Identification of Extremely Premature Infants at Low Risk for Early-Onset Sepsis

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abstract

BACKGROUND: Premature infants are at high risk of early-onset sepsis (EOS) relative to term infants, and most are administered empirical antibiotics after birth. We aimed to determine if factors evident at birth could be used to identify premature infants at lower risk of EOS.

METHODS: Study infants were born at 22 to 28 weeks' gestation in Neonatal Research Network centers from 2006 to 2014. EOS was defined by isolation of pathogenic species from blood or cerebrospinal fluid culture at ≤72 hours age. Infants were hypothesized as "low risk" for EOS when delivered via cesarean delivery, with membrane rupture at delivery, and absence of clinical chorioamnionitis. Frequency of prolonged antibiotics (≥5 days) was compared between low-risk infants and all others. Risks of mortality, EOS, and other morbidities were assessed by using regression models adjusted for center, race, antenatal steroid use, multiple birth, sex, gestation, and birth weight.

RESULTS: Of 15 433 infants, 5759 (37%) met low-risk criteria. EOS incidence among infants surviving >12 hours was 29 out of 5640 (0.5%) in the low-risk group versus 209 out of 8422 (2.5%) in the comparison group (adjusted relative risk = 0.24 [95% confidence interval, 0.16–0.36]). Low-risk infants also had significantly lower combined risk of EOS or death ≤12 hours. Prolonged antibiotics were administered to 34% of low-risk infants versus 47% of comparison infants without EOS.

CONCLUSIONS: Delivery characteristics of extremely preterm infants can be used to identify those with significantly lower incidence of EOS. Recognition of differential risk may help guide decisions to limit early antibiotic use among approximately one-third of these infants.

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WHAT'S KNOWN ON THIS SUBJECT: Characteristics known at birth including gestational age identify infants at highest risk of early-onset sepsis (EOS). It is unknown if delivery characteristics can be used to identify premature infants at lowest risk of EOS to guide empirical antibiotic therapy.

WHAT THIS STUDY ADDS: Specific criteria can identify premature infants with a 76% lower adjusted risk for EOS. A substantial proportion of these infants received prolonged antibiotics despite their lower a priori risk. Recognition of this differential risk may reduce early antibiotic exposures.

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Accurately estimating individual risk of early-onset sepsis (EOS) among very premature infants is challenging because of the relatively high incidence of clinical instability among these infants and the associated concern for sepsis as a treatable cause of such instability.[1,2] Antibiotics are initiated in the majority of extremely preterm infants and are frequently continued despite sterile blood cultures.[3–5] Of concern, prolonged early antibiotic exposure has been associated with increased subsequent risk of late-onset sepsis (LOS), necrotizing enterocolitis (NEC), severe retinopathy of prematurity, and death.[3,6–9] Identification of premature infants at low risk of EOS may help guide decisions for initiating and/or discontinuing empirical antibiotic treatments in the first days of life and would be a critical first step in promoting antibiotic stewardship among these infants.

The pathogenesis of EOS is predominantly that of ascending colonization of the uterine and fetal compartments with maternal recto-vaginal flora, progressing to inflammation and infection.[10,11] Preterm onset of labor and preterm rupture of amniotic membranes are both significantly associated with risk of EOS.[12,13] However, a proportion of preterm deliveries occur because of maternal medical indications (such as preeclampsia) or for chronic fetal conditions (such as growth restriction).[14] In the absence of labor or rupture of membranes (ROM), the risk of EOS in preterm infants delivered via cesarean delivery (CD) should be substantially lower compared with preterm infants delivered because of preterm labor or premature ROM. We accessed data collected by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) and used delivery characteristics to define a group of extremely preterm infants we hypothesized would be at lower risk for EOS. Our objectives were to compare the incidence of culture-confirmed EOS and the prevalence of prolonged early antibiotic treatment among infants with and without low EOS risk criteria.

METHODS

Study Population

Infants were born at NRN centers between January 1, 2006, and December 31, 2014, and enrolled in a registry maintained by the NRN. Inclusion criteria for the cohort studied were: gestational age (GA) 22 weeks, 0 days to 28 weeks, 6 days; birth weight (BW) 401 to 1500 g; inborn; and no major congenital anomaly. Registry data included prospectively collected maternal pregnancy and delivery information; infant data from birth until death, hospital discharge or transfer, or 120 days of age; and if hospitalized at 120 days, final discharge or transfer date or death up to 1 year of age.[15] Participation in the registry was approved at most sites by the local institutional review board under a waiver of consent; 3 sites required parental consent.

Delivery Criteria for Categorizing Infants as Hypothetically "Low Risk" for EOS

Preterm labor was not recorded in the registry during the study period. Delivery characteristics likely to capture infants delivered for maternal health indications without preterm onset of labor were used to define a hypothesized low-risk group for EOS. Low-risk infants had all of the following characteristics: delivery by CD, ROM at delivery, and no documentation of maternal clinical chorioamnionitis in the obstetrical record. Infants without low-risk criteria were denoted as the "comparison" group for description of study results. In a secondary analysis, the low-risk group was further defined to also exclude infants of mothers with histologic diagnosis of chorioamnionitis on the basis of placental pathologic examination.

Hospital Outcomes and Clinical Interventions

Hospital morbidities and clinical interventions were recorded for infants who survived >12 hours. EOS (≤72 hours of age) and LOS (>72 hours of age) were defined by blood or cerebrospinal fluid (CSF) cultures positive for pathogenic bacteria or fungi and antibiotic therapy ≥5 days or intent to treat and death within 5 days. *Micrococcus*, *Propionibacterium*, *Corynebacterium*, *Bacillus*, and coagulase-negative staphylococci (CONS) grown on cultures of blood or CSF ≤72 hours of age were considered contaminants for the primary outcome of EOS incidence. Cultures growing ≥1 species of which at least 1 was considered a true pathogen were counted as EOS cases. For a secondary analysis, infants with CONS were included as EOS cases. CONS grown from LOS cultures were included as true pathogens. Other morbidities included respiratory distress syndrome defined by clinical features in the first 24 hours, pneumothorax, pulmonary hemorrhage, pulmonary interstitial emphysema, patent ductus arteriosus, NEC stage 2 to 3,[16,17] spontaneous intestinal perforation (SIP), severe intracranial hemorrhage (ICH) grade 3 or 4[18] based on a cranial sonogram taken within 28 days of birth, periventricular leukomalacia (PVL), and bronchopulmonary dysplasia (BPD) defined as need for supplemental oxygen at 36 weeks postmenstrual age (PMA). Surviving infants discharged or transferred before 36 weeks PMA were classified on the basis of their status at 36 weeks, if known, or on the basis of oxygen use at discharge or transfer. Small for gestational age (SGA) was

defined as BW <10th percentile for sex and GA.[19]

Prolonged early antibiotic therapy was defined as receipt of antibiotics for ≥5 days starting <72 hours of age (or intent to treat for ≥5 days in an infant who died within 5 days and was receiving antibiotics). Those who did not receive prolonged antibiotics were either not started on antibiotics <72 hours, or had antibiotics initiated but discontinued before 5 days. Other interventions recorded included receipt of surfactant, nitric oxide, treatment of hypotension, and duration and type of respiratory support.

Statistical Analysis

Characteristics and outcomes were compared between infants in the low-risk and comparison groups. Additionally, we compared outcomes for low-risk infants with and without early prolonged antibiotics, excluding infants with any of the following at <7 days of age: positive blood or CSF culture results (including isolates considered contaminants in this study) and/or a diagnosis of NEC or SIP. Statistical significance for unadjusted comparisons between groups was determined by χ^2 test for categorical variables and Wilcoxon test for continuous variables. Poisson regression models with robust variance estimators[20] were used to assess risk of mortality, the primary outcome EOS, and other binary outcomes in comparison groups while adjusting for study center, maternal race and/or ethnicity, antenatal steroid use, multiple birth, sex, GA (categorical by week), and BW (continuous). Adjusted relative risks (aRRs), 95% confidence intervals (CIs), and *P* values by the score or Wald χ^2 test from these models were reported. Morbidity outcomes were compared between low-risk and comparison infants surviving >12 hours, accounting for the age at which assessment took place. Combined death or morbidity outcomes were also examined to

TABLE 1 Maternal, Delivery, and Neonatal Characteristics

N (Column %) or as Shown[a]	Low Risk of EOS (*N* = 5759)	Comparison Group (*N* = 9674)	*P*[b]
Study Criteria for Infants With Low Risk of EOS			
CD	5759 (100.0)	3899 (40.3)	≤.001
ROM before delivery	0 (0.0)	7330 (76.2)	<.001
Maternal clinical chorioamnionitis	0 (0.0)	2538 (26.2)	<.001
Placental pathology performed	4898 (85.3)	8258 (85.6)	.58
Histologic chorioamnionitis reported	1042/4884 (21.3)	5457/8221 (66.4)	<.001
Maternal and delivery characteristics			
Maternal age in y, median (IQR)	28 (23–32)	27 (22–32)	<.001
Gravida			.003
1	1876 (32.6)	3001 (31.0)	
2	1378 (23.9)	2279 (23.6)	
3	992 (17.2)	1589 (16.4)	
4+	1512 (26.3)	2802 (29.0)	
Maternal race and/or ethnicity[c]			<.001
African American, non-Hispanic	2141 (37.3)	3846 (39.9)	
White, non-Hispanic	2415 (42.1)	3648 (37.9)	
Hispanic	878 (15.3)	1620 (16.8)	
Other	304 (5.3)	523 (5.4)	
At least 1 prenatal visit	5536 (96.2)	9141 (94.5)	<.001
Maternal insulin-dependent diabetes	332 (5.8)	428 (4.4)	<.001
Maternal hypertension	2677 (46.5)	1204 (12.4)	<.001
Antepartum hemorrhage	917 (15.9)	2038 (21.1)	<.001
Maternal antibiotics during delivery admission	3105 (54.1)	7767 (80.6)	<.001
Antenatal steroids	5062 (88.1)	7995 (82.8)	<.001
Magnesium sulfate during delivery admission[d]	1858/2473 (75.1)	2977/4124 (72.2)	.009
Multiple birth	1928 (33.5)	2175 (22.5)	<.001
Infant characteristics			
GA, weeks, median (IQR)	27 (25–28)	26 (24–27)	<.001
By GA week			<.001
22	16 (0.3)	601 (6.2)	
23	181 (3.1)	1207 (12.5)	
24	662 (11.5)	1445 (14.9)	
25	916 (15.9)	1488 (15.4)	
26	1089 (18.9)	1504 (15.5)	
27	1353 (23.5)	1661 (17.2)	
28	1542 (26.8)	1768 (18.3)	
BW, g, median (IQR)	820 (660–1000)	820 (640–1028)	.64
SGA	844 (14.7)	299 (3.1)	<.001
Male	2836 (49.3)	5171 (53.5)	<.001
Apgar <5 at 5 min	1030 (17.9)	2487 (26.0)	<.001
Infants surviving >12 h	5640	8422	—
Surfactant	4883 (86.6)	6549 (77.8)	<.001
Nitric oxide	371 (6.6)	777 (9.2)	<.001
Median (IQR) highest base deficit in first 24 h[b]	6 (4–9)	5 (3–8)	<.001
Treated for hypotension in first 24 h[e]	684/2429 (28.2)	948/3683 (25.7)	.04
Median (IQR) DOL first enteral feed	4 (3–6)	4 (2–5)	<.001
Infants who survived >24 h	5608	8321	—
Respiratory support at 24 h[f]	5297 (94.7)	7606 (91.6)	<.001
Mechanical ventilation at 24 h	3562 (63.7)	4773 (57.5)	<.001
Infants who survived >3 d	5499	8131	—
Any respiratory support day 1–3[f]	5440 (99.0)	7932 (97.6)	<.001
Any mechanical ventilation day 1–3	4698 (85.5)	6371 (78.4)	<.001

DOL, day of life; IQR, interquartile range; —, not applicable.

[a] Information was missing as follows: CD, 3; ROM before delivery, 60; placental pathology performed, 49; histologic chorioamnionitis, 51; maternal age, 1 infant; gravida, 4; maternal race and/or ethnicity, 58; prenatal care, 7; maternal insulin dependent diabetes, 6; maternal hypertension, 7; antepartum hemorrhage, 4; maternal antibiotics, 54; antenatal steroids, 29; SGA, 4; infant sex, 4; Apgar score, 116; first temperature within 60 min, 125; temperature if within 60 min, 10; surfactant, 1 infant; nitric oxide, 17 infants; timing of enteral feeds, 3 infants; respiratory support at 24 h, 30 infants; respiratory support day 1–3, 12 infants.

TABLE 1 Continued

[b] *P* value by the χ^2 test (categorical variables) or the Wilcoxon test (continuous variables).

[c] Maternal white or African American race with missing ethnicity information (4.6% of African Americans, 0.8% of whites) were classified as non-Hispanic. Other races included Asian American and/or Pacific Islander, American Indian and/or Alaskan native, >1 race, other not specified, with non-Hispanic ethnicity.

[d] Maternal magnesium sulfate use was collected beginning April 1, 2011.

[e] Infant hypotension treatment and highest base deficit were collected beginning April 1, 2011. In this group, hypotension treatment was missing for 2 infants and highest base deficit was missing for 263 infants.

[f] Respiratory support was defined as any one of mechanical ventilation (high frequency or conventional), nasal synchronized intermittent mandatory ventilation, or continuous positive airway pressure received at 24 h or during any of the first 3 d of life.

TABLE 2 Mortality and EOS

N (Column %)	Low Risk of EOS	Comparison Group	Adjusted RR for Outcome (95% CI): Low Risk of EOS Versus the Comparison Group[a]
All infants	5759	9674	—
Died before discharge	938 (16.3)	2629 (27.2)	0.88 (0.82–0.94)
Died ≤12 h	119 (2.1)	1252 (12.9)	0.42 (0.35–0.52)
EOS or death ≤12 h[b]	148 (2.6)	1461 (15.1)	0.36 (0.30–0.43)
By GA, wk			
22	7/16 (43.8)	497/601 (82.7)	0.61 (0.35–1.05)
23	31/181 (17.1)	480/1207 (39.8)	0.50 (0.36–0.68)
24	44/662 (6.6)	200/1445 (13.8)	0.46 (0.34–0.63)
25	21/916 (2.3)	107/1488 (7.2)	0.28 (0.18–0.45)
26	19/1089 (1.7)	73/1504 (4.9)	0.29 (0.18–0.48)
27	16/1353 (1.2)	50/1661 (3.0)	0.31 (0.17–0.53)
28	10/1542 (0.6)	54/1768 (3.1)	0.17 (0.08–0.33)
EOS (incl. CONS) or death ≤12 h	165 (2.9)	1484 (15.3)	0.39 (0.33–0.46)
Infants who survived >12 h	5640	8422	—
EOS[c]	29 (0.5)	209 (2.5)	0.24 (0.16–0.36)
EOS (incl. CONS)	46 (0.8)	232 (2.8)	0.33 (0.24–0.46)

RR, relative risk; —, not applicable.

[a] RRs of each outcome for infants in the low risk of EOS group versus the comparison group were adjusted for center, maternal race and/or ethnicity, antenatal steroids, multiple birth, GA, BW, and sex.

[b] The RRs for EOS or death within 12 h of delivery varied by GA (group GA interaction, $P = .015$).

[c] The RRs for EOS did not vary significantly by GA (group GA interaction, $P = .94$). In the model assessing the interaction, GA 22 and 23 wk were combined.

TABLE 3 Distribution of EOS Cases Among 5640 Infants in the Low Risk of EOS Group and 8422 Infants in the Comparison Group Who Survived >12 Hours Based on Maternal Clinical and Histopathology Diagnosis of Chorioamnionitis

	Clinical Chorioamnionitis			No Clinical Chorioamnionitis		
	HC[a]	No HC	No Pathology	HC	No HC	No Pathology
Low risk, *N*	0	0	0	1018	3771	851
EOS cases, *N* (%)	0	0	0	16 (1.6)	10 (0.3)	3
Comparison, *N*	1632	289	252	3081	2166	1002
EOS cases, *N* (%)	83 (5.1)	4 (1.4)	15	70 (2.3)	20 (0.9)	17

HC, histological chorioamnionitis.

[a] In the low-risk group, placental pathology was not performed for 820 infants; pathology was performed but results were missing for 13 infants; and information about whether pathology was done was missing for 18 infants. In the comparison group, placental pathology was not performed for 1192 infants; pathology was performed but results were missing for 34 infants; and information about whether pathology was done was missing for 28 infants.

account for the competing risk of death before evaluation. For analyses of low-risk infants with and without early prolonged antibiotics, morbidities were examined among infants who survived >7 days to allow for exposure to prolonged antibiotics to have occurred. For these analyses, combined death or morbidity outcomes included all deaths after 7 days and before discharge to examine risk of death in addition to morbidity before discharge.

A *P* value < .05 was considered significant; no adjustment was made for multiple comparisons. Analyses were performed by using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

Between January 1, 2006, and December 31, 2014, 16 185 infants with GA 22 to 28 weeks and BW 401 to 1500 g were born at NRN centers. Of these, 640 (4%) infants with a major congenital anomaly, 111 (0.7%) infants with insufficient information (maternal clinical chorioamnionitis, 54; ROM, 43; EOS or antibiotic information, 10; delivery type, 4), and 1 infant with congenital syphilis were excluded. Thus, 15 433 infants were studied, of whom 5759 (37.3%) were classified into the low-risk group and 9674 (62.7%) into the comparison group.

Maternal and Infant Characteristics

By definition, all infants in the low-risk group were delivered by CD, without ROM before delivery, and none had maternal clinical chorioamnionitis (Table 1). Maternal histologic chorioamnionitis was reported for a smaller proportion of infants in the low-risk group versus the comparison group (21% vs 66%). Mothers in the low-risk group were more likely to suffer complications such as hypertension, more likely to receive antenatal corticosteroids, and less likely to receive antenatal antibiotics. Median gestation was higher in the low-risk group, as was the proportion of female infants, multiple births, and SGA infants. In all measures except 1 (nitric oxide therapy), a significantly greater proportion of infants in the low-risk group had markers of illness and clinical intervention (Table 1).

Mortality and Early-Onset Infection

The proportion of infants who died in the first 12 hours after birth was smaller in the low-risk group than in the comparison group (Table 2). Risk

TABLE 4 Morbidities Among Infants Surviving >12 Hours

N (Column %)[a]	Low Risk of EOS	Comparison Group	Adjusted RR for Outcome (95% CI): Low Risk of EOS Versus Comparison Group[b]
Infants who survived >12 h	5640	8422	—
RDS	5575 (98.8)	8219 (97.6)	1.01 (1.00–1.01)
Pneumothorax	319 (5.7)	483 (5.7)	1.00 (0.87–1.16)
Pulmonary hemorrhage	418 (7.4)	445 (5.3)	1.50 (1.31–1.72)
PIE[c]	191/2430 (7.9)	352/3684 (9.6)	0.97 (0.81–1.15)
PDA	2648 (47.0)	3612 (42.9)	1.15 (1.11–1.20)
NEC in the first 7 d	54 (1.0)	65 (0.8)	1.12 (0.75–1.68)
NEC before discharge	561 (9.9)	864 (10.3)	0.97 (0.87–1.08)
SIP in the first 7 d	93 (1.6)	139 (1.7)	1.06 (0.81–1.40)
SIP before discharge	195 (3.5)	321 (3.8)	1.04 (0.87–1.25)
Infants who survived >3 d	5499	8131	—
LOS on DOL 4–7	135 (2.5)	270 (3.3)	0.95 (0.76–1.19)
LOS before discharge	1363 (24.8)	2130 (26.2)	1.00 (0.94–1.06)
Infants evaluated with cranial imaging	5517	8233	—
Severe ICH or PVL	784/5502 (14.2)	1456/8199 (17.8)	0.97 (0.89–1.05)
Infants who survived to 36 wk PMA	4938	7190	—
BPD	2286/4900 (46.7)	3115/7128 (43.7)	1.02 (0.98–1.06)

DOL, day of life; ICH, intracranial hemorrhage; PDA, patent ductus arteriosus; PIE, pulmonary interstitial emphysema; RDS, respiratory distress syndrome; RR, relative risk; —, not applicable.

[a] Information was missing as follows: RDS, 1 infant; pulmonary hemorrhage, 1 infant; PDA, 11 infants; NEC in the first 7 d, 4 infants; NEC before discharge, 2 infants; SIP in the first 7 d, 12 infants; SIP before discharge, 6 infants; LOS on days 4–7, 13 infants; LOS before discharge, 5 infants; ICH and/or PVL, 49 infants; BPD, 100 infants.

[b] RRs of each outcome for infants in the low risk of EOS group versus the comparison group were adjusted for center, maternal race and/or ethnicity, antenatal steroids, multiple birth, GA (categorical), BW (continuous), and sex, except as noted below. Because of the small number of infants with the outcome, center was not included in the model assessing risk of NEC in the first 7 d of life. Only 1 infant born at GA 22 wk had NEC or SIP in the first 7 d of life; GAs 22 and 23 wk were combined for the purpose of assessing these outcomes. All infants born at GA 22 wk had RDS; therefore, GA 22 and 23 wk were combined for the purpose of assessing the outcome RDS.

[c] PIE was collected beginning April 1, 2011.

of the composite outcome of death within 12 hours or EOS was also reduced for infants in the low-risk group (2.6% vs 15.1%; aRR [95% CI]: 0.36 [0.30–0.43]). Among infants surviving >12 hours, 29 out of 5640 (0.5%) in the low-risk group and 209 out of 8422 (2.5%) in the comparison group had EOS (aRR [95% CI]: 0.24 [0.16–0.36]). The risk of EOS in the low-risk group was consistently lower than in the comparison group for infants born at each GA, as well as when CONS cases were included. *Escherichia coli* was the most frequent pathogen isolated in both the low-risk group (9 out of 29 cases) and the comparison group (103 out of 209 cases) (Supplemental Tables 8 and 9). The predictive performance of risk categorization by study criteria is shown in Supplemental Table 10. The likelihood of not having EOS was 3 times greater for low-risk infants than for infants in the comparison group.

Placental pathology was available for 4802 out of 5622 (85.4%) low-risk infants and 7202 out of 8394 (85.7%) comparison infants surviving >12 hours (excluding those with no information). The proportion of infants with EOS was similar for those with and without placental pathology (with versus without pathology, low-risk group: 0.5% vs 0.4%; comparison group: 2.5% vs 2.5%; $P = .86$ for overall difference). Among low-risk infants surviving >12 hours and born to mothers without a histologic diagnosis of chorioamnionitis on placental pathology, 10 out of 3771 (0.3%) infants had EOS (Table 3).

Other Morbidities Before Discharge

Among infants who survived >12 hours, the adjusted risks of respiratory distress syndrome, pulmonary hemorrhage, and patent ductus arteriosus were higher in the low-risk group compared with the comparison group (Table 4). The composite risks of death within 12 hours and each of pneumothorax, pulmonary interstitial emphysema, NEC, and SIP, were lower in the low-risk group, as was the risk of LOS or death within 3 days, and the risk of intraventricular hemorrhage

TABLE 5 Antibiotic Use in Low-Risk and Comparison Infants Surviving >12 Hours

N (Column %) or as Shown	Low Risk of EOS, *N* = 5640	Comparison Group, *N* = 8422	*P*[a]
Antibiotics for ≥5 d starting within 72 h	1940 (34.4)	4106 (48.8)	<.001
Antibiotics in the absence of EOS	1911/5611 (34.1)	3897/8213 (47.4)	<.001
Antibiotics in the absence of positive EOS culture (cases and contaminants)[b]	1890/5590 (33.8)	3862/8177 (47.2)	<.001
Antibiotics in the absence of a positive blood or CSF culture result, NEC, or SIP ≤7 d[c]	1771/5334 (33.2)	3649/7752 (47.1)	<.001
No. infants given prolonged early antibiotics per EOS case	66	19	<.001

[a] *P* value by the χ^2 test.

[b] Of the 5640 infants in the low-risk group who survived >12 h, 50 infants with a positive blood or CSF culture result within 72 h of age were excluded (29 counted as EOS cases and 21 with an organism considered a contaminant: 17 CONS, 3 *Bacillus* sp., 1 *Micrococcus* sp.). Of the 8422 infants in the other group, 245 were excluded (209 counted as EOS cases and 36 with an organism considered a contaminant: 23 CONS, 3 *Bacillus* sp., 5 *Micrococcus* sp., 4 *Corynebacterium* sp., 1 *Lactobacillus* sp.).

[c] In the low-risk group, 256 infants with NEC, SIP, or LOS within the first 7 d of life were excluded in addition to the 50 infants previously noted (44 infants with NEC, 79 with SIP, 113 with LOS, and 20 with ≥2 of NEC, SIP, or LOS). In the comparison group, 425 infants with NEC, SIP, or LOS within 7 d were excluded in addition to the 245 previously noted (49 infants with NEC, 110 with SIP, 232 with LOS, and 34 with 2 or more of NEC, SIP, or LOS).

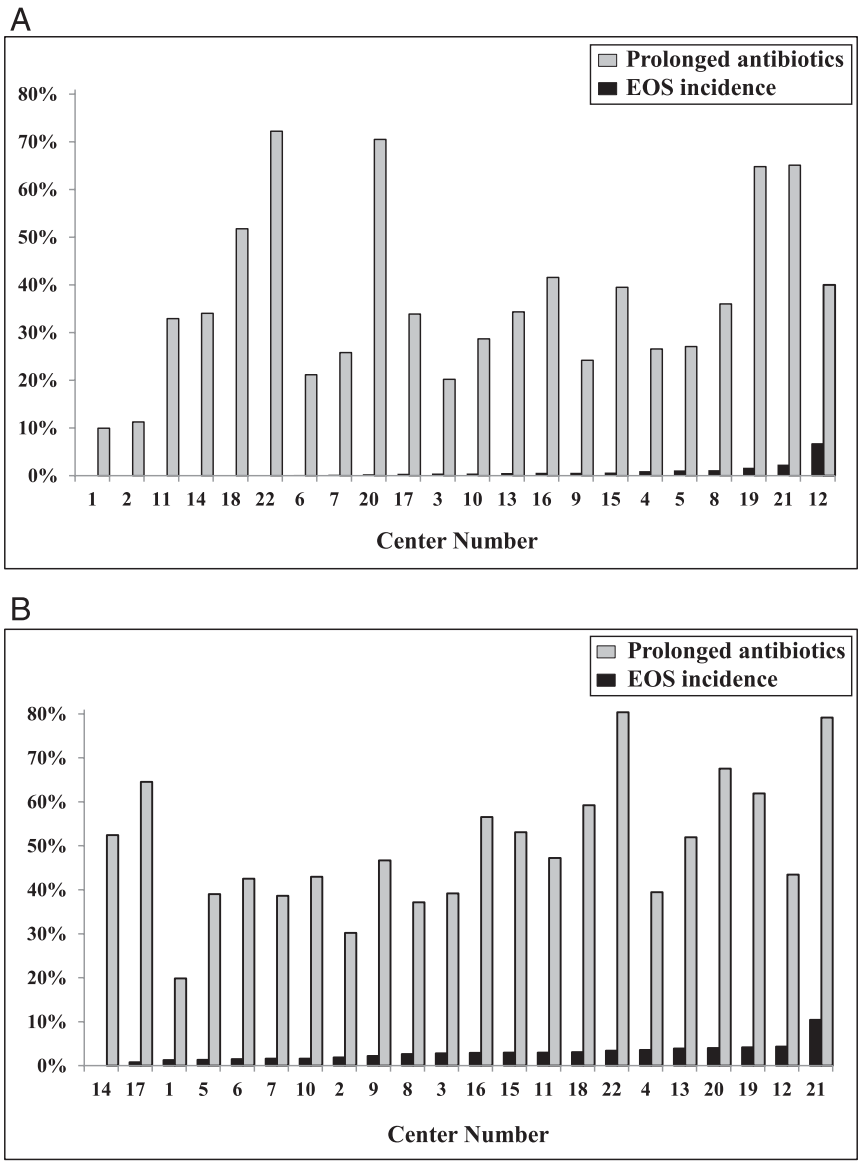

FIGURE 1

Center variation in proportion of infants treated with prolonged antibiotics. Shown are the proportion of infants treated with prolonged antibiotics (gray bars) and EOS incidence (black bars) by NRN center, expressed as percent of total infants at each center. Centers are sorted by increasing incidence of EOS. A, Low-risk infant cohort. The rate of EOS was 0% at centers 1, 2, 11, 14, 18, and 22 and 0.2% at centers 6 and 7. B, Comparison infant cohort. The rate of EOS was 0% at center 14. Two centers were excluded from the Figure: 1 center that left the NRN in 2006 and had no low-risk infants and another center that left the NRN in 2011 and had only 2 low-risk infants.

and/or PVL or death within 28 days without evaluation (data not shown).

Prolonged Early Antibiotic Therapy in the Absence of Positive Culture Results

Among infants surviving >12 hours without EOS, 34.1% of infants in the low-risk group received prolonged early antibiotics compared with 47.4% in the comparison group, $P < .001$ (Table 5). This difference persisted when infants with standard indications for antibiotic use (positive culture results, NEC, and/or SIP ≤7 days of life) were excluded. For each EOS case, 66 low-risk infants received prolonged early antibiotics compared with 19 infants in the comparison group, $P < .001$. Among low-risk and comparison infants, the proportion of infants who received prolonged early antibiotics varied by center (Fig 1). In comparison with the incidence of EOS cases, the proportion of infants treated with prolonged antibiotics was many times higher at all centers in both groups.

Comparing Low-Risk Group Infants With and Without Prolonged Early Antibiotic Therapy

Maternal and delivery characteristics did not differ significantly between the 1771 infants in the low-risk group who received prolonged early antibiotics without a positive culture result and/or a diagnosis of NEC or SIP ≤7 days of life and the 3563 who did not (Supplemental Table 11). However, the low-risk infants who received prolonged early antibiotics were significantly younger and smaller at birth, more likely to be boys, SGA, and have 5 minute Apgar score <5, and more likely to have received surfactant and other interventions (Table 6). After adjustment for GA and other covariates, the adjusted risk of death after 7 days and before discharge and the composite outcomes of death and/or either NEC, SIP, or LOS were increased for low-risk infants who received prolonged early antibiotics compared with low-risk infants who did not (Table 7). Risks of pulmonary outcomes were also higher among low-risk infants who received prolonged early antibiotics, including the risk of BPD among survivors to 36 weeks PMA (aRR [95% CI]: 1.28 [1.20–1.36]).

DISCUSSION

In this NRN cohort of extremely low gestation infants, characteristics evident at birth were able to be used to identify a group of infants with significantly lower risk of EOS. A third of the infants in the study cohort fulfilled the defined low-risk delivery criteria. The lower incidence of EOS in this group was, however, not associated with a proportional reduction in prolonged early antibiotic therapy, presenting an opportunity to revisit current antibiotic prescribing practices.

TABLE 6 Neonatal Characteristics and Early Clinical Interventions for Low-Risk Infants Who Survived >12 Hours, Excluding Infants With a Positive Blood or CSF Culture Result and/or NEC or SIP ≤7 Days

N (Column %) or as Shown	Prolonged Early Antibiotics (*N* = 1771)	No Prolonged Early Antibiotics (*N* = 3563)	*P*[a]
Infant characteristics[b]			
GA, wk, median (IQR)	26 (25–27)	27 (26–28)	<.001
By GA week			<.001
22	5 (0.3)	4 (0.1)	
23	67 (3.8)	67 (1.9)	
24	251 (14.2)	311 (8.7)	
25	327 (18.5)	492 (13.8)	
26	350 (19.8)	670 (18.8)	
27	394 (22.2)	904 (25.4)	
28	377 (21.3)	1115 (31.3)	
BW, g, median (IQR)	754 (620–930)	865 (710–1040)	<.001
SGA	353 (19.9)	411 (11.5)	<.001
Male	947 (53.5)	1683 (47.2)	<.001
Apgar <5 at 5 min	340 (19.2)	527 (14.8)	<.001
First temperature ≤60 min of birth	1644 (93.5)	3314 (93.5)	.92
Temperature (°F) if ≤60 min, median (IQR)	97.5 (96.5–98.2)	97.7 (96.8–98.3)	<.001
Clinical interventions[c]			
Surfactant	1653 (93.3)	2941 (82.6)	<.001
Nitric oxide	184 (10.4)	153 (4.3)	<.001
Treated for hypotension in first 24 h[d]	296/689 (43.0)	357/1621 (22.0)	<.001
Highest median (IQR) base deficit in 24 h[d]	7 (5–9)	6 (4–8)	<.001
Enteral feeds	1648 (93.1)	3393 (95.2)	.001
If yes, median (IQR) DOL first enteral feed	5 (3–8)	4 (2–5)	<.001
Infants who survived >24 h	1764	3538	—
Respiratory support at 24 h[e]	1695 (96.1)	3306 (93.8)	<.001
Mechanical ventilation at 24 h	1325 (75.2)	2014 (57.1)	<.001
Infants who survived >3 d	1742	3454	—
Any respiratory support day 1–3[e]	1736 (99.7)	3401 (98.6)	<.001
Any mechanical ventilation day 1–3	1621 (93.1)	2795 (81.0)	<.001

Of the 5640 infants in the low risk of EOS group who survived >12 h, the following 306 infants were excluded: 50 with a positive blood or CSF culture result within 72 h of age (29 counted as EOS cases and 21 with an organism considered a contaminant: 17 CONS, 3 *Bacillus* sp., 1 *Micrococcus* sp.), 44 with NEC ≤7 d, 79 with SIP ≤7 d, 113 with LOS on days 4–7, and 20 with 2 or more of NEC, SIP, or LOS ≤7 d. DOL, day of life; IQR, interquartile range; —, not applicable.

[a] *P* value by the χ^2 test (categorical variables) or the Wilcoxon test (continuous variables).

[b] Information was missing as follows: SGA, 2 infants; infant sex, 2; Apgar score, 4; first temperature within 60 min, 32; temperature if within 60 min, 2.

[c] Information was missing as follows: surfactant, 1 infant; nitric oxide, 3; timing of enteral feeds, 2; respiratory support at 24 h, 13 infants; respiratory support day 1–3, 4 infants.

[d] Infant hypotension treatment and highest base deficit were collected beginning April 1, 2011. In this group, hypotension treatment was missing for 1 infant and highest base deficit was missing for 92 infants.

[e] Respiratory support was defined as any one of mechanical ventilation (high frequency or conventional), nasal synchronized intermittent mandatory ventilation, or continuous positive airway pressure received at 24 h or during any of the first 3 d of life.

The lower incidence of EOS in the low-risk cohort confirmed our hypothesis that the absence of factors that might reflect (eg, preterm labor) or promote (eg, membrane rupture) the pathogenesis of ascending infection would be associated with a reduced occurrence of infection. However, 29 cases of EOS were identified in the low-risk group. These cases may be due to imprecision in our definition of these risk factors. The NRN database does not record presence of preterm labor, unexplained fetal distress, or criteria leading to a diagnosis of clinical chorioamnionitis. Therefore, we used CD with ROM at delivery and absence of clinical chorioamnionitis as indirect estimators. It is likely that we included some mothers who labored before being taken for a CD delivery before ROM, providing opportunity for ascending infection. Prospective collection of delivery criteria in real-time practice could improve capture of EOS risk factors and subsequently the precision of identifying infants at low risk for EOS. Hematogenous spread of infection across the placenta and infection after invasive intrauterine procedures can also rarely cause fetal infection.[21] Emerging evidence also points to a placental and amniotic fluid microbiome whose disturbance may be associated with preterm labor.[22]

Despite these limitations, the 76% lower risk of EOS among low-risk infants compared with the comparison group is substantial and warrants consideration in making management decisions. We recently reported a similar single-center study that included detailed maternal chart review of EOS cases among very low birth weight (VLBW) infants (BW <1500 g). In that study, we found a 92% lower unadjusted risk for EOS among VLBW infants delivered by CD to mothers with a diagnosis of preeclampsia and without diagnoses of preterm ROM or chorioamnionitis, compared with VLBW infants born without these characteristics (1 out of 605 [0.17%] vs 45 out of 2143 [2.1%], *P* = .001).[23] The incidence of EOS in the current study was even lower (0.3% vs 0.5%) among low-risk infants when the definition was refined to exclude infants born in the setting of histologic as well as clinical chorioamnionitis. Placental histopathology results obtained shortly after delivery may further aid in decisions to continue early empirical antibiotic therapy beyond the first few days of age.

Our findings suggest that clinicians did not recognize the differential incidence of EOS among low-risk infants or failed to account for it in their antibiotic management decisions. Although prolonged empirical antibiotic use was lower among low-risk infants than among the comparison infants, the ratio of prolonged antibiotics to number of EOS cases was 3 times higher in the low-risk group. Fewer low-risk infants died at ≤12 hours, but those

TABLE 7 Mortality for Low-Risk Infants Who Survived >12 Hours and Morbidities in Survivors >7 Days, Excluding Infants With a Positive Blood or CSF Culture Result and/or With NEC or SIP ≤7 Days

N (Column %)[a]	Prolonged Early Antibiotics (*N* = 1771)	No Prolonged Early Antibiotics (*N* = 3563)	Adjusted RR for Outcome (95% CI): Prolonged Early Antibiotics Versus No Antibiotics[b]
Died >12 h and before discharge	315 (17.8)	429 (12.0)	1.16 (1.01–1.32)
Died >7 d	236 (13.3)	258 (7.2)	1.52 (1.28–1.80)
Infants who survived >7 d	1692	3392	—
RDS	1683 (99.5)	3339 (98.4)	1.01 (1.00–1.01)
Pneumothorax	117 (6.9)	123 (3.6)	1.83 (1.38–2.43)
Pulmonary hemorrhage	148 (8.7)	127 (3.7)	1.96 (1.52–2.52)
PIE[c]	83/664 (12.5)	76/1547 (4.9)	1.80 (1.31–2.45)
PDA	951 (56.2)	1477 (43.6)	1.15 (1.08–1.22)
NEC >7 d	173 (10.2)	315 (9.3)	0.97 (0.80–1.17)
NEC >7 d or death before discharge	346 (20.4)	469 (13.8)	1.22 (1.07–1.40)
SIP >7 d	55 (3.3)	40 (1.2)	1.86 (1.23–2.82)
SIP >7 d or death before discharge	263 (15.5)	286 (8.4)	1.46 (1.24–1.71)
LOS >7 d	436 (25.8)	746 (22.0)	1.00 (0.89–1.11)
LOS >7 d or death before discharge	583 (34.5)	878 (25.9)	1.12 (1.03–1.23)
Infants evaluated with cranial imaging	1692	3365	—
Severe ICH or PVL	316/1687 (18.7)	321/3357 (9.6)	1.65 (1.40–1.94)
Infants who survived to 36 wk PMA	1500	3194	—
BPD	919/1491 (61.6)	1220/3167 (38.5)	1.28 (1.20–1.36)

Of the 5640 infants in the low risk of EOS group who survived >12 h, the following 306 infants were excluded: 50 with a positive blood or CSF culture result within 72 h of age (29 counted as EOS cases and 21 with an organism considered a contaminant: 17 CONS, 3 *Bacillus* sp., 1 *Micrococcus* sp.), 44 with NEC ≤7 d, 79 with SIP ≤7 d, 113 with LOS on days 4–7, and 20 with ≥2 of NEC, SIP, or LOS ≤7 d. ICH, intracranial hemorrhage; PDA, patent ductus arteriosus; PIE, pulmonary interstitial emphysema; RDS, respiratory distress syndrome; RR, relative risk; —, not applicable.

[a] Information was missing for survivors >7 d as follows: PDA, 2 infants; SIP, 2 infants; LOS, 2 infants; ICH and/or PVL, 13 infants; BPD, 36 infants.

[b] RRs of each outcome for infants who received antibiotics for ≥5 days started within 72 h of birth versus those who either did not receive antibiotics within 72 h or received antibiotics for <5 d were adjusted for center, maternal race and/or ethnicity, antenatal steroids, multiple birth, GA (categorical), BW (continuous), and sex except as noted below. Because of the number of centers with no infants who had the outcome (or, for RDS, centers with no infants without the outcome), center was not included in models assessing risk of RDS and SIP. All infants born at GA 22–24 wk had RDS; therefore, GA 22–25 wk were combined for the purpose of assessing RDS. GAs 22 and 23 wk were combined in the models assessing SIP and BPD (only 1 of the 9 infants included who were born at GA 22 wk and survived >7 d had SIP before discharge; all 5 infants born at GA 22 wk who survived to 36 wk PMA had BPD).

[c] PIE was collected beginning April 1, 2011.

who survived were as sick as or sicker than comparison infants. Maternal morbidity, SGA status, and a stressed in utero environment in infants delivered for maternal indications are associated with greater respiratory morbidity and may explain the greater initial morbidity observed in the low-risk infants.[24–26] Administration of antibiotics for increasing clinical instability and attribution of such instability to culture negative sepsis is well-documented in neonatal care.[4,27,28] A previous study revealed that >90% of all infants in an earlier NRN cohort were treated with antibiotics at birth.[3] We speculate that the greater need for intensive care interventions in the low-risk cohort and persistence of illness beyond 48 hours led to a reluctance to stop antibiotic treatment. These decisions are likely driven by clinical uncertainties and provider preference more than biology because we observed marked variation around prolonged antibiotic administration across study centers that did not correlate with variation in the incidence of EOS at these centers.

Clinicians make antibiotic and other treatment decisions to protect sick newborns, yet multiple reports now suggest harm from early and prolonged empirical antibiotics.[3,6–9] We addressed this issue with an analysis restricted to the low-risk group. To focus on potentially modifiable use of antibiotics, we limited this analysis to low-risk infants who received prolonged early antibiotics despite negative blood culture results and/or NEC or SIP in the first week of life. After adjusting for baseline characteristics associated with increased risk of morbidity and mortality, we still found higher subsequent mortality and increased incidence of BPD and other pulmonary outcomes among the low-risk infants who received prolonged early antibiotics. The decision to extend early empirical therapy may reflect a severity of initial illness that strongly influences subsequent morbidity and mortality in a manner for which we could not adequately account in our risk-adjusted analyses. However, there is evidence for the critical role of the early life microbiome in the development of neonatal immune responses and for the significant disruption of that microbiome induced by antibiotic exposure.[29–33] Although with this study we cannot determine why it may be, our findings reveal that among infants with a low previous probability of EOS, extended empirical administration of early antibiotics for critical illness may not be beneficial and could potentially be harmful.

Our study is limited by its retrospective design. During the study period, the registry lacked information on the indication for preterm delivery. We have no information on the presence of preterm labor, attempts to induce labor, or unexplained fetal distress. Information about antibiotic therapy was limited to whether antibiotics were started in the first 72 hours after birth and continued for ≥5 days. Types of antibiotics, total duration of antibiotic administration during the NICU admission, and indication for therapy were not recorded.

CONCLUSIONS

Delivery characteristics of infants born at 22 to 28 weeks GA were useful in identifying those with significantly

lower risk of EOS. Prolonged early antibiotics were administered to a large proportion of these infants despite their lower a priori risk, and this was associated with higher adjusted incidence of death and pulmonary morbidity. Recognition of differential EOS risk may help guide early empirical antibiotic use among approximately one-third of extremely preterm infants.

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ABBREVIATIONS

aRR: adjusted relative risk
BPD: bronchopulmonary dysplasia
BW: birth weight
CD: cesarean delivery
CONS: coagulase-negative staphylococci
CSF: cerebrospinal fluid
EOS: early-onset sepsis
GA: gestational age
LOS: late-onset sepsis
NEC: necrotizing enterocolitis
NRN: Neonatal Research Network
PMA: postmenstrual age
PVL: periventricular leukomalacia
ROM: rupture of membranes
SGA: small for gestational age
SIP: spontaneous intestinal perforation
VLBW: very low birth weight

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