Routine Early Antibiotic Use in SymptOmatic Preterm Neonates: A Pilot Randomized Controlled Trial

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We enrolled 98 infants (gestational age <33 weeks) in a pilot randomized trial of antibiotics vs no antibiotics; 55 were randomized (lower maternal infectious risk; symptoms expected for gestation). Adverse events did not differ significantly between the randomization arms. This trial establishes a framework for a larger multicentered trial. *(J Pediatr 2021;229:294-98).*

Antibiotics are routinely used in symptomatic preterm infants after birth for presumed early-onset sepsis, but without clear evidence to guide this practice. Observational studies support an association between routine early antibiotic use in preterm infants and increased risk for morbidities.[1-4] Despite concerns for these morbidities and data showing low rates of culture-confirmed early-onset sepsis, most preterm infants are treated with antibiotics in the first days after birth as a standard of care.[5-7] This practice is based on the hypothesis that preterm deliveries may be precipitated by an infection, and that it may be difficult to distinguish between symptoms such as respiratory distress related to prematurity and early-onset sepsis. Emerging evidence from our group[8-11] and others[12,13] has shown that necrotizing enterocolitis and late-onset sepsis[14] are preceded by intestinal dysbiosis, characterized by shifts in bacterial taxa associated with antibiotic use.[15] Furthermore, recent literature has described a connection between intestinal microbial and fungal dysbiosis and antibiotics and lung inflammation.[16-18] Thus, most infants born at <33 weeks of gestation are exposed soon after birth to a therapy with risks that may outweigh benefits. Systematic studies that challenge the current therapeutic approach and provide evidence supporting or contradicting this practice are needed. Here we present the results of our pilot study randomizing low-risk preterm infants with symptoms of prematurity to antibiotics or no antibiotics after birth.

Methods

Following multiple discussions with the neonatology group at the University of Florida (UF), consensus was achieved regarding the safety of the study protocol, group allocation, and laboratory evaluation. Routine Early Antibiotic use in SymptOmatic preterm Neonates was an un-blinded, randomized, pragmatic, pilot clinical trial at a single academic center. Routine Early Antibiotic use in SymptOmatic preterm Neonates was designed to evaluate the feasibility and safety of a larger multicenter trial evaluating the risks and benefits of current practices around the prescribing of antibiotics for preterm infants. The trial was registered at ClinicalTrials.gov: NCT02784821.

BPD	Bronchopulmonary dysplasia
IRB	Institutional Review Board
NICU	Neonatal intensive care unit
UF	University of Florida

Participants

The planned enrollment was 300 mother–infant dyads (150 infants) during a 1-year study period. In accordance with the Institutional Review Board (IRB) policy, mothers are enrolled separately if any information from their medical records is to be collected. Written consents for infants and mothers were obtained prenatally or immediately after birth in eligible infants. All infants born at <33 weeks of gestation and admitted to the UF neonatal intensive care unit (NICU) without major congenital anomalies affecting viability were eligible.

Enrolled infants were assigned to 1 of 3 groups (A, B, or C) based on the risk of infection and neonatal symptoms. Group allocation was established by the research team after reviewing the maternal and infant charts and discussing the infant's status with the bedside clinician (**Figure 1**; available at www.jpesd.com).

Group A consisted of newborn infants with symptoms not clearly associated with prematurity or who were at high risk for infection (due to, eg, maternal chorioamnionitis or

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colonization with group B streptococcus without prophylaxis). Infants in this group were treated with antibiotics and were not randomized. Group B consisted of asymptomatic infants at low risk for infection. Antibiotics were not indicated in this group, and infants were not randomized.

Group C consisted of infants eligible for randomization. These infants had symptoms associated with prematurity (eg, respiratory distress requiring respiratory support, apnea or bradycardia, ineffective thermoregulation, hypoglycemia) that historically had been considered indications for treatment with antibiotics after birth. These infants did not meet criteria for group A and were randomized to either group C/antibiotics (antibiotics prescribed at birth) or group C/no antibiotics (no antibiotics prescribed at birth).

Participants were randomized within 1 hour of birth by block randomization using random block sizes of 2 and 4 created in SAS and uploaded in REDCap for the use of the study team. The randomization group was disclosed to the bedside clinician who would order the antibiotics for infants assigned to group C/antibiotics. The intent was that infants in group C/antibiotics would receive antibiotics for 48 hours, assuming negative cultures.

Risks of Intervention and Safety Mechanisms

Infants assigned to receive antibiotics immediately after birth if symptomatic (group A or C/antibiotics) or not receiving antibiotics when asymptomatic (group B) were exposed to no additional risk due to study enrollment. Symptomatic infants randomized to group C/no antibiotics could have potentially been exposed to higher risk of infection, morbidity, and mortality. To minimize the risks, the study team recommended obtaining our standard NICU laboratory tests, including blood culture, complete blood cell count with differential, and C-reactive protein in all infants. The medical team was allowed to prescribe antibiotics for infants in group C/no antibiotics or group B, based on their clinical judgment.

Outcomes

The primary outcome was defined prospectively as a composite outcome of late-onset sepsis (defined as culture-positive infection >48 hours after birth), bronchopulmonary dysplasia (BPD) (defined as oxygen requirement at 36 weeks of corrected gestational age), necrotizing enterocolitis (defined as Bell stage II or greater), and death. Secondary outcomes were defined as early-onset sepsis (defined as culture-positive infection in the first 48 hours after birth), intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, and spontaneous intestinal perforation. These outcomes were assessed by a review of the medical record at the time of discharge from the NICU.

Data from both mothers and infants were collected from electronic medical record system and transferred into REDCap.

A sample size of 50 per group was planned to obtain sufficiently precise rates of anticipated admission to the NICU, consent, and estimates of clinical outcomes to plan a larger trial. Our enrollment goal of 300 infant-mother dyads was not achievable during the study period owing to a lower than expected admission rate of infants born at <33 weeks of gestation to the UF NICU. We reduced our goal to 200 infant-mother dyads (100 infants). Descriptive statistics, means and rates, were calculated, with corresponding 95% CIs to inform plausible ranges of the feasibility and safety outcomes of interest. Statistical comparisons among groups were made using the *t* test, ANOVA, and the χ^2 test for continuous and categorical data, respectively. Our primary focus was on the comparison of the 2 randomized groups (groups C/antibiotics and C/no antibiotics). ORs (and 95% CIs) were calculated to compare adverse event rates between the randomized groups. Data management and descriptive analyses were conducted using SAS 9.4 (SAS Institute). Group C infants were analyzed on an intention-to-treat basis. A secondary post hoc analysis of group C compared outcomes in infants who received antibiotics and those who did not receive antibiotics in the first 48 hours after birth.

The study protocol was approved by the UF IRB in September 2016, and enrollment occurred between January 2017 and January 2019. The study was paused for a full IRB review due to a high number of adverse outcomes and was then resumed given that the incidence of adverse events was similar to the national standard as demonstrated by Vermont Oxford Network data. There were 46 reportable events during the course of the study.

Results

Enrollment and Outcome Data

Ninety-eight infants and 88 mothers were enrolled (**Figure 2**). The baseline characteristics were similar in the randomized groups, group C/antibiotics and group C/no antibiotics (**Table I**; available at www.jpeds.com). Twenty-seven infants were assigned to group C/no antibiotics, and 13 of these infants (48%) received antibiotics within the first postnatal 48 hours. Initiation of antibiotics was triggered by a change in clinical status or abnormal laboratory test results (**Figure 2**).

Safety and Adverse Events

Individual adverse events were not significantly different among the groups (**Table II**). Rates of the composite outcome were significantly different among groups A, B, and C. Group B had significantly fewer adverse events than groups A and C. The composite outcome was nonsignificantly increased in randomized group C/no antibiotics compared with group C/antibiotics (51% vs 32.1%; $P = .14$) (**Table II**). When group C was analyzed by treatment received, irrespective of randomization assignment, there were no significant differences in any individual or composite adverse outcomes. The composite outcome was nonsignificantly increased in the infants receiving antibiotics in the first 48 hours after birth

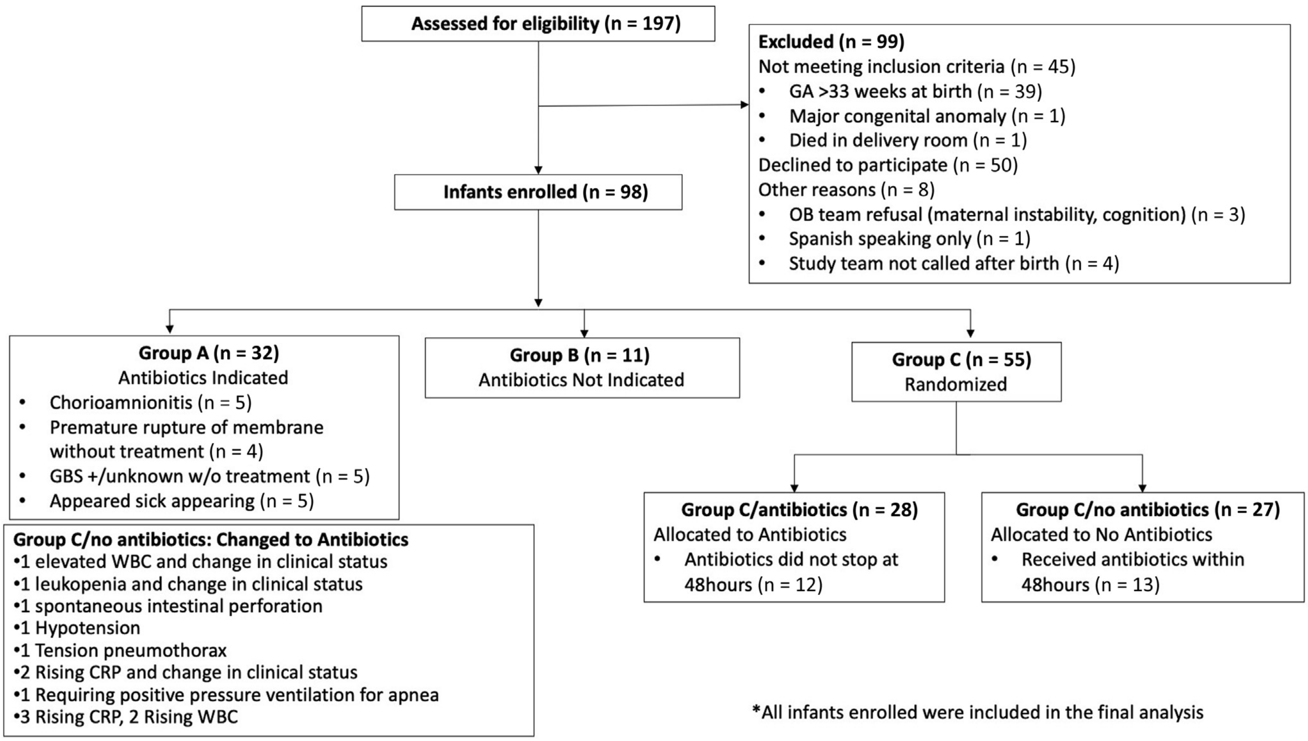

Figure 2. CONSORT diagram. *CRP*, C-reactive protein; *GA*, gestational age; *GBS*, Group B streptococcus; *OB*, obstetrics.

compared with those who did not (composite outcome: 46.3% vs 28.6%; P = .24) (**Table III**; available at www.jpeds.com).

One infant developed early-onset sepsis and died in the first 24 hours after birth. This infant was in group C/no antibiotics and was switched to receive antibiotics at approximately 1 hour after birth at the clinician's discretion based on a clinical change and laboratory abnormality. Mortality was not significantly different among group A, group C/antibiotics, and group C/no antibiotics (**Table II**). Group B had no mortality and a shorter length of stay compared with groups A and C, concordant with an older gestational age.

Discussion

We have shown that a study that challenges the current practice of routinely prescribing antibiotics in newborn infants with symptoms expected for prematurity is feasible. Our study risk-stratified and randomized premature infants to receive or not receive antibiotics in the first 48 hours after birth. Limitations of our study demonstrate the need for and provide guidance on how a multicenter randomized (and, ideally, blinded) trial can be conducted to evaluate and expand on our present findings.

Enrollment was slower than expected, due in part to IRB reviews for adverse events, mostly in the first 23-24 weeks of gestation and in group A. Future trials evaluating antibiotic use after birth should consider excluding infants with a high likelihood of early morbidity and mortality, such as periviable infants and infants with high illness severity scores. Newly developed scoring systems, such as the neonatal sequential organ failure assessment score, may aid the risk-stratifying process.[19] Although the enrollment goal was not met, the number of subjects in this pilot study was deemed sufficient to determine feasibility for a larger trial.

An increase in the composite outcome that did not meet statistical significance was seen in group C/no antibiotics vs group C/antibiotics when analyzed as on an intent-to-treat basis, mostly related to differing rates of BPD in the randomized groups. Because treatment switching was common in group C/no antibiotics, we performed a secondary analysis and analyzed group C by the use of antibiotics in the first 48 postnatal hours. In this analysis, more infants who received antibiotics had composite adverse events and BPD (P = .24) (**Table III**, online only) The increase in adverse events in infants treated with antibiotics could be due to greater illness severity, but this was not specifically studied.

The most common reason for switching treatment for the infants in group C/no antibiotics was clinical and laboratory abnormalities. The notion of "treatment switching" is a known phenomenon in clinical trials, and statistical methods to account for treatment switching have been developed.[20] Although we did not have the sample size to use these methods here, our preliminary data on the rates of switching will be useful in planning larger trials that can use these methods while ensuring sufficient statistical power.

Table II. Adverse events outcomes across study groups

		All study groups				Randomized infants				
Outcomes	Overall	Group A (antibiotics)	Group B (no antibiotics)	Group C randomized	*P* value*	Group C antibiotics	Group C no antibiotics	*P* value*	OR (95% CI), unadjusted	OR (95% CI), adjusted for gestational age
Number	98	32	11	55		28	27			
Necrotizing enterocolitis, n (%)	4 (4.1)	1 (3.1)	—	3 (5.5)	.67	2 (7.1)	1 (3.7)	.57	0.50 (0.04-5.86)	0.44 (0.04-5.41)
Late-onset sepsis, n (%)	15 (15.3)	6 (18.8)	—	9 (16.4)	.31	5 (17.9)	4 (14.8)	.76	0.80 (0.19-3.36)	0.64 (0.14-3.01)
BPD, n (%)	24 (24.5)	12 (37.5)	1 (9.1)	11 (20.0)	.08	3 (10.7)	8 (29.6)	.08	3.51 (0.82-15.03)	3.53 (0.73-17.16)
Death, n (%)	14 (14.3)	5 (15.6)	—	9 (16.4)	.35	4 (14.3)	5 (18.5)	.67	1.36 (0.32-5.74)	1.14 (0.24-5.43)
Adverse events composite outcome, n (%)†	43 (43.9)	19 (59.4)	1 (9.1)	23 (41.8)	.01	9 (32.1)	14 (51.9)	.14	2.27 (0.76-6.80)	2.43 (0.68-8.71)

OR referent group: C/antibiotics.
*χ^2 test.
†Adverse event composite outcome: any of the following: necrotizing enterocolitis, late-onset sepsis, BPD, or death.

Antibiotics have been proposed to decrease inflammation and subsequently decrease ventilation requirements, which could decrease BPD. However, recent studies have demonstrated a connection between airway and intestinal dysbiosis with abnormal inflammation that alters lung development, subsequently increasing the risk of BPD.[16,17] In our study, 8 infants in group C/no antibiotics developed BPD, but 6 of these infants were switched to received antibiotics in the 48 hours after birth. Based on the small numbers, it does not appear that withholding antibiotics in the first 48 hours led to BPD, but this requires further study.

Limitations of this study include the randomization of periviable infants at high risk of adverse events, use of an unblinded approach, and a lack of definition of symptoms associated with prematurity as entry criteria for the randomization group. Future trials should better define the symptoms of prematurity for randomization eligibility.

The safety of randomizing premature infants to antibiotics vs no antibiotics has been a major concern in neonatology. Although we do not claim safety, our pilot study's pragmatic design showed no evidence of harm. Allowing the primary physicians to provide antibiotics based on their clinical judgment was a necessary compromise, because more objective validated criteria are lacking in this population. The antibiotics were initiated for abnormal laboratory findings or acute events, such as tension pneumothorax or spontaneous intestinal perforation. One infant in the study had culture-positive early-onset sepsis. This infant was randomized to group C/no antibiotics, but ampicillin and gentamicin were administered within 1 hour after birth due to a clinical status change and laboratory evaluation, as outlined in the study algorithm. In this infant, the bacterial strain was resistant to the prescribed antibiotics. This infant's case was reviewed by the UF Data Safety and Monitoring Board, Neonatology Division, and IRB. It was determined that the death was not study-related, as serial examinations and early laboratory evaluation accurately detected the infant's severity of illness, and treatment was initiated in a timely manner consistent with the NICU practice. The low rate of early-onset sepsis observed in this cohort is similar to that reported previously and reinforces the goal of challenging the practice of routine antibiotic use in preterm infants.[7,21]

Future randomized trials should consider methods for blinding the treatment group to improve consistency and safely decrease the rate of treatment switching in infants randomized to no antibiotics. There is a trend toward decreasing antibiotic utilization in premature infant care, which suggests a growing concern with unnecessary use.[6] However, overall use remains high, demonstrating the need for a multicenter trial evaluating the use of antibiotics in neonatal care.

This study demonstrates the feasibility of a randomized trial of early antibiotics vs no antibiotics in risk-stratified premature infants and provides guidance for larger randomized trials, which in turn may improve clinical care of preterm infants. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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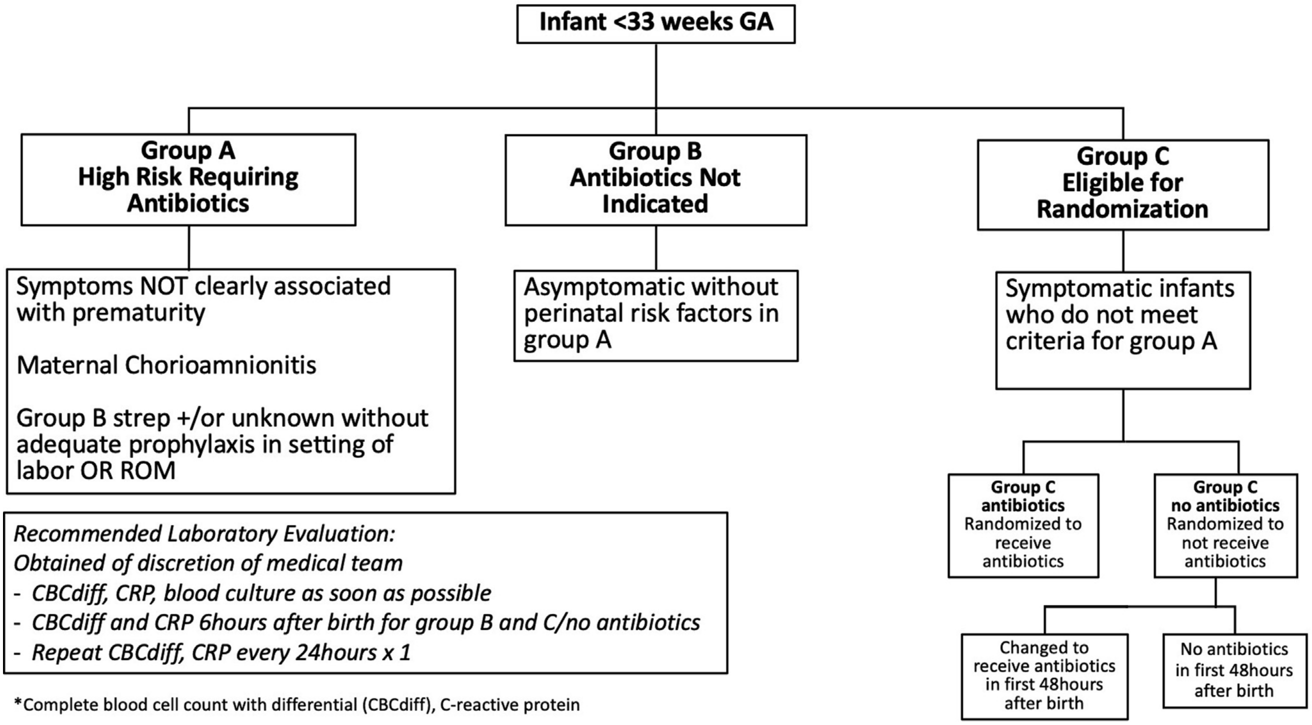

Figure 1. Study algorithm. *CBCdiff*, complete blood count with differential; *CRP*, C-reactive protein; *GA*, gestational age; *ROM*, rupture of membranes.

Table I. Baseline characteristics

Characteristics	Overall	All study groups				Randomized infants		
		Group A/antibiotics	Group B/no antibiotics	Group C randomized	*P* value*	Group C/antibiotics	Group C/no antibiotics	*P* value*
Number	98	32	11	55		28	27	
Male sex, n (%)	50 (51.0)	16 (50.0)	4 (36.4)	30 (54.6)	.54	13 (46.4)	17 (63.0)	.21
Cesarean delivery, n (%)	58 (59.8)†	19 (59.4)	3 (27.3)	36 (66.7)†	.05	17 (63.0)†	19 (70.4)	.56
Singleton, n (%)	75 (76.5)	24 (75.0)	10 (90.9)	41 (74.6)	.48	20 (71.4)	21 (77.8)	.59
Gestational age, wk, mean ± SD (range)	29.1 ± 2.8 (23.1-32.9)	28.2 ± 2.9 (23.1-32.9)	32.1 ± 1.0 (29.3-32.9)	29.0 ± 2.6 (23.7-32.7)	.0002	29.2 ± 2.5 (23.7-32.7)	28.8 ± 2.8 (23.7-32.7)	.59
Birth weight, g, mean ± SD (range)	1240 ± 479 (490-2770)	1138 ± 446 (490-2132)	1900 ± 417 (1110-2770)	1167 ± 407 (525-2425)	<.0001	1234 ± 424 (525-2425)	1098 ± 384 (605-2116)	.22
Length of stay, d, mean ± SD (range)	56.4 ± 37.1 (0.0-184.0)	64.5 ± 40.5 (0.0-184.0)	26.5 ± 19.7 (9.0-81.0)	57.7 ± 35.2 (1.0-147.0)	.01	53.9 ± 30.0 (13.0-134.0)	61.6 ± 40.1 (1.0-147.0)	.42

*χ^2 test or ANOVA.
†n missing = 1; did not obtain consent to collect maternal data.

Table III. Adverse events outcomes within randomized infants

Outcomes	Group C (N = 55)		P value†
	Received antibiotics*	Did not receive antibiotics	
Number (%)	41 (74.6)	14 (25.5)	
Necrotizing enterocolitis, n (%)	3 (7.3)	—	.3
Late-onset sepsis, n (%)	7 (17.1)	2 (14.3)	.8
BPD, n (%)	9 (22.0)	2 (14.3)	.53
Death, n (%)	8 (19.5)	1 (7.1)	.28
Adverse events outcome composite, n (%)	19 (46.3)	4 (28.6)	.24

*Infants in group C receiving antibiotics in the first postnatal 48 hours regardless of assigned treatment group.
†χ^2 test.