Antibiotic Exposure and Risk for Death or Bronchopulmonary Dysplasia in Very Low Birth Weight Infants

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We assessed the association between antibiotic exposure in the first 2 weeks of life and development of bronchopulmonary dysplasia in a cohort of very low birth weight infants. After controlling for the severity of illness, each additional day of antibiotic therapy was associated with both an increased risk for and severity of bronchopulmonary dysplasia. *(J Pediatr 2017;181:289-93).*

Bronchopulmonary dysplasia (BPD) remains a significant cause of neurodevelopmental delay, readmission, and mortality for very low birth weight (VLBW; <1500 g) infants.[1-3] The pathophysiology of BPD is closely linked with perinatal inflammation and circulating cytokines.[4] It is hypothesized that normal commensal flora (ie, the microbiome) can modulate inflammation in the neonatal gut, but very little is known about the lung microbiome in newborns. In older children and adults, the lung microbiome impacts chronic lung diseases including asthma, cystic fibrosis, and chronic obstructive pulmonary disease.[5-7] An higher abundance of phyla Bacteroidetes and Firmicutes (eg, *Lactobacillus*) has been associated with improved asthma control scores; in contrast, loss of bacterial diversity and higher proportions of proteobacteria (eg, *Escherichia coli* and *Klebsiella*) is associated with increased inflammation and decreased asthma control.[7,8] Such proteobacteria "surges" occur within the gut microbiome immediately after antibiotic exposure and are associated with subsequent development of necrotizing enterocolitis.[9] However, the extent to which antibiotic exposure alters the lung microbiome or impacts subsequent risk for BPD in VLBW infants is unknown. The objectives of this study were to (1) to determine if early empiric antibiotic therapy is associated with the development of BPD in VLBW infants after controlling for prematurity and severity of illness and (2) determine if the severity level of BPD is associated with increased exposure to empiric antibiotic therapy.

Methods

This retrospective cohort analysis used prospectively collected data for all VLBW infants born at ≤32 weeks' gestation admitted to the Memorial Hospital neonatal intensive care unit, Temple, Texas, from January 1, 2000, to December 31, 2015. Infants with major congenital anomalies were excluded, as were infants who were transferred or developed any of the following before 14 days of age: culture-proven sepsis, necrotizing enterocolitis (modified Bell stage ≥ IIA), or death. Demographic, clinical, laboratory, and outcome data were collected by study personnel and were reviewed by senior authors to ensure the accuracy of the abstracted data. Empiric antibiotic therapy for early onset sepsis is ampicillin and gentamicin; empiric antibiotic therapy for late-onset sepsis was historically vancomycin and gentamicin. Piperacillin/tazobactam was reserved for suspected necrotizing enterocolitis or signs of septic shock. This study was approved by the Baylor/Scott and White Health institutional review board.

Antibiotic therapy was recorded for all infants from birth up to and including day 14 of life. Antibiotic therapy was analyzed using days of therapy, an aggregate sum of the days of exposure for each antibiotic determined by multiplying the total number of antibiotic doses by the dosing interval, then dividing by 24 hours.[10] Severity of illness was calculated for all infants using the Clinical Risk Index in Babies – II (CRIB-II) score, a validated predictor of mortality in infants ≤32 weeks' gestation that incorporates gestational age, birth weight, sex, temperature on admission, and initial base deficit.[11] Intrauterine growth restriction was defined as birth weight below the 10th percentile for gestational age and sex.[12] Sepsis was defined as culture of a proven pathogen from a normally sterile site. Coagulase-negative staphylococci were considered pathogens only if recovered from ≥2 cultures or 1 culture if clinical signs of sepsis were present and the infant received ≥5 days of effective antibiotic therapy.[13]

The primary outcome was a composite of death before 36 weeks postmenstrual age or BPD; severity of BPD was a secondary outcome. BPD was defined using the National Institutes of Health severity-based consensus definition.[14] Infants were defined as having BPD if they required supplemental oxygen for ≥28 days, with severity assigned at 36 weeks

BPD	Bronchopulmonary dysplasia
CRIB-II	Clinical Risk Index in Babies – II
VLBW	Very low birth weight

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postmenstrual age (mild, no supplemental oxygen requirement; moderate, <30%; severe, ≥30% or need for positive pressure ventilation).

Statistical Analyses

Descriptive statistics included mean values and SD for normally distributed continuous variables, median and interquartile range for skewed continuous variables, and frequencies and percentages for categorical variables. For bivariate analysis, comparisons for non-ordinal categorical measures were conducted using χ^2 or Fisher exact test, comparisons for ordinal categorical variables and nonsymmetric continuous variables were conducted using the Kruskal-Wallis test. Risk for BPD and severity of BPD were predicted using a binary and stepwise logistic regression model, respectively, using the backwards selection procedure and model diagnostics, including the Hosmer-Lemeshow test and residual plots. Risk was reported as OR along with 95% CI. The CRIB-II score and year of birth were included in final models a priori; other risk adjusted predictors were included in the multivariable models if $P < .20$. Models used 3 different groups of data: all observations, gestational age ≤ 28 weeks, and gestational age ≥ 29 weeks. Model fit for the multivariable logistic regression model was assessed using the Hosmer-Lemeshow statistic with $P > .05$ providing adequate fit of the model to the data. SAS (version 9.4; SAS Institute, Cary, North Carolina) was used for all statistical analyses. An interim analysis was planned a priori; therefore, statistical significance is indicated by a 2-tailed $P < .025$ to control the type I error rate.

Results

There were 1324 infants who met the inclusion criteria. Of those, 184 were excluded (**Figure**; available at www.jpeds.com). Demographic and clinical characteristics of the remaining 1140 infants are shown in **Table I**. There were 571 infants (50.1%) who developed the composite outcome of either death before 36 weeks postmenstrual age (n = 14) or BPD (n = 557). Bivariate analysis is shown in **Table I**. In multivariable analysis (**Table II**), after controlling for CRIB-II score, each additional antibiotic day was associated with increased risk for the combined outcome of death or BPD (OR, 1.13; 95% CI, 1.09-1.16) and an increased risk for a more severe level of BPD (OR, 1.06; 95% CI, 1.04-1.08). Each unit increase in the CRIB-II score was also associated with risk for BPD (OR, 1.8; 95% CI,

Table I. Characteristics of VLBW infants with and without the primary outcome of BPD or death admitted from 2000 to 2015

	All infants	BPD or death	Neither	*P*
Number of infants	1140	571	569	
Maternal age (years, mean ± SD)	26.3 ± 6.1	26.6 ± 6.1	26.1 ± 6	.18
Maternal parity	2 (1-3)	2 (1-3)	2 (1-3)	.39
Maternal chorioamnionitis, %	7.9	11.5	4.5	<.001
Maternal corticosteroids, %	82.5	83.3	82.2	.64
Vaginal delivery, %	35.5	37.2	34	.26
Female sex, %	51.8	51.9	52.0	.96
Multiple gestation,%				.011
Singleton	74.7	77.9	71.4	
Twins	20.9	18.3	23.4	
Triplets or greater	4.5	3.8	5.3	
Gestational age (weeks, mean ± SD)	28.1 ± 2.5	26.3 ± 1.9	30 ± 1.5	<.001
≤26, n	363	345	18	
27-29, n	430	192	238	
30-32, n	347	34	313	
Birth weight (grams, mean ± SD)	1031 ± 290	838 ± 231	1230 ± 198	<.001
Intrauterine growth restriction, %	14.2	13.8	14.6	.71
CRIB-II score	8 (5-11)	10 (8-13)	5 (4-7)	<.001
1-minute Apgar	6 (4-7)	5 (3-7)	7 (5-8)	<.001
5-minute Apgar	8 (7-9)	8 (7-8)	8 (7-9)	<.001
Surfactant doses	1 (0-1)	1 (1-1)	0 (0-1)	<.001
Days of antibiotic therapy (mean ± SD)	9.5 (±7.6)	14.1 (±8.1)	4.8 (±6.5)	<.001
Ampicillin	3.6 (±2.8)	5.2 (±6.3)	2 (±2.2)	
Gentamicin	4.3 (±3.4)	6.4 (±5.7)	2.2 (±2.3)	
Vancomycin	0.9 (±2.1)	1.4 (±3.4)	0.4 (±1.1)	
Piperacillin/tazobactam	0.2 (±1.1)	0.4 (±2.2)	0.1 (±0.6)	
Other*	0.4 (±1.4)	0.7 (±2.8)	0.1 (±0.5)	
Days of mechanical ventilation	2 (0-17)	6 (2-19)	1 (0-8)	<.001
Sepsis, %	9.6	14.6	4.1	<.001
Positive endotracheal culture, %	9.3	17.9	0.7	<.001
Postnatal steroids, %	17	33.1	0.9	<.001
BPD or death†	50.1			
Mild BPD	25.3			
Moderate BPD	9.6			
Severe BPD	14.6			
Death	1.6			

Data shown as median values (interquartile range) or percentage unless otherwise indicated.
*Amikacin (52%), cefotaxime (26%), metronidazole (14%), nafcillin (7%), meropenem (2%).
†Four infants died after BPD severity assigned at 36 weeks postmenstrual age, 3 infants owing to complications of moderate or severe BPD and 1 infant with mild BPD owing to intestinal perforation.