significantly higher rates of death and NEC or death, and a trend toward a higher rate of NEC alone even after adjusting for study center, gestational age, and other perinatal factors. A supplemental analysis of their data showed that LOS or death was significantly associated with prolonged initial empirical antibiotic therapy when organisms other than coagulase-negative *Staphyococcus* caused LOS. Althoughe Cotten did not address confounding by infant feedings, we found that even though human milk feeding was independently protective, it did not confound the relationship between antibiotic therapy and adverse outcomes.

Limitations of this study are the inability to control for all factors that indicate severity of illness. Although we sought to enhance characterization of severity of illness by using established respiratory indices through day of life 7, this eliminated potential study subjects with early LOS, NEC or death. As a result our study cohort size was reduced, limiting the power to detect potential differences in death alone or NEC alone. Additionally, elimination of infants who developed early sepsis limited the utility of early leukocyte indices and acute phase reactants in identifying culture-negative infants that might benefit from a prolonged duration of antibiotics.

Prolonged initial treatment with antibiotics may be indicated for preterm newborns when the likelihood of sepsis is high; however, the broad use of prolonged antibiotics might impair important transitional events required for intestinal homeostasis. Antibiotic therapy is known to alter colonization of the gastrointestinal tract, and predispose to the emergence of pathogens and resistant organisms. Animal studies of intestinal development underscore abnormal interaction between the intestinal epithelium and the luminal microbial milieu when colonization is interrupted by housing animals in germ-free conditions or treating them with broad-spectrum antibiotics [23, 24]. Activation of toll like receptors by commensal bacteria appears to be critical for protection against gut injury and associated mortality [25]. The lack of bacterial species diversity and abundance of Proteobacteria species associated with widespread use of antibiotics may predispose to inflammatory stimulation that may help explain the susceptibility of premature newborns to LOS and NEC [13, 26].

Our study suggests that there may be inherent risks associated with initial empirical antibiotic treatment and that each day of antibiotic therapy increases the odds of severe outcomes. Although it may be prudent to discontinue antibiotics for many premature infants with suspected EOS when cultures are negative, we do not propose limiting antibiotic treatment duration in all premature infants because blood-sampling limitations and maternal antepartum antibiotic coverage may preclude optimal culture sensitivity [27]. We do advocate rigorous review of ongoing empirical antibiotic treatment and prompt discontinuation of therapy if blood cultures are negative and clinical and laboratory, measurements indicate a low risk of sepsis. Automated blood culture systems now provide positive culture results within 48 hours after initiation of culture[28]. Also, adjuvant diagnostic tests such as leukocyte indices, serum acute phase reactants, leukocyte cell surface markers, and certain pro-inflammatory cytokines may be used to estimate sepsis risk or to determine adequacy of treatment thus allowing discontinuation of antibiotic therapy [29, 30]. Microbial molecular genetic methods under development will likely transform clinical practice early, sensitive detection of microbial pathogens and thus, prompt discontinuation of antibiotic therapy when test results are negative [29, 31]. Finally, molecular

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genetic techniques now being applied to characterize the developing intestinal microbiota will enhance our understanding of the effects of antibiotic exposure on intestinal colonization and predisposition of premature infants to LOS, NEC, and death[13]. Such knowledge may inform rational therapeutic use of antibiotics, prebiotics and probiotics.

The data from this and other retrospective studies suggests that prolonged initial empirical antibiotic treatment may predispose to adverse outcomes in premature infants. Adopting a standardized approach to empirical antibiotic prescription using clinical indicators, adjuvant diagnostic tests, and molecular techniques may enable clinicians to achieve more judicious use of antimicrobials using predefined clinical criteria. Prospective trials are needed to determine whether judicious restriction of early antibiotic treatment might reduce the risk of LOS, NEC, and death for premature infants.

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ABBREVIATIONS

AR	attributable risk
CI	confidence interval
ELBW	extremely low birth weight
EOS	early-onset sepsis
IL	interleukin
IQR	interquartile range
LOS	late-onset sepsis
NEC	necrotizing enterocolitis
NICHD NRN	Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network
NNH	Number needed to harm
OR	odds ratio
SD	standard deviation
VLBW	very low birth weight

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Table 1

Characteristics of study infants by initial empirical antibiotic use

Variable	Description	Initial Empirical Antibiotic Therapy			p-value
		0 days 60 (16.4%)	1–4 days 175 (48%)	≥5 days 130 (35.6%)	
Infant Baseline Characteristics					
Birth weight (grams)+	Mean (SD)	1203 (227)	1069 (276)	935 (253)*	<0.001
Gestational age (weeks)+	Mean (SD)	30.4 (1.9)	28.2 (2.2)	26.5 (2.1)*	<0.001
Non-Hispanic black+	No. (%)	11 (18.3%)	52 (29.7%)	43 (33%)	0.11
Male^	No. (%)	24 (40%)	76 (43.4%)	66 (50.8%)	0.29
Maternal and Prenatal Information					
Prenatal steroids given (any)+	No. (%)	55 (91.7%)	154 (88%)	113 (86.9%)	0.64
Hypertension/eclampsia+	No. (%)	33 (55%)	43 (34.6%)	13 (10%)*	<0.001
Prenatal care (≥1 prenatal visit)+	No. (%)	60 (100%)	168 (96%)	123 (94.6%)	0.19
Married+	No. (%)	40 (66.7%)	106 (60.6%)	67 (51.5%)	0.10
Antepartum antibiotic therapy	No. (%)	32 (53.3%)	108 (61.7%)	102 (78.5%)*	<0.001
Multiple Birth^	No. (%)	20 (33%)	67 (38.3%)	32 (24.6%)*	0.04
Prepartum hemorrhage^	No. (%)	6 (10%)	31 (17.7%)	28 (21.5%)	0.15
Labor and Delivery Information					
Cesarean section delivery	No. (%)	46 (76.7%)	123 (70.3%)	71 (54.6%)*	0.003
Chorioamnionitis	No. (%)	1 (1.7%)	10 (5.8%)	58 (47.9%)*	<0.001
Rupture of membranes >24 hours	No. (%)	6 (10%)	36 (20.6%)	34 (26.2%)	0.04

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Variable	Description	Initial Empirical Antibiotic Therapy			p-value
		0 days 60 (16.4%)	**1–4 days 175 (48%)**	**≥5 days 130 (35.6%)**	
Delivery room resuscitation	No. (%)	40 (66.7%)	158 (90.3%)	123 (94.6%)	<0.001
Type delivery room resuscitation					
• Positive pressure ventilation	No. (%)	37 (92.5%)	124 (78.5%)	45 (36.6%)*	<0.001
• Endotracheal intubation	No. (%)	4 (10%)	35 (22.2%)	79 (64.2%)*	<0.001
• Epinephrine	No. (%)	0	7 (4.4%)	7 (5.7%)	0.31
• Chest compressions	No. (%)	0	8 (5.1%)	11 (8.9%)	0.09
5-min Apgar score of 3–6+	No. (%)	0	33 (19.9%)	35 (26.9%)*	<0.001
5-min Apgar score of >6+		60 (100%)	137 (78.3%)	79 (60.8%)	
Received surfactant	No. (%)	5 (8.3%)	84 (48%)	99 (76.2%)*	<0.001
Clinical features of respiratory distress syndrome+	No. (%)	35 (58.3%)	162 (92.6%)	126 (96.9%)	<0.001
Infant Information to Day 7					
Number of days with conventional ventilation at day 7^	Median (range)	0 (0–5)	0 (0–7)	2* (0–7)	<0.001
Number of days with high-frequency ventilation at day 7^	Median (range)	0 (0–5)	0 (0–4)	0* (0–7)	<0.001
Highest oxygen (FiO_2) concentration at day 7^	Median (range)	0.21 (0.21–0.70)	0.21 (0.21–1.0)	0.35* (0.21–1.0)	<0.001

Clinical factors in Table 1 previously associated with higher survival rates (+) or associated with a higher risk of death (^) from birth to day 7 of life that had complete data for analysis in this study.[25]

*Comparisons between infants who received antibiotics 1–4 vs. infants who received antibiotics ≥5 days statistically significant

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Table 2

Initial empirical antibiotics, total antibiotic exposure, and select adverse outcomes

	Description	Initial Empirical Antibiotic Therapy			p-value
		0 days 60 (16.4%)	1–4 days 175 (48%)	≥5 days 130 (35.6%)	
Total days treated with antibiotics during hospital course	Median (range) [IQR]	0 (0–21) [0–0]	3 (1–55) [3–8])	14* (5–84) [8–27]	<.0001
Composite[+]	No. (%)	7 (11.7%)	31 (17.7%)	53 (40.8%)*	<.0001
Late onset sepsis	No. (%)	7 (11.7%)	23 (13.1%)	46 (35.4%)*	<.0001
NEC	No. (%)	0	8 (4.6%)	9 (6.9%)	0.11
Death	No. (%)	0	8 (4.6%)	12 (9.2%)	0.03

[+]Any outcome of death, sepsis, or NEC after 7 days of life

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Table 3

Multivariable logistic regression for 305 infants who had received any empirical antibiotic therapy

	Odds Ratio	95% Confidence Interval	p-value
Composite outcome: NEC, LOS, Death after DOL 7*			
Initial Empirical ABX duration per day	1.24	1.07, 1.44	0.005
Initial Empirical ABX duration ≥5 days	2.66	1.12, 6.30	0.016
Outcome: LOS after DOL 7*			
Initial Empirical ABX duration per day	1.27	1.09, 1.49	0.003
Initial Empirical ABX duration ≥5 days	2.45	1.28, 4.67	0.007
Outcome: NEC after DOL 7**			
Initial Empirical ABX duration per day	1.08	0.83, 1.40	0.57
Initial Empirical ABX duration ≥5 days	1.28	0.42, 3.93	0.66
Outcome: Death after DOL 7†			
Initial Empirical ABX duration per day	1.04	0.82, 1.33	0.74
Initial Empirical ABX duration ≥5 days	1.12	0.40, 3.10	0.83

*Controlling for birth weight, gestational age, race, prolonged premature rupture of membranes, number of days on high frequency ventilation in first week of life, amount of breast milk received in first 14 days of life

**Controlling for gestational age, race, number of days on mechanical ventilation in first week of life, amount of breast milk received in first 14 days of life

†Controlling for birth weight, race, 5-minute apgar <5, amount of breast milk received in first 14 days of life

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