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Impact of Early-Onset Sepsis and Antibiotic Use on Death or Survival with Neurodevelopmental Impairment at 2 Years Among Extremely Preterm Infants

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Abstract

Objective: To evaluate the hypothesis that early-onset sepsis increases risk of death or neurodevelopmental impairment (NDI) among preterm infants; and that among infants without EOS, prolonged early antibiotics alters risk of death/NDI.

Study design: Retrospective cohort study of infants born at NICHD Neonatal Research Network centers (2006-2014) at 22-26 weeks gestation and birth weight 401-1000 grams. EOS defined as growth of a pathogen from blood or cerebrospinal fluid culture 72 hours after birth. Prolonged

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Data Sharing: Data reported in this paper may be requested through a data use agreement. Further details are available at <https://neonatal.rti.org/index.cfm?fuseaction=DataRequest.Home>.

early antibiotics was defined as antibiotics initiated ≤ 72 hours and continued ≥ 5 days without culture-confirmed infection, necrotizing enterocolitis or spontaneous perforation. Primary outcome was death before follow-up or NDI assessed 18-26 months corrected age. Poisson regression was used to estimate adjusted relative risk (aRR) and confidence interval (CI) for EOS outcomes. A propensity score (PS) for receiving prolonged antibiotics was derived from early clinical factors and used to match infants (1:1) with and without prolonged antibiotic exposure. Log binomial models were used to estimate aRR for outcomes in matched infants.

Results: Among 6565 infants, those with EOS had higher aRR (95% CI) for death/NDI compared with infants managed with prolonged antibiotics [1.18 (1.06-1.32)] and to infants without prolonged antibiotics [1.23 (1.10-1.37)]. PS matching was achieved for 4362 infants. No significant difference in death/NDI [1.04 (0.98-1.11)] was observed with or without prolonged antibiotics among the matched cohort.

Conclusion: EOS was associated with increased risk of death/NDI among extremely preterm infants. Among matched infants without culture-confirmed infection, prolonged early antibiotic administration was not associated with death/NDI.

The American Academy of Pediatrics recommends discontinuation of empiric antibiotics when blood cultures for early-onset sepsis (EOS) remain sterile after 48 hours' incubation (1). However, neonatal providers frequently diagnose "culture-negative infection" when an infant's perinatal history, clinical condition or laboratory testing suggest infection even when bacterial cultures are sterile (2). Antibiotics are continued in such cases to prevent the mortality and morbidity associated with culture-confirmed infection (3). The use of prolonged early antibiotics for presumed culture-negative infection varies widely across hospitals (4–7). We previously reported that the proportion of extremely preterm infants administered prolonged early antibiotics among Neonatal Research Network (NRN) centers ranges from 10-72% for infants identified as at low risk for EOS based on delivery characteristics, and from 20-80% among the remaining infants (8). In contrast, rates of culture-confirmed EOS ranged from 0-6.7% and 0-10.4% across sites, respectively (8). Wide center-level variation in prolonged antibiotic use provides the opportunity to investigate outcomes of clinically similar infants managed with different antibiotic regimens.

There is increasing appreciation of the impact of antibiotic exposures on the developing neonatal microbiome (9), including evidence for interaction of the microbiota with brain development and function (10,11). Extremely preterm infants have a high prevalence of both antibiotic administration and of neurological sequelae (7,12). In this study, our first objective was to assess the composite risk of death or neurodevelopmental impairment (NDI) at 18-26 months corrected age (CA) for infants with culture-confirmed EOS, compared with infants with sterile cultures managed with or without prolonged early antibiotics. Our next objective was to compare the risk of death or NDI between infants with sterile cultures managed with and without prolonged early antibiotics, using propensity score (PS) methods (13) to control for potential differences in illness severity.

METHODS

This is a retrospective cohort study of infants born at NRN centers between 01/01/2006 and 12/31/2014 and enrolled in a registry of high-risk infants maintained by the NRN. Eligibility criteria were: gestational age (GA) 22 0/7-26 6/7 weeks, birth weight (BW) 401-1000 grams, inborn and survival >12 hours. Infants with major birth defects (14) may differ in indications for early antibiotics and in outcomes compared with infants without birth defects and were excluded. The registry includes prospectively collected maternal pregnancy and delivery information; infant data from birth until death, discharge/transfer, or 120 days of age; and if hospitalized at 120 days, final date of discharge/transfer or death up to one year of age (15). Surviving infants were eligible for a follow-up assessment. The institutional review board at each center approved participation in the registry and follow-up, with written parental consent or waiver of consent determined by each center's board.

EOS was defined as blood or cerebrospinal fluid (CSF) culture obtained \leq 72 hours of age that grew pathogenic bacteria or fungi, for which the infant received antibiotics \leq 5 days or died with intent to receive antibiotics \leq 5 days. *Micrococcus*, *Propionibacterium*, *Corynebacterium*, *Bacillus* species, and coagulase-negative staphylococci were considered contaminants. Prolonged early antibiotics was defined as a "yes" response to the question "Did the infant receive antibiotics for \leq 5 days, starting within the first 72 hours?", and included intended use \leq 5 days in an infant who died.

For both objectives, the primary composite outcome was death before follow-up or NDI in survivors. Death, NDI in survivors, and components of NDI were investigated as secondary outcomes. Surviving infants were evaluated at visits between 10/2007-8/2017 and were assessed at 18-22 months CA (births before 07/01/2012) or 22-26 months CA (births on or after 07/01/2012). Follow-up assessments included review of the medical history with the primary caretaker. The child's vision and hearing status were determined by history, testing after discharge (if available), and examination at the visit. Neurologic examination and a developmental evaluation using the Bayley Scales of Infant Development, Third Edition (Bayley-3) were administered by certified examiners (16). Cerebral palsy (CP) was defined using the gross motor function classification system (GMFCS) as mild (level 1), moderate (level 2-3), or severe (level 4-5) (17). NDI was defined as one or more of the following: bilateral blindness (corrected vision <20/200 in both eyes), hearing impairment (permanent hearing loss affecting communication with or without amplification), GMFCS level \geq 2 with or without CP, or a Bayley-3 cognitive composite score <85 (18).

Statistical Analyses:

Infants with missing exposure variables were excluded from all analyses. Neurodevelopmental outcomes were considered missing if assessment occurred at <14 or >30 months CA (2% of those assessed). All analyses were adjusted for maternal education, maternal insurance, maternal race/ethnicity, maternal hypertension, antepartum hemorrhage, antenatal steroids, maternal antibiotics received during the delivery admission, clinical chorioamnionitis, membrane rupture >18 hours, cesarean delivery, infant GA (categorical), BW (continuous), male sex, intubation at birth, temperature <60 minutes of birth, severe

intraventricular hemorrhage (IVH) ≥ 7 days age and start of enteral feeds ≥ 3 days age (12,19–22). IVH classified by Papile criteria as grade 3 or 4 was considered severe (23).

Each study objective had additional exclusions and different analytic approaches. **To assess the effect of EOS**, infants who died ≤ 12 hours of age; infants with necrotizing enterocolitis (NEC, defined by modified Bell stage \geq IIA (24,25)), spontaneous intestinal perforation (SIP, defined as intestinal perforation without proven NEC) at ≥ 3 days or infants with blood or CSF culture obtained at ≥ 3 days growing a contaminant were excluded. Poisson regression models with robust variance estimators (26) were used to assess risk of the primary outcome of death >12 hours and before follow-up or survival with NDI while adjusting for the covariates listed above as well as for study center.

Adjusted relative risks (aRR), 95% confidence intervals (CI), and p-values by the Wald chi-square test from these models were reported. **To assess the effect of prolonged early antibiotics**, infants who died or were diagnosed with NEC or SIP ≥ 5 days and infants with a blood or CSF culture obtained at ≥ 5 days growing a pathogen or contaminant were excluded. We used a PS-based analysis to adjust for imbalance of baseline characteristics in infants with and without prolonged early antibiotic exposure. A logistic regression model was fit to the dependent variable “prolonged early antibiotic exposure” to derive a propensity score defined as the probability of antibiotic use conditional on the covariates listed above as well as the highest respiratory support at 24 hours. Greedy nearest-neighbor matching without replacement using a caliper width of 0.2 of the standard deviation of the logit of the PS was used to match each infant managed with prolonged antibiotics with an infant managed without prolonged antibiotics but with similar PS (27). Adequacy of matching was assessed by comparing proportions and means of variables in the two groups before and after matching and by standardized mean differences (13,28). Absolute differences <0.10 were considered acceptable (28, 29). Composite of death >5 days of age and before follow-up or survival with NDI and secondary outcomes were assessed in the matched cohort using log binomial models to estimate relative risks (RR) and 95% CI while accounting for the paired nature of the matched sample by using generalized estimating equations methods (13). For secondary analyses, we constructed models that included post-matching adjustment for key confounders (GA, BW, male sex, severe IVH diagnosed ≥ 7 days and maternal education); study center; and for high frequency ventilation, a variable with residual imbalance after PS matching (30). Analyses were completed using SAS statistical software version 9.4 (SAS Institute, Cary, NC).

RESULTS

During the study period, 7631 infants with GA 22-26 weeks and BW 401-1000 grams were born at the 24 NRN centers and survived >12 hours. Of these, 238 infants with birth defects (3%), and 39 infants missing exposure variables were excluded, leaving 7354 (96%) infants in the base cohort before additional analysis-specific exclusions.

EOS:

After exclusions, 6565 infants were analyzed (Figure 1; available at www.jpeds.com). The proportion of eligible infants who survived to follow-up but were excluded due to missing

neurodevelopmental assessment was similar among infants with EOS (8/98, 8%), with prolonged antibiotics (345/2615, 13%) and without prolonged antibiotics (367/2700, 14%), $p=0.29$. Culture-confirmed EOS occurred in 153 infants (2.3%). Among infants without EOS, 3191 (48.6%) received prolonged early antibiotics and 3221 (49.1%) did not. Most maternal and neonatal characteristics differed among the three groups (Table 1). After adjusting for these characteristics, the composite outcome of death >12 hours or survival with NDI was increased for infants who had EOS (Table 2). Forty-one percent of infants with EOS died compared with 29% of culture-negative infants given prolonged early antibiotics and 28% without prolonged early antibiotics. Among survivors, risk of NDI was higher for infants with EOS compared with culture-negative infants who received prolonged early antibiotics and compared with infants who did not receive prolonged early antibiotics. Details of EOS infecting organisms are provided in Table 3; **online**. No difference was found in death/NDI among infants without EOS who were managed with and without prolonged antibiotics (Table 2).

Prolonged early antibiotic use:

After exclusions, 5807 infants were analyzed (Figure 1). Of these, 2978 infants (51%) received prolonged early antibiotics and 2829 (49%) did not. Propensity scores generated for the two groups showed good overlap (Figure 2; available at www.jpeds.com) and PS matching resulted in 2181 pairs (75% of the eligible cohort). After matching, differences in means and proportions of baseline characteristics were reduced between the groups and standardized mean differences of <0.10 were achieved in all variables except high-frequency ventilation at 24 hours (Table 4). Fifty percent of infants with prolonged early antibiotic exposure died >5 days or survived with NDI compared with 48% of matched infants without exposure to prolonged early antibiotics [RR 1.04 (95% CI: 0.98-1.11), $P= .18$] (Table 5). Estimated relative risk of death alone, NDI in survivors and components of NDI were also similar. Post-matching adjustment did not substantially alter these comparisons.

DISCUSSION

In this study, infants who had culture-confirmed EOS were more likely to die or survive with NDI as assessed at 18-26 months CA compared with infants without EOS who did or did not receive prolonged early antibiotics, when accounting for multiple confounders and other predictors of this outcome. When we compared infants without EOS, NEC, or SIP, we found the composite outcome of death or NDI at 18-26 months CA was 4% more likely to occur in infants managed with prolonged antibiotics with the confidence limits crossing zero and ranging from a 2% lower risk to an 11% higher risk. For this comparison, we used a propensity score matched cohort, and also employed post-matching adjustment to rigorously address the issue of confounding. We also made this comparison using the full cohort from which our PS analysis was derived, and found similar results. Our results demonstrate that risk of death/NDI for infants with culture-confirmed EOS is higher compared with infants without this diagnosis. This finding is likely no surprise to neonatal clinicians. Perhaps less expected is our observation that among those without culture-confirmed EOS, the administration of prolonged antibiotics was not associated with any significant difference in outcomes of death and/or NDI. One straightforward explanation is that the infants receiving

prolonged antibiotics did not have bacterial infection and antibiotics made no difference to their outcomes. Another possible explanation is that any advantage or disadvantage offered by prolonged antibiotics administration does not impact mortality or NDI as measured in this study.

Although epidemiologic studies address EOS-attributable mortality (31–34), information on the impact of culture-confirmed EOS on neurodevelopmental outcomes among preterm infants is scarce. A study from Israel demonstrated that very-low birth weight (VLBW, BW <1500 grams) infants with EOS are more likely to have brain injury compared with uninfected infants, but this report had no information on post-discharge outcomes (35). A prior study conducted among extremely preterm infants cared for in NRN centers from 1993-2001 found an increased risk of death or NDI among infants with culture-confirmed infection (34). The contribution of EOS to these findings is difficult to determine because the analysis combined cases of EOS and late-onset sepsis (LOS), and <3% of the infected study cohort had EOS alone. In a French study of infants born at 22-32 weeks gestation, those who had both EOS and LOS had a higher risk of CP at 5 years of age than uninfected infants (36). No difference was observed among those who had EOS alone, although this finding was based on evaluation of only 11 children. Our study demonstrates the negative overall impact of EOS in a large cohort of extremely preterm infants: 68% of those with EOS died or survived with NDI compared with 53% of infants without culture-confirmed EOS.

Because culture-confirmed EOS is universally treated with antibiotics, the potential impacts of the infection itself versus the antibiotics used cannot be separated. In contrast, provider and institutional variation in early antibiotic administration duration in the absence of culture-confirmed EOS provides the opportunity to assess the impact of prolonged early antibiotics after adjustment for patient-level risk factors. Multiple prior studies have reported adverse hospital outcomes among preterm infants administered prolonged early antibiotics (37–39). A study of extremely preterm infants born 1998-2001 and cared for at NRN centers reported that prolonged early antibiotic administration was associated with increased odds for in-hospital death (37), although a similar study of those born 2008-2014 reported less frequent use of prolonged early antibiotics and a smaller association between treatment and death (adjusted odds ratio 1.17 [95% CI: 0.99–1.40] $p=0.07$) (5). Initial antibiotic duration among VLBW infants admitted to centers in the Canadian Neonatal Network (CNN) was associated with increased odds of a composite outcome of mortality or significant morbidity (severe neurologic injury, retinopathy of prematurity, NEC, LOS or bronchopulmonary dysplasia), although the association with death at >7 days was not significant (40).

Few studies have explored the impact of prolonged antibiotics on outcomes after hospital discharge among preterm infants. CNN investigators assessed the relationship of antibiotic utilization rate (AUR), defined as total days of antibiotics divided by the length of stay, with death and severe NDI at 18-21 months among infants born at <29 weeks' gestation (41). They measured antibiotics administered in the absence of standard indications as quartiles of AUR (41). Comparing infants with the highest quartile of AUR to infants with the lowest quartile of AUR, this study found elevated adjusted odds for the composite outcome of death or NDI and for death alone, but not for NDI among survivors. A limitation of this study is

that mortality effects length of stay which may in turn influence the association between high AUR and death. We restricted our analysis of prolonged early antibiotic exposure to infants who survived >5 days to ensure the exposure could occur in all eligible infants. We found no evidence that prolonged early antibiotics either contribute to or protect against the composite or individual outcomes of death or NDI. The differing results for the outcome of death may be driven by the different approaches in the two studies.

Confounding by indication is a common concern in retrospective studies addressing the impact of antibiotic administration. It is likely that in many cases, infants who receive prolonged early antibiotics for culture-negative infection are sicker than those infants who do not. Prior studies approached this by adjusting for covariates in a regression model. Using this approach, we found no difference in outcomes between infants without EOS conditional on prolonged antibiotic use. We then applied a different approach to allow visualization of the balance of early clinical status among infants receiving prolonged antibiotics or not. We used propensity scores to match infants on multiple demographic and clinical characteristics that may influence management decisions and ultimately contribute to a child's risk of the composite outcome. This approach allowed us to focus on the 75% of infants among whom there is the most clinical variation in care, as it eliminates infants for whom most clinicians administered prolonged antibiotics, as well as those for whom most clinicians did not. Characteristics such as younger gestational age, maternal chorioamnionitis, and prolonged rupture of membranes that were more frequent among infants who received prolonged early antibiotics were better balanced in the matched cohort. We additionally conducted post-match adjustment of key variables and variables with residual imbalance after matching. Despite these adjustments, we cannot entirely rule out an impact of residual confounding.

Our study has additional limitations. In the database we used for this study, information about early antibiotics did not include type, indication and total duration of use. We did not collect additional laboratory data that can influence persistent antibiotic use, nor did we have information regarding probiotic use. Using the PS to match infants with and without prolonged antibiotic exposure provides balance on the characteristics considered, but unmeasured characteristics may still be unequally distributed between the groups resulting in biased estimates. As noted, approximately 25% of the cohort could not be matched (Table 6; **online**), largely due to a lack of practice variation among these infants.

We do not interpret the lack of association in our study as 'safety' of prolonged antibiotics but as an absence of benefit. Death and NDI are not appropriate outcomes to gauge safety; they are the key metrics of anticipated benefit. We did not have the data to compare interim outcomes such as drug side effects, alterations in microbiota or longer-term outcomes such as atopy and allergies to inform true safety. To our knowledge, no study addressing the impact of antibiotics administered to preterm infants has reported a benefit of prolonged antibiotics when used in the absence of culture-confirmed infection. Yet neonatal providers continue to express concerns about poor detection rates of microbiological cultures and rely on inflammatory biomarkers to guide antibiotic duration. Given the existing evidence of potential harm from antibiotic-associated dysbiosis and the lack of demonstrable benefit, we must question the practice of prolonged antibiotic use among extremely preterm infants when optimally-collected microbiological cultures are sterile.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix (online)

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Abbreviations:

aRR	Adjusted relative risk
BW	Birth weight
CA	Corrected age
CI	Confidence interval
CP	Cerebral palsy
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal fluid
EOS	Early-onset sepsis
GA	Gestational age
GMFCS	Gross motor function classification system
IVH	Intraventricular hemorrhage
LOS	Late-onset sepsis
NDI	Neurodevelopmental impairment
NEC	Necrotizing enterocolitis
NICHD	<i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development
NRN	Neonatal Research Network
PS	Propensity score
ROM	Rupture of membranes
SIP	Spontaneous intestinal perforation

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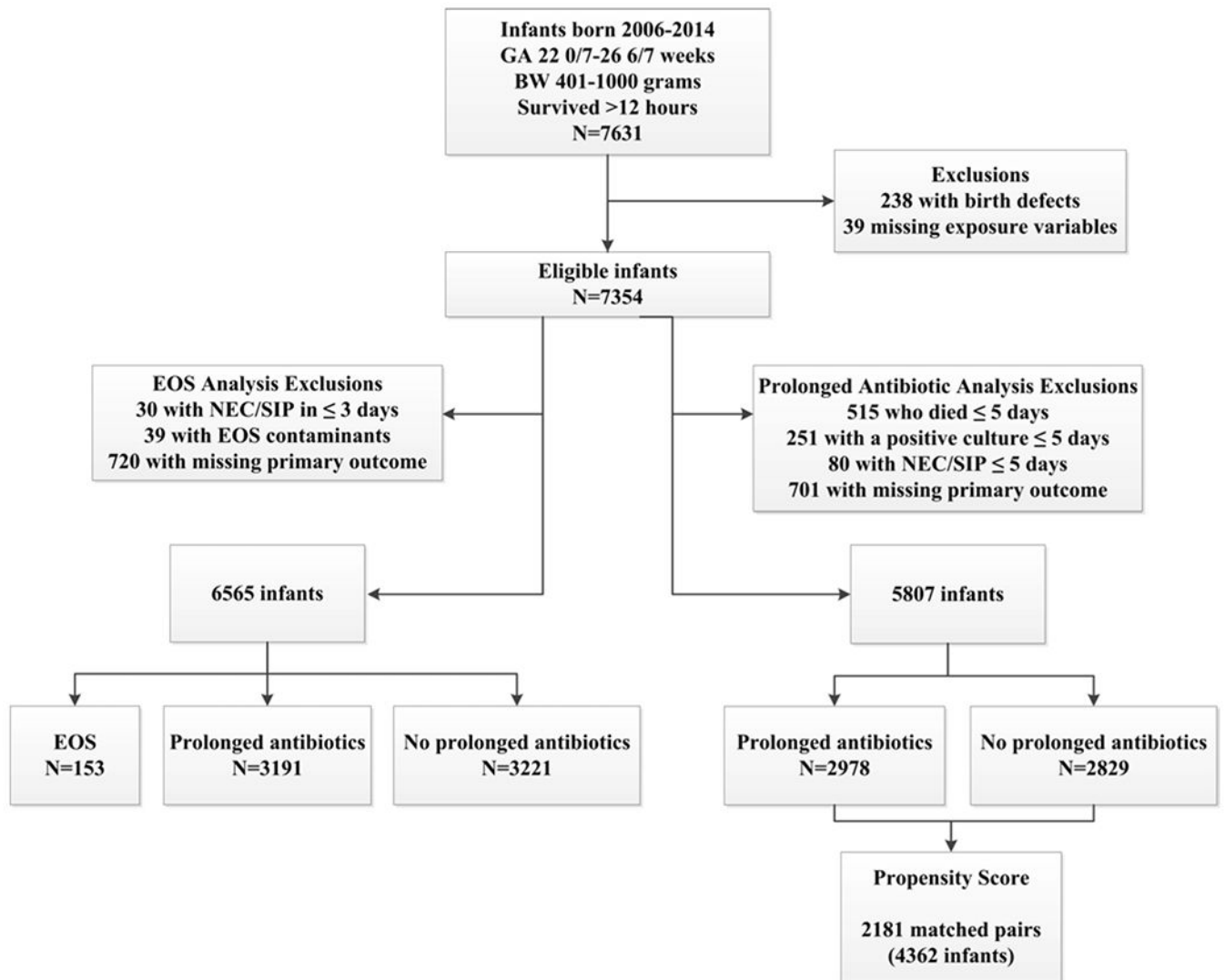
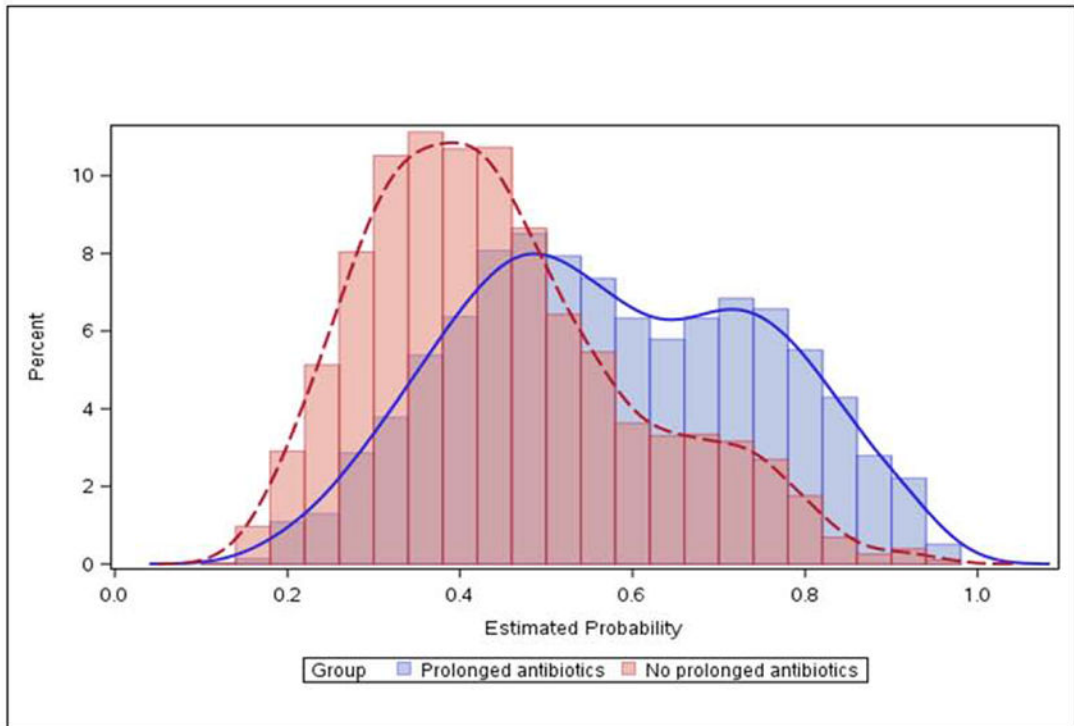


Figure 1, online: Derivation of study cohorts.

Figure 1, online legend: The 720 infants excluded from the EOS analysis due to missing outcome included 481 infants lost to follow-up, 140 with incomplete assessment, and 99 infants assessed outside of the allowable age. The 701 infants excluded from the prolonged antibiotic analysis due to missing outcome included 468 infants lost to follow-up, 135 with incomplete assessment, and 98 infants assessed outside of the allowable age. Abbreviations: GA, gestational age; BW, birth weight; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; EOS, early onset sepsis.



Propensity Score Information										
Observations	Prolonged antibiotics					No prolonged antibiotics				
	N	Mean	Std Dev	Minimum	Maximum	N	Mean	Std Dev	Minimum	Maximum
All with non-missing covariates	2936	0.576	0.177	0.154	0.969	2786	0.446	0.157	0.139	0.952
Matched	2181	0.515	0.155	0.154	0.956	2181	0.491	0.147	0.153	0.952

Figure 2,
online: Distribution of propensity score generated from demographics and early clinical presentation.

Table 1:

Maternal and Neonatal Characteristics for EOS analysis

n (column % or mean (standard deviation)) ^a	EOS N=153	Prolonged antibiotics N=3191	No prolonged antibiotics N=3221	p-value ^b
Maternal education				0.008
< High School degree	16 (13.2)	649 (22.8)	598 (21.3)	
High School degree	35 (28.9)	835 (29.3)	910 (32.4)	
> High School degree	70 (57.9)	1,361 (47.8)	1,298 (46.3)	
Unknown/missing	32	346	415	
Maternal medical insurance				0.007
Private	66 (44.9)	1,276 (40.6)	1,190 (37.2)	
Public/self-pay/other	81 (55.1)	1,864 (59.4)	2,005 (62.8)	
Unknown/missing	6	51	26	
Maternal race/ethnicity				0.03
Black, non-Hispanic	56 (37.3)	1,381 (43.3)	1,354 (42.2)	
White, non-Hispanic	57 (38.0)	1,160 (36.4)	1,236 (38.6)	
Hispanic	28 (18.7)	473 (14.8)	491 (15.3)	
Other	9 (6.0)	174 (5.5)	125 (3.9)	
Maternal hypertension	20 (13.1)	647 (20.3)	812 (25.2)	<0.001
Antepartum hemorrhage	32 (20.9)	628 (19.7)	709 (22.0)	0.07
Maternal clinical chorioamnionitis	65 (43.0)	769 (24.2)	323 (10.1)	<0.001
Maternal antibiotics during delivery admission	130 (85.5)	2,404 (75.9)	2,274 (70.8)	<0.001
Antenatal steroids	132 (87.4)	2,779 (87.4)	2,839 (88.3)	0.51
Cesarean section	87 (56.9)	1,908 (59.8)	2,159 (67.0)	<0.001
Membrane rupture				<0.001
>18 hours	77 (52.0)	983 (31.2)	639 (20.1)	
18 hours	71 (48.0)	2,164 (68.8)	2,536 (79.9)	
Unknown/missing	5	44	46	
Male	75 (49.0)	1,643 (51.5)	1,630 (50.7)	0.70
BW grams, mean (SD)	713(131)	700 (137)	726 (140)	<0.001

n (column %) or mean (standard deviation) ^a	EOS N=153	Prolonged antibiotics N=3191	No prolonged antibiotics N=3221	p-value ^b
GA weeks, mean (SD)	24.4 (1.1)	24.6 (1.1)	24.8 (1.0)	<0.001
By GA week				<0.001
22	7 (4.6)	63 (2.0)	50 (1.6)	
23	28 (18.3)	475 (14.9)	325 (10.1)	
24	49 (32.0)	915 (28.7)	785 (24.4)	
25	40 (26.1)	959 (30.1)	1,034 (32.1)	
26	29 (19.0)	779 (24.4)	1,027 (31.9)	
Endotracheal intubation at birth	141 (92.2)	2,742 (86.0)	2,571 (79.8)	<0.001
Infant temperature within 60 minutes of birth				0.04
96.5 F	111 (77.6)	2,127 (72.2)	2,244 (74.9)	
<96.5 F	32 (22.4)	819 (27.8)	753 (25.1)	
Unknown/missing	10	245	224	
Severe IVH diagnosed within 7 days				<0.001
Yes	27 (18.8)	328 (10.5)	233 (7.6)	
No	117 (81.3)	2,789 (89.5)	2,832 (92.4)	
No sonogram/missing	9	74	156	
Enteral feeds started within 3 days	22 (14.4)	805 (25.2)	1,146 (35.6)	<0.001
Survived > 24 hours, N	146	3,170	3,144	
Highest respiratory support at 24 hours				<0.001
High-frequency ventilation	56 (38.4)	770 (24.3)	325 (10.4)	
Conventional ventilation	72 (49.3)	1,810 (57.2)	1,873 (59.7)	
NIMV	3 (2.1)	121 (3.8)	172 (5.5)	
CPAP	12 (8.2)	389 (12.3)	674 (21.5)	
Other/no support	3 (2.1)	75 (2.4)	95 (3.0)	

BW, birth weight; CPAP, continuous positive airway pressure; GA, gestational age; IVH, intraventricular hemorrhage; NIMV, non-invasive intermittent mandatory ventilation;

^aMissing information is shown when missing for 1% of infants. Otherwise, information missing: maternal race/ethnicity, 21; maternal hypertension, 8; antepartum hemorrhage, 6; clinical chorioamnionitis, 20; antenatal antibiotics, 37; antenatal steroids, 18; cesarean section, 1; sex, 4; endotracheal intubation, 2; enteral feeds, 4; highest respiratory support at 24 h, 10 infants.

^bP-value by chi-square test (categorical variables) or T test (continuous variables).

Table 2.

Study Outcomes in EOS Analysis

	EOS n (%)	Prolonged antibiotics n (%)	No prolonged antibiotics n (%)	Adjusted RR ^a (95% CI) p-value	
				EOS vs. Prolonged antibiotics	EOS vs. No prolonged antibiotics
Infants, N	153	3,191	3,221		
Death/ NDI	104 (68.0)	1,732 (54.3)	1,640 (50.9)	1.18 (1.06-1.32) 0.003	1.23 (1.10-1.37) <0.001
Death	63 (41.2)	921 (28.9)	888 (27.6)	1.16 (0.97-1.40) 0.11	1.16 (0.96-1.40) 0.12
NDI Evaluation, N	90	2,270	2,333		
NDI	41 (45.6)	811 (35.7)	752 (32.2)	1.26 (0.99-1.60) 0.06	1.34 (1.05-1.71) 0.02
Bayley 3 cognitive composite score <85	38 (42.2)	745 (33.1)	695 (30.0)	1.26 (0.98-1.63) 0.07	1.34 (1.04-1.74) 0.02
GMFCS level 2	15 (16.7)	234 (10.3)	193 (8.3)	1.50 (0.91-2.46) 0.11	1.74 (1.05-2.88) 0.03
Bilateral blindness ^b	0 (0.0)	39 (1.7)	29 (1.2)	- 0.40	- 0.62
Hearing impairment ^b	2 (2.2)	75 (3.3)	59 (2.5)	0.67 (0.17-2.69) 0.77	0.88 (0.22-3.54) 1.0
Blindness or hearing impairment ^c	2 (2.2)	106 (4.7)	86 (3.7)	0.50 (0.12-2.01) 0.33	0.56 (0.14-2.29) 0.42

^aRR adjusted for study center, maternal education (<, =, > high school, missing), maternal insurance (private, public/other), maternal race/ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, other), maternal hypertension, antepartum hemorrhage, chorioamnionitis, antenatal antibiotics and steroids, cesarean, membrane rupture >18 hours, GA (22-26), BW (continuous), male sex, intubation, temperature 60 minutes, enteral feeds 3 days, severe IVH 7 days. Statistical significance determined by the Wald chi-square test.

^bRR of bilateral blindness not estimated for EOS comparisons. Unadjusted p-values and RRs for bilateral blindness and hearing impairment are shown.

^cStudy center could not be included in the model fit to the combined outcome blindness or hearing impairment as some centers had no children with either outcome.

Table 3,

online: EOS causing organisms

Organism(s)--Blood	Organism(s)--CSF ^a	n (column %)
Gram positive		42 (27.5)
	Viridans streptococci	1 (0.7)
Group B strep		28 (18.3)
Staph aureus		3 (2.0)
Viridans streptococci		3 (2.0)
Enterococcus		2 (1.3)
MRSA		2 (1.3)
Strep pneumoniae		2 (1.3)
Alpha hemolytic strep		1 (0.7)
Gram negative		100 (65.4)
	E. coli	1 (0.7)
E. coli		65 (42.5)
E. coli	E. coli	7 (4.6)
Haemophilus		10 (6.5)
Klebsiella		4 (2.6)
Acinetobacter		2 (1.3)
Capnocytophaga		2 (1.3)
Citrobacter		2 (1.3)
Morganella morganii		2 (1.3)
Bacteroides		1 (0.7)
Campylobacter		1 (0.7)
Eikenella corrodens		1 (0.7)
Pseudomonas aeruginosa		1 (0.7)
Sphingomonas paucimobilis		1 (0.7)
Fungi		2 (1.3)
Candida albicans		1 (0.7)
Saccharomyces		1 (0.7)
Polymicrobial		6 (3.9)
	Acinetobacter baumannii, Acinetobacter lwoffii, Micrococcus	1 (0.7)
E. coli, CONS		1 (0.7)
E. coli, Group B strep		1 (0.7)
E. coli, Strep viridans		1 (0.7)
Neisseria, Haemophilus		1 (0.7)
Strep bovis, Corynebacterium		1 (0.7)
Not specified		3 (2.0)
Missing		2 (1.3)

Organism(s)--Blood	Organism(s)--CSF ^a	n (column %)
Other bacteria (699)		1 (0.7)
Total number of cases		153

^aThree of the 10 infants with a positive CSF culture had meningitis alone (1 Viridans streptococci, 1 E. coli, 1 Acinetobacter plus Micrococcus); 7 had E. coli on both blood and CSF cultures.

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Table 4. Smaller Standardized Difference for Maternal and Neonatal Characteristics After Propensity Score Matching^a.

	Original Sample			Matched Sample		
	Prolonged antibiotics n=2936	No prolonged antibiotics n=2786	Standardized difference	Prolonged antibiotics n=2181	No prolonged antibiotics n=2181	Standardized difference
Maternal education						
< High School degree	597 (20.3)	533 (19.1)	0.030	442 (20.3)	439 (20.1)	0.003
High School degree	788 (26.8)	813 (29.2)	0.052	605 (27.7)	618 (28.3)	0.013
> High School degree	1,280 (43.6)	1,176 (42.2)	0.028	929 (42.6)	924 (42.4)	0.005
Maternal medical insurance						
Private	1,174 (40.0)	1,029 (36.9)	0.063	826 (37.9)	828 (38.0)	0.002
Maternal race/ethnicity						
Black, non-Hispanic	1,278 (43.5)	1,194 (42.9)	0.014	965 (44.2)	972 (44.6)	0.006
White, non-Hispanic	1,063 (36.2)	1,072 (38.5)	0.047	786 (36.0)	779 (35.7)	0.007
Hispanic	433 (14.7)	418 (15.0)	0.007	330 (15.1)	336 (15.4)	0.008
Maternal hypertension	591 (20.1)	733 (26.3)	0.147	501 (23.0)	518 (23.8)	0.019
Antepartum hemorrhage	571 (19.4)	597 (21.4)	0.049	432 (19.8)	442 (20.3)	0.011
Maternal clinical chorioamnionitis	719 (24.5)	269 (9.7)	0.402	323 (14.8)	269 (12.3)	0.067
Maternal antibiotics during delivery admission	2,243 (76.4)	1,992 (71.5)	0.112	1,606 (73.6)	1,583 (72.6)	0.024
Antenatal steroids	2,586 (88.1)	2,504 (89.9)	0.057	1,930 (88.5)	1,936 (88.8)	0.009
Cesarean section	1,764 (60.1)	1,887 (67.7)	0.160	1,370 (62.8)	1,407 (64.5)	0.035
Membrane rupture > 18 hours	927 (31.6)	569 (20.4)	0.256	563 (25.8)	527 (24.2)	0.038
GA week						
22	47 (1.6)	30 (1.1)	0.046	24 (1.1)	26 (1.2)	0.008
23	414 (14.1)	226 (8.1)	0.191	246 (11.3)	216 (9.9)	0.044
24	836 (28.5)	652 (23.4)	0.116	589 (27.0)	568 (26.0)	0.022
25	900 (30.7)	923 (33.1)	0.053	708 (32.5)	706 (32.4)	0.002
BW grams, mean (SD)	705 (137)	735 (138)	0.223	716 (137)	721 (137)	0.043
Male	1,509 (51.4)	1,371 (49.2)	0.044	1,118 (51.3)	1,105 (50.7)	0.012

	Original Sample		Standardized difference	Matched Sample		Standardized difference
	Prolonged antibiotics n=2936	No prolonged antibiotics n=2786		Prolonged antibiotics n=2181	No prolonged antibiotics n=2181	
Endotracheal intubation at birth	2,520 (85.8)	2,192 (78.7)	0.188	1,826 (83.7)	1,815 (83.2)	0.013
Infant temperature within 60 minutes of birth						
96.5 F	1,977 (67.3)	1,998 (71.7)	0.095	1,507 (69.1)	1,505 (69.0)	0.002
< 96.5 F	741 (25.2)	612 (22.0)	0.077	519 (23.8)	528 (24.2)	0.010
Highest respiratory support at 24 hours						
High-frequency ventilation	689 (23.5)	230 (8.3)	0.426	317 (14.5)	230 (10.5)	0.112
Conventional ventilation	1,684 (57.4)	1,652 (59.3)	0.039	1,366 (62.6)	1,402 (64.3)	0.033
NIMV	117 (4.0)	166 (6.0)	0.091	101 (4.6)	111 (5.1)	0.021
CPAP	375 (12.8)	650 (23.3)	0.277	340 (15.6)	378 (17.3)	0.046
Severe IVH diagnosed within 7 days	252 (8.6)	120 (4.3)	0.175	142 (6.5)	117 (5.4)	0.047
Enteral feeds started within 3 days	773 (26.3)	1,091 (39.2)	0.276	635 (29.1)	649 (29.8)	0.014

BW, birth weight; CPAP, continuous positive airway pressure; GA, gestational age; IVH, intraventricular hemorrhage; NIMV, non-invasive intermittent mandatory ventilation; SD, standard deviation.

^aN (%) are shown for all variables except BW reported as mean and standard deviation. Standardized differences are shown as absolute value. The original sample includes 5722 infants with all non-missing values of the covariates included in the propensity score model from the total 5807 infants in the complete cohort. Categorical variables with missing values for 1% of infants were entered in the model with a level indicating missing in order to minimize the number of observations excluded due to missing values (maternal education, 10% missing; maternal medical insurance, 1%; membrane rupture >18 hours, 1%; infant temperature within 60 minutes of birth, 7%; severe IVH diagnosed with 7 days, 1%).

Table 5.

Study Outcomes in Propensity-Score Matched Sample

	Prolonged antibiotics	No prolonged antibiotics	RR (95% CI) ^a	p-value ^d
In infants, n	2,181	2,181		
Death/NDI, n (%) - with adjustment for key covariates ^b	1,091 (50.0)	1,047 (48.0)	1.04 (0.98-1.11)	0.18 0.09
Death before follow-up, n (%) - with adjustment for key covariates ^b	512 (23.5)	469 (21.5)	1.09 (0.98-1.22)	0.12 0.17
Survived to follow-up and evaluated, n	1,669	1,712		
NDI, n (%) - with adjustment for key covariates ^b	579 (34.7)	578 (33.8)	1.03 (0.94-1.13)	0.57 0.25
Bayley 3 cognitive composite score <85 - with adjustment for key covariates ^b	530 (32.0)	533 (31.4)	1.02 (0.92-1.13)	0.70 0.29
GMFCS level 2 - with adjustment for key covariates ^b	162 (9.7)	155 (9.1)	1.07 (0.87-1.33)	0.50 0.14
Bilateral blindness	27 (1.6)	24 (1.4)	1.15 (0.67-1.97)	0.61
Hearing impairment	58 (3.5)	49 (2.9)	1.22 (0.85-1.76)	0.29
Blindness or hearing impairment - with adjustment for key covariates ^{b,c}	79 (4.8)	71 (4.2)	1.15 (0.84-1.56)	0.38 0.36

^aRelative risks (RR) and confidence intervals (CI) from log binomial (for primary comparisons) or Poisson regression models (for models with post-match adjustment) using methods that account for the matched pair design with statistical significance determined by the Wald chi-square test. Poisson models were used due to convergence problems with log binomial models when covariates were added.

^bCovariates used in post-matching adjustment included important confounders (study center; maternal education; infant GA; BW; male sex; severe IVH diagnosed within 7 days of birth), as well as highest respiratory support at 24 hours of life due to some evidence of residual imbalance after matching based on a standardized mean difference between groups >0.10 for one level (High-Frequency ventilation, 0.112).

^cStudy center could not be included in the model fit to the combined outcome blindness or hearing impairment as some centers had no children with either outcome.

Table 6,

online: Characteristics of unmatched infants

n (column % or mean (standard deviation)) ^a	Prolonged antibiotics n=797	No prolonged antibiotics n=648	p-value ^b
Maternal education			0.001
< High School degree	164 (22.8)	101 (17.6)	
High School degree	193 (26.8)	205 (35.7)	
> High School degree	363 (50.4)	269 (46.8)	
Unknown/missing	77	73	
Maternal medical insurance			<0.001
Private	360 (46.9)	220 (34.1)	
Public/self-pay/other	408 (53.1)	425 (65.9)	
Unknown/missing	29	3	
Maternal race/ethnicity			<0.001
Black, non-Hispanic	326 (41.0)	233 (36.8)	
White, non-Hispanic	296 (37.2)	306 (48.3)	
Hispanic	109 (13.7)	87 (13.7)	
Other	64 (8.1)	8 (1.3)	
Unknown/missing	2	14	
Maternal hypertension	98 (12.4)	221 (34.3)	<0.001
Antepartum hemorrhage	149 (18.7)	166 (25.7)	0.001
Maternal clinical chorioamnionitis	402 (50.9)	7 (1.1)	<0.001
Maternal antibiotics during delivery admission	651 (84.0)	430 (67.0)	<0.001
Unknown/missing	22	6	
Antenatal steroids	684 (86.9)	602 (93.8)	<0.001
Unknown/missing	10	6	
Cesarean section	420 (52.8)	513 (79.2)	<0.001
Membrane rupture			<0.001
>18 hours	374 (47.6)	54 (8.5)	
18 hours	412 (52.4)	583 (91.5)	

n (column %) or mean (standard deviation) ^a	Prolonged antibiotics n=797	No prolonged antibiotics n=648	p-value ^b
Unknown/missing	11	11	
GA weeks, mean (SD)	24.3 (1.1)	25.3 (0.8)	<0.001
By GA week			<0.001
22	25 (3.1)	4 (0.6)	
23	174 (21.8)	11 (1.7)	
24	262 (32.9)	96 (14.8)	
25	201 (25.2)	230 (35.5)	
26	135 (16.9)	307 (47.4)	
BW grams, mean (SD)	673 (130)	785 (130)	<0.001
Male	414 (52.0)	285 (44.2)	0.003
Endotracheal intubation at birth	731 (91.8)	414 (64.0)	<0.001
Infant temperature within 60 minutes of birth			<0.001
96.5 F	495 (68.1)	525 (84.8)	
< 96.5 F	232 (31.9)	94 (15.2)	
Unknown/missing	70	29	
Highest respiratory support at 24 hours			<0.001
High-frequency ventilation	385 (48.6)	1 (0.2)	
Conventional ventilation	338 (42.7)	276 (42.9)	
NIMV	17 (2.1)	55 (8.5)	
CPAP	38 (4.8)	282 (43.8)	
Other/no support	14 (1.8)	30 (4.7)	
Severe IVH diagnosed within 7 days			<0.001
Yes	114 (14.4)	4 (0.6)	
No	679 (85.6)	637 (99.4)	
No sonogram/missing	4	7	
Enteral feeds started within 3 days	147 (18.5)	454 (70.4)	<0.001

BW, birth weight; CPAP, continuous positive airway pressure; EOS, early-onset sepsis; GA, gestational age; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; NIMV, non-invasive intermittent mandatory ventilation; SIP, spontaneous intestinal perforation.

^aThe number of infants with unknown/missing information is shown for characteristics with information missing for 1% of infants. Otherwise, information was missing for: maternal hypertension, 7; antepartum hemorrhage, 4; maternal clinical chorioamnionitis, 12; cesarean section, 1; male sex, 4; endotracheal intubation, 2; highest respiratory support at 24 h, 9; enteral feeds within 3 days, 4 infants.

p -value by chi-square test (categorical variables) or T test (continuous variables).

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