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Neurodevelopmental Outcomes following Neonatal Late-Onset Sepsis and Blood Culture-Negative Conditions

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Abstract

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Objective: Determine risk of death or neurodevelopmental impairment (NDI) in infants with late-onset sepsis (LOS) versus late-onset, antibiotic-treated, blood culture-negative conditions (LOCNC).

Design: Retrospective cohort study

Setting: 24 neonatal centers.

Patients: Infants born 1/1/2006–12/31/2014, at 22–26 weeks gestation, with birth weight 401–1000 grams and surviving >7 days were included. Infants with early-onset sepsis, necrotizing enterocolitis, intestinal perforation, or both LOS and LOCNC were excluded.

Exposures: LOS and LOCNC were defined as antibiotic administration for ≥5 days with and without a positive blood/CSF culture, respectively. Infants with these diagnoses were also compared to infants with neither condition.

Outcomes: Death or NDI assessed at 18–26 months corrected age follow-up. Modified Poisson regression models were used to estimate relative risks adjusting for covariates occurring ≤7 days of age.

Results: Of 7354 eligible infants, 3940 met inclusion criteria: 786 (20%) with LOS, 1601 (41%) with LOCNC, and 1553 (39%) with neither. Infants with LOS had higher adjusted relative risk [95% CI] for death/NDI (1.14 [1.05–1.25]) and death before follow-up (1.71 [1.44–2.03]) than those with LOCNC. Among survivors, risk for NDI did not differ between the two groups (0.99 [0.86–1.13]) but was higher for LOCNC infants (1.17 [1.04–1.31]) compared to unaffected infants.

Conclusions: Infants with LOS had higher risk of death, but not NDI, compared to infants with LOCNC. Surviving infants with LOCNC had higher risk of NDI compared to unaffected infants. Improving outcomes for infants with LOCNC requires study of the underlying conditions and the potential impact of antibiotic exposure.

Keywords

Neonatology; Epidemiology; Intensive Care Medicine

INTRODUCTION

Preterm infants are diagnosed with late-onset sepsis (LOS), defined as positive blood or cerebrospinal fluid (CSF) culture obtained >72 hours of age, at rates varying from 10–30%.[1, 2] Infants with culture-confirmed infections are at higher risk for abnormal neuroimaging findings and neurodevelopmental impairment (NDI) compared to uninfected infants.[3–10] In analyses of infants born 1993–2001 with birth weight 401–1000 grams and admitted to hospitals in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN), infants administered antibiotics ≥5 days in the absence of a positive blood culture also had a higher risk of NDI compared to uninfected infants.[6]

Although many studies refer to the concept of “culture-negative sepsis” there is uncertainty regarding this entity, including whether in some cases, infection is truly present.[11] LOS and late-onset, blood-culture negative conditions (LOCNCs) share clinical presentations

and by definition, both are managed with antibiotics. While LOS is a culture-based diagnosis,[1, 8, 9, 12] LOCNC is variably defined as a combination of clinical signs suggesting sepsis with or without inflammatory markers, sterile blood cultures and the clinical team's decision to administer variable durations of antibiotics.[6, 7, 9, 10, 12, 13] LOCNC is frequently considered as the equivalent of 'missed' LOS. Studies often describe outcomes for preterm infants with LOS or LOCNC separately and compared with uninfected infants as reference; few studies directly compare outcomes of infants with LOS and LOCNC.[14] Such a comparison would reveal differences between the two conditions, measuring not whether these conditions have an effect on outcomes but whether the effects differ in magnitude or character between the two diagnoses.

Our objective was to compare risk of death or NDI among infants with LOS compared to infants with LOCNC. Infants with LOS or LOCNC were also compared to unaffected infants.

METHODS

Setting:

This is a retrospective cohort study of infants with gestational age (GA) 22 0/7–26 6/7 weeks, birth weight (BW) 401–1000 grams, no major birth defect, born at NRN centers 1/1/2006–12/31/2014 and enrolled in the NRN registry of extremely preterm infants. The registry included clinical information prospectively collected during the birth hospitalization of infants. Details of the registry are noted in the Supplementary Appendix. Surviving infants were eligible for a follow-up developmental assessment. The institutional review board at each center approved participation in the registry and the follow-up study, with waiver of consent or written parental consent as required by individual sites.

Study definitions:

LOS was defined as isolation of a pathogen from blood or CSF obtained >72 hours of age and appropriate therapy for ≥5 days (≥7 days for CSF growth) or death before completed treatment. Cultures growing Bacillus, Micrococcus, and Corynebacterium were considered contaminants and were excluded. Polymicrobial cultures were counted as LOS cases if at least one species was a pathogen. Cultures growing coagulase-negative staphylococci (CoNS) were counted as LOS cases unless an additional contaminant organism was also isolated. Six infants whose only positive culture grew Bacillus species were excluded. LOCNC was defined as antibiotics administered for ≥5 days or death before completed treatment, without a positive blood culture obtained >72 hours of age. Brain injury was defined as cranial imaging with ≥1 of the following: severe (≥Grade 3) intraventricular hemorrhage (IVH),[15] periventricular leukomalacia, porencephalic cyst, ventriculomegaly, or cerebellar hemorrhage.

Three exposure groups were identified: (1) LOS: infants with ≥1 episode of LOS and no episode of LOCNC; (2) LOCNC: infants with ≥1 episode of LOCNC and no LOS episode; (3) Unaffected: infants without either LOS or LOCNC. We excluded infants with conditions

whose management overlaps with LOS or LOCNC including infants with both conditions, culture-confirmed early-onset sepsis, necrotizing enterocolitis[16] and intestinal perforation.

Due to early mortality, many extremely preterm infants do not live long enough to suffer LOS/LOCNC.[17] To decrease survival bias, we restricted analysis to infants surviving >7 days, which still allowed us to capture the majority of LOS cases (Supplementary Figure 1). We also excluded survivors missing neurodevelopmental assessment.

Outcomes:

The primary outcome was survival with NDI or death at >7 days age and before follow-up. Secondary outcomes were death and NDI assessed separately. *Neurodevelopmental assessment*: Surviving infants were assessed at 18–22 months (births before 7/1/2012) or 22–26 months (births on or after 7/1/2012) corrected age (CA). Neurodevelopmental outcomes assessed at <14 months or >30 months CA (2% of those assessed) were considered missing data. Assessment included a physical examination of the child and an interview with the primary caretaker to review clinical history. A neurologic examination and a developmental evaluation using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-3) were administered by certified examiners.[18] Motor function was classified using the gross motor function classification system (GMFCS) and cerebral palsy (CP) was classified using the GMFCS scores: mild (level 1), moderate (level 2–3), or severe (level 4–5).[19] Bilateral blindness was defined as corrected vision <20/200 in both eyes. Hearing impairment was defined as permanent hearing loss with or without amplification. NDI was defined as ≥1 of the following: bilateral blindness, hearing impairment, GMFCS level ≥2 with or without CP, or a Bayley-3 cognitive composite score <85.

Statistical analysis:

Statistical significance for unadjusted comparisons between infants was determined by $\chi 2$ test for categorical variables and student's *t* test for continuous variables. Poisson regression models with robust variance estimators[20] were used to assess risk of outcomes in the exposure groups while adjusting for the following pre-exposure covariates: maternal education, insurance, race/ethnicity, antenatal antibiotics, antenatal steroids, antepartum hemorrhage, infant GA, BW, sex, temperature at ≤60 minutes of birth, intubation at birth, maximum respiratory support ≤24 hours of age, enteral feeds started ≤3 days of birth, receipt of antibiotics for ≥5 days starting ≤72 hours of age, severe IVH diagnosed ≤7 days of birth and center. Maternal hypertension, chorioamnionitis, delivery mode and membrane rupture were not associated with death/NDI in univariate comparisons and not included in the models. Categorical variables with missing values for ≥1% of infants were entered in models with a level indicating missing. Risk of NDI associated with multiple episodes was assessed in a separate model that categorized exposure group as 0, 1, 2, or 3+ LOS or LOCNC episodes. Adjusted relative risks, 95% confidence intervals (CI), and p-values by the Wald $\chi 2$ test from these models were reported. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study population:

After exclusions, 3940 infants were included (Figure 1): 786 (20%) infants were diagnosed with LOS, 1601 (41%) with LOCNC, and 1553 (39%) were unaffected. Across study sites, the prevalence of infants diagnosed with LOS ranged from 8–37% and with LOCNC ranged from 23–63% (Supplementary Figure 2). All centers, except two, had a higher frequency of LOCNC diagnosis than LOS, and there was no relation between center-specific rates of LOS and LOCNC. Overall, 579 (15%) infants in the study cohort died before follow-up and 3881 (87%) surviving infants were evaluated for NDI. Follow-up visits were completed between October 2007 and August 2017.

Microbiology:

LOS pathogens were isolated only from blood in 742 cases, only from CSF in 13 cases and from both in 31 infants (Supplementary Table 1). The most common organisms isolated from blood were CoNS (52%), *Staphylococcus aureus* (13%), and *Escherichia coli* (7%). Among 44 cases of meningitis, CoNS (17/44, 39%) was the most common organism. The median age of LOS diagnosis was 14 days (interquartile range 9–22) for the first episode and 29 days (interquartile range 18–41) for the second episode (Supplementary Figure 1). The age of onset was not recorded for LOCNC.

Clinical characteristics:

Most maternal characteristics did not differ between the three groups, although several infant characteristics differed, mainly between infants with LOS or LOCNC and unaffected infants (Table 1). Infant characteristics were not different between infants with LOS and LOCNC except infants with LOCNC were born at higher GA (p=0.03) and a greater proportion of them had received early (≤72 hours) antibiotics for ≥5 days without culture-confirmed infection (44% LOS vs. 57% LOCNC, p<0.001).

In-hospital morbidities were also higher among infected versus unaffected infants (Table 2). Infants with LOS had higher frequency of brain injury than infants with LOCNC (29% vs. 24%, p=0.005) and lower survival at 36 weeks CA (77% LOS vs. 91% LOCNC, p<0.001). Among infants surviving to 36 weeks CA, bronchopulmonary dysplasia was more prevalent in infants with LOCNC (66%) than infants with LOS (60%), p=0.01.

Death and NDI:

LOS vs. LOCNC: The adjusted relative risk for the primary composite outcome of death or NDI was significantly higher for infants with LOS compared to those with LOCNC, as was the risk of death alone before follow-up (Table 3). Among survivors assessed at follow-up, the proportion of infants with NDI was similar in the LOS (32%) and LOCNC (33%) groups and the infants had a comparable adjusted risk for NDI. Surviving infants with LOCNC had a higher risk for GMFCS level ≥2 than infants with LOS.

LOS/LOCNC vs. unaffected infants: Infants with either LOS or LOCNC were at significantly higher risk for death/NDI than unaffected infants (Table 3). Infants with LOS

had a greater risk of death than unaffected infants but infants with LOCNC did not. While the adjusted risk estimates for NDI among survivors with LOS and LOCNC were higher than that for unaffected infants, the risk was statistically significant only for LOCNC infants. Differences in risk for components of NDI were found between those with LOCNC and unaffected infants but not between infants with LOS and unaffected infants.

Multiple episodes:

Among infants assessed at follow-up, more infants had repeated episodes of LOCNC (36%) than LOS (23%) (Table 4). Risk of NDI was increased for infants who had ≥2 episodes of LOCNC compared to those with one episode. While the proportion of infants with NDI increased from 31% to 35% to 42% among infants who had 1, 2 or ≥3 LOS episodes the adjusted risk of multiple episodes was not significantly different compared to one episode.

DISCUSSION

While infants with LOS and LOCNC did not differ in most clinical characteristics, those with LOS had higher risk of the combined outcome of death or NDI and of death alone before follow-up, when compared to either infants with LOCNC or to unaffected infants. Risk of death did not differ for infants with LOCNC and unaffected infants. The relationships between LOS, LOCNC and NDI among surviving infants were less straightforward. While brain injury was more common among infants with LOS than with LOCNC and in both groups approximately one-third of surviving infants had NDI compared to one-fourth of unaffected infants, the adjusted relative risk of NDI for infants with LOS compared to unaffected infants did not reach statistical significance. In contrast, the adjusted risk of NDI was greater for infants with LOCNC compared to those with no identified infection. The risk of NDI also increased significantly with repeated episodes of LOCNC, but not with LOS episodes. The smaller number of surviving infants with LOS (compared with LOCNC) may have contributed to these findings.

Few studies have specifically compared infants with LOS to infants with LOCNC.[14] In doing so, we found a significantly increased risk of mortality among infants with LOS (Table 3). We eliminated from the analysis 875 infants (11.9% of eligible) with both LOS and LOCNC, to ensure a clear comparison. We defined LOCNC by administration of ≥5 days of antibiotics in the absence of blood or CSF-confirmed infection. This diagnosis can be due to non-systemic bacterial infection, missed bacterial infection, or to non-bacterial or non-infective conditions.[21, 22] Etiologies such as urinary tract infection have a lower mortality risk than bacteremia and may have contributed to our findings. Frequently, however, LOCNC diagnoses reflect a concern for ‘false negative’ blood cultures.[21, 22] Inadequate inoculant volume is reported as one driver of false negative cultures.[23–25] The lower mortality observed among LOCNC infants (compared to infants with LOS) would not support the concern that LOCNC cases were predominantly due to false negatives from inadequate inoculant. A second concern is that of ‘low-level’ bacteremia.[26] The vast majority of organisms between 1–10 CFU/mL can be detected reliably with one mL of blood.[27, 28] Whether the majority of LOCNC cases occur due to low-level bacteremia and whether standard antibiotic regimens are effective or necessary in such cases requires

further study.[11] Finally, LOCNC may also simply reflect non-infectious causes of infant decompensation difficult to distinguish from bacterial sepsis using clinical judgment and laboratory markers – causes that would not respond to antibiotic therapy and may have a differential risk of mortality and morbidity.[21, 22, 29]

Bacteremia/meningitis in premature infants is known to be associated with white matter abnormalities[5, 30] and NDI in early childhood[6, 12, 31] that persists at school age.[8–10, 32] However, the association of LOCNC and NDI is less clear. A prior NRN study found higher odds of NDI among infants with culture-confirmed infection and with LOCNC compared to uninfected infants.[6] Culture-confirmed infection in that study, however, included early-onset sepsis and did not address infants with exclusive LOS versus LOCNC. Two other studies of infants born at <28 weeks gestation, in contrast, reported no difference in developmental outcomes at 10 years of age for infants with presumed infection compared to uninfected infants.[10, 33] A similar lack of association has been reported by other investigators.[9, 12] Some of the differences between studies may be from different definitions of presumed infection and inclusion of localized infection in the definition of culture-confirmed infection.[9, 10] We found significantly increased risk for NDI with LOCNC that increased with multiple episodes (Table 3, 4). The mechanisms for neurologic injury attributed to LOCNC are likely related to its etiology. When attributable to bacteremia/meningitis not isolated in culture, or to localized bacterial infection, LOCNC-associated NDI may share pathogenesis with LOS. However, when viral infection or non-infectious causes of clinical decompensation lead to LOCNC diagnosis, injury may be attributed to a failure to provide appropriate therapies, as well as to dysbiosis from ineffective antibiotics.[21, 22, 34–36]

Our study is limited by the fact that dates of LOCNC episodes were not collected, and therefore we could not do an age-based comparison between the three groups. Specific information about the clinical conditions recorded as LOCNC, and clinical parameters associated with LOS and LOCNC that could define severity of illness were not collected. Thus, we cannot say with certainty whether LOCNC infants actually were infected with a bacterial/fungal pathogen the team failed to isolate; or if they were evaluated and treated with antibiotics for clinical instability that was non-infectious in origin, or due to a viral pathogen – and the reason for that instability led to neurodevelopmental consequences. Future studies that include data on type and severity of the clinical instability, for both LOS and LOCNC episodes, may be better able to distinguish specific outcome patterns to inform prevention and intervention strategies.

CONCLUSIONS

LOCNC is a commonly diagnosed condition, occurring twice as often in our study compared to LOS and with more frequent recurrences. Conservatively, this translated to ~2.8 times more antibiotic courses for LOCNC than for LOS. While less life-threatening than LOS, LOCNC was associated with worse neurological outcomes compared to unaffected infants. It remains unclear whether this injury is due to the etiology of decompensation or due to management decisions, including use of antibiotics. We use the term “late-onset culture-negative condition” rather than “late-onset culture-negative sepsis” to underscore the uncertainty in this diagnosis, and highlight the need for better diagnostic tools to

evaluate sick newborns. Quality improvement efforts to reduce the incidence of LOS have successfully relied on interventions targeting LOS pathophysiology.[1, 37] Poor understanding of both the etiology of LOCNC and of the impact of antibiotic exposures on brain development, presents a barrier to improving outcomes.[11, 13, 34, 35] In the era of antibiotic stewardship, knowing the suspected adverse consequences of antibiotic misuse, a more accurate diagnosis would allow us to limit antibiotic usage to infants with clear need, and devise targeted interventions for other etiologies of LOCNC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BPD	Bronchopulmonary dysplasia

BW	Birth weight
CA	Corrected age
CoNS	Coagulase-negative Staphylococci
CP	Cerebral palsy
CSF	Cerebrospinal fluid
ELBW	Extremely low birth weight infant
GA	Gestational age
LOS	Late-onset sepsis
LOCNC	Late-onset blood culture negative condition
NEC	Necrotizing enterocolitis
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NRN	Neonatal Research Network
PMA	Postmenstrual age
PVL	Periventricular leukomalacia
SIP	Spontaneous intestinal perforation

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What is already known on this topic:

Compared to unaffected infants, infants with late-onset sepsis and antibiotic-treated, blood culture-negative conditions have variably higher risks for death and neurodevelopmental impairment.

What this study adds:

Extremely preterm infants with late-onset sepsis had higher risk of death but similar risk of neurodevelopmental impairment, compared to infants with blood culture-negative conditions.

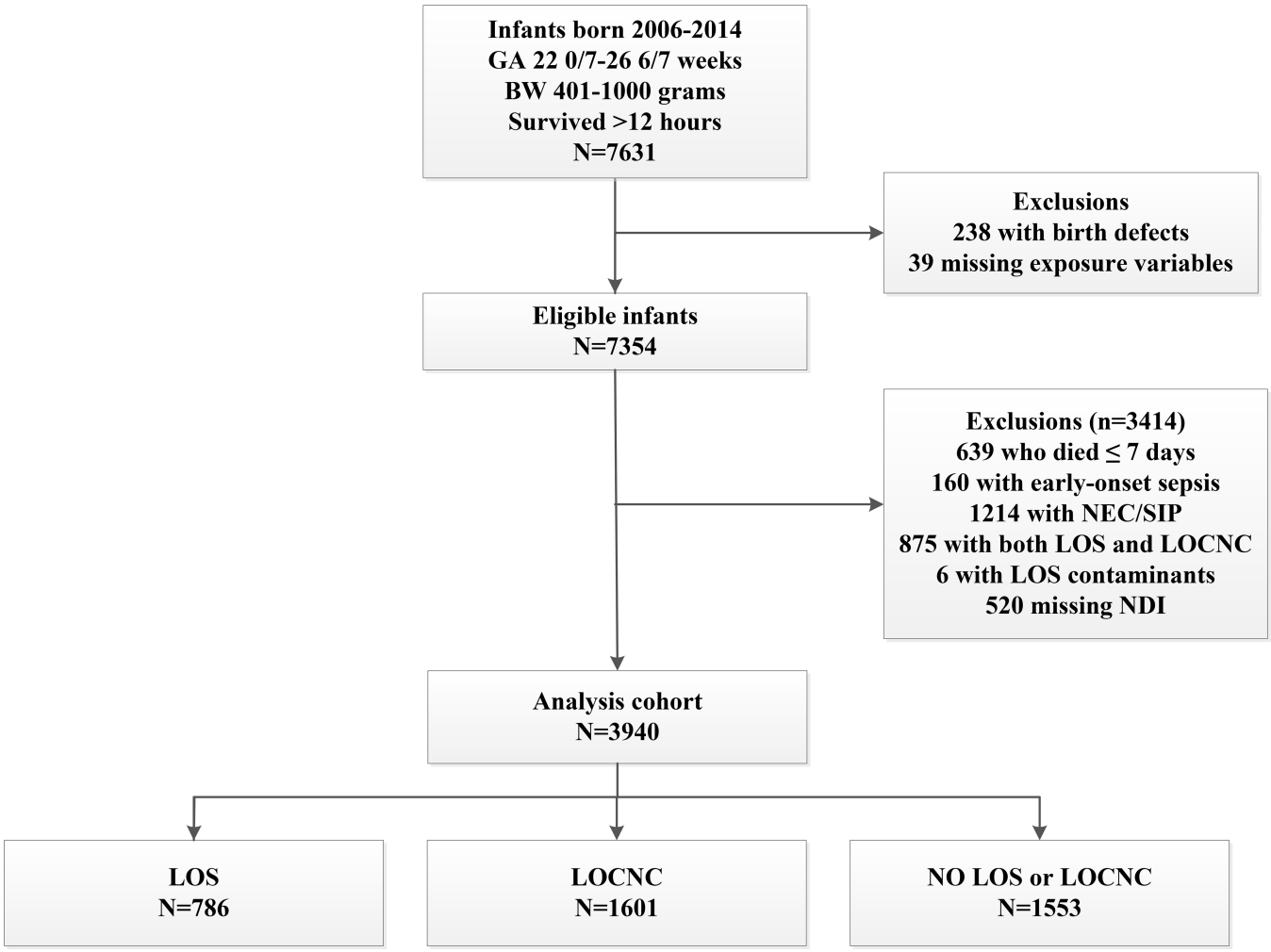

Figure 1. Derivation of the study cohort.

BW, birth weight. GA, gestational age. LOS, late-onset sepsis. LOCNC, late-onset blood culture-negative condition. NEC, necrotizing enterocolitis. NDI, neurodevelopmental impairment. SIP, spontaneous intestinal perforation.

Table 1:

Maternal, Delivery, and Neonatal Characteristics

n (column %) or mean (standard deviation)[1]	LOS n=786	LOCNC n=1601	Unaffected n=1553	p-value[2]
Maternal and delivery characteristics				
Maternal education				0.17
< High school degree	162 (22.9)	298 (20.0)	303 (21.0)	
High school degree	223 (31.5)	467 (31.4)	412 (28.6)	
> High school degree	322 (45.5)	724 (48.6)	725 (50.3)	
Unknown/missing	79	112	113	
Maternal medical insurance				0.32
Private	298 (38.3)	645 (40.6)	640 (41.6)	
Public/self-pay/other	480 (61.7)	944 (59.4)	900 (58.4)	
Maternal race/ethnicity				0.10
Black, non-Hispanic	317 (40.5)	710 (44.4)	630 (40.8)	
White, non-Hispanic	293 (37.4)	612 (38.3)	615 (39.8)	
Hispanic	130 (16.6)	210 (13.1)	231 (15.0)	
Other	43 (5.5)	67 (4.2)	69 (4.5)	
Maternal hypertension	185 (23.5)	386 (24.1)	337 (21.7)	0.27
Antepartum hemorrhage	163 (20.8)	306 (19.1)	328 (21.1)	0.35
Maternal clinical chorioamnionitis	107 (13.6)	281 (17.6)	274 (17.7)	0.03
Maternal antibiotics during delivery admission	568 (72.5)	1,161 (72.7)	1,172 (75.8)	0.09
Antenatal steroids	697 (88.8)	1,426 (89.3)	1,379 (89.0)	0.92
Cesarean section	502 (63.9)	1,052 (65.8)	1,027 (66.1)	0.54
Rupture of membranes				0.02
>18 hours	179 (23.2)	418 (26.5)	442 (28.9)	
≤ 18 hours	591 (76.8)	1,162 (73.5)	1,090 (71.1)	
Unknown/missing	16	21	21	
Infant characteristics				
GA weeks, mean (SD)	24.7 (1.0)	24.8 (1.0)	25.1 (1.0)	<0.001
By GA week				<0.001
22	10 (1.3)	16 (1.0)	11 (0.7)	
23	94 (12.0)	152 (9.5)	96 (6.2)	
24	216 (27.5)	441 (27.5)	275 (17.7)	
25	261 (33.2)	509 (31.8)	511 (32.9)	
26	205 (26.1)	483 (30.2)	660 (42.5)	
BW grams, mean (SD)	708 (135)	717 (135)	762 (137)	<0.001
Male	389 (49.6)	827 (51.7)	670 (43.2)	<0.001
Endotracheal intubation at birth	661 (84.1)	1345 (84.0)	1205 (77.6)	<0.001
Infant temperature ≤60 minutes age				<0.001

n (column %) or mean (standard deviation)[1]	LOS n=786	LOCNC n=1601	Unaffected n=1553	p-value[2]
≥ 96.5 F	527 (72.6)	1105 (74.2)	1170 (79.8)	
< 96.5 F	199 (27.4)	385 (25.8)	296 (20.2)	
Unknown/missing	60	111	87	
Highest respiratory support at 24 hours of age				<0.001
High-frequency ventilation	123 (15.7)	275 (17.2)	192 (12.4)	
Conventional ventilation	459 (58.6)	959 (59.9)	804 (51.9)	
NSIMV	41 (5.2)	77 (4.8)	96 (6.2)	
CPAP	129 (16.5)	255 (15.9)	400 (25.8)	
Other/no support	31 (4.0)	34 (2.1)	58 (3.7)	
Antibiotics ≥ 5 days started <72 hours of age for suspected early-onset sepsis[3]	346 (44.0)	911 (56.9)	684 (44.0)	<0.001
Enteral feeds started within 3 days	225 (28.7)	522 (32.6)	632 (40.7)	<0.001

BW, birth weight. CPAP, continuous positive airway pressure. GA, gestational age. LOS, late-onset sepsis. LOCNC, late-onset blood culture-negative condition. NSIMV, nasal synchronized intermittent mandatory ventilation.

[1]The number of infants with unknown/missing information is shown for characteristics with information missing for ≥1% of infants. Otherwise, information was missing for (n) infants: maternal medical insurance (33); maternal race/ethnicity (13); maternal hypertension (4); antepartum hemorrhage (2); maternal clinical chorioamnionitis (7); maternal antibiotics (14); antenatal steroids (8); cesarean section delivery (1); male sex (3); highest respiratory support at 24 hours of age (7); enteral feeds within 3 days (4).

[2]P-value by chi-square test (categorical variables) or T test (continuous variables).

[3]Exact duration of antibiotic use was not collected.

Table 2:

In-hospital morbidities

n (column %)[1]	LOS n=786	LOCNC n=1601	Unaffected n=1553	p-value[2]
Infants with cranial imaging, N	781	1597	1547	
IVH any grade	295 (37.9)	525 (33.0)	447 (28.9)	<0.001
Severe IVH	167 (21.5)	262 (16.5)	225 (14.6)	<0.001
Severe IVH diagnosed within 7 days of birth	48 (6.2)	77 (4.8)	89 (5.8)	0.33
Ventriculomegaly	200 (25.6)	334 (20.9)	242 (15.6)	<0.001
Cerebellar hemorrhage[3]	7/291 (2.4)	19/717 (2.6)	11/794 (1.4)	0.20
Periventricular leukomalacia	39 (5.0)	96 (6.0)	54 (3.5)	0.004
Porencephalic cyst	14 (1.8)	45 (2.8)	29 (1.9)	0.13
Brain injury[4]	228 (29.3)	381 (23.9)	290 (18.8)	<0.001
Survived in-hospital at 28 d, N	634	1490	1414	
Had ROP exam	609	1456	1390	
ROP	474 (77.8)	1100 (75.5)	883 (63.5)	<0.001
ROP stage 3 or worse	137 (22.5)	319 (21.9)	194 (14.0)	<0.001
Survived to status[5], N	598	1449	1412	
Had ROP assessed	586	1414	1343	
Severe ROP [6]	76 (13.0)	187 (13.2)	87 (6.5)	<0.001
Survived to 36 weeks PMA, N	602	1459	1414	
BPD [7]	361 (60.2)	957 (66.0)	667 (47.5)	<0.001

BPD, bronchopulmonary dysplasia. IVH, intraventricular hemorrhage. LOS, late-onset sepsis. LOCNC, late-onset blood culture-negative condition. PMA, post-menstrual age. PVL, periventricular leukomalacia. ROP, retinopathy of prematurity.

[1] Information was missing for (n) infants: IVH (9); PVL (1); porencephalic cyst (1); brain injury (6); BPD, (21).

[2] P-value by chi-square test.

[3] Cerebellar hemorrhage was collected beginning April 2011.

[4] Brain injury was defined as one or more of the following findings on cranial imaging: severe IVH, PVL, ventriculomegaly, porencephalic cyst, or cerebellar hemorrhage.

[5] Includes infants discharged home or transferred before 120 days or still in the hospital at 120 days.

[6] ROP determined was considered severe if either eye met one of the following criteria: had ROP surgery, anti-VEGF injection, or retinal detachment from ROP.

[7] BPD was defined as oxygen use at 36 weeks PMA.

Table 3:

Mortality and neurodevelopmental outcomes

	LOS	LOCNC	Unaffected	Adjusted RR (95% CI) p-value[1]		
				LOS vs. LOCNC	LOS vs. Unaffected	LOCNC vs. Unaffected
Infants, n	786	1601	1553			
Death/NDI, n (%)	394 (50.1)	662 (41.3)	513 (33.0)	1.14 (1.05–1.25)	1.29 (1.17–1.42)	1.13 (1.03–1.23)
				0.003	<0.001	0.008
Death before follow-up, n (%)	207 (26.3)	206 (12.9)	166 (10.7)	1.71 (1.44–2.03)	1.79 (1.48–2.16)	1.04 (0.87–1.26)
				<0.001	<0.001	0.64
Survived and evaluated at 18–26 months follow-up, n	579	1,395	1,387			
NDI, n (%)	187 (32.3)	456 (32.7)	347 (25.0)	0.99 (0.86–1.13)	1.15 (0.99–1.34)	1.17 (1.04–1.31)
				0.86	0.07	0.01
Components of NDI, n (%)						
Bayley 3 cognitive composite score <85	173 (29.9)	422 (30.4)	327 (23.7)	0.98 (0.85–1.13)	1.12 (0.96–1.31)	1.15 (1.01–1.30)
				0.80	0.14	0.03
GMFCS level ≥ 2	35 (6.1)	130 (9.3)	54 (3.9)	0.61 (0.42–0.88)	1.16 (0.77–1.76)	1.91 (1.40–2.60)
				0.008	0.48	<0.001
Bilateral blindness [2]	7 (1.2)	19 (1.4)	7 (0.5)	0.89 (0.37–2.10)	2.40 (0.84–6.80)	2.70 (1.14–6.41)
				1.0	0.14	0.03
Hearing impairment [2]	16 (2.8)	34 (2.4)	21 (1.5)	1.13 (0.63–2.04)	1.83 (0.96–3.47)	1.61 (0.94–2.76)
				0.64	0.07	0.10
Blindness or hearing impairment [3]	23 (4.0)	51 (3.7)	26 (1.9)	1.01 (0.62–1.66)	1.83 (1.03–3.25)	1.81 (1.12–2.92)
				0.96	0.04	0.01

LOS, late-onset sepsis. LOCNC, late-onset blood culture-negative condition. NDI, neurodevelopmental impairment.

[1]Relative risks (RR) and confidence intervals (CI) with adjustment for pre-exposure covariates. Pre-exposure covariates included study center, maternal education (< high school degree, high school degree, > high school degree, unknown/missing), maternal medical insurance (private, public/self-pay/other), maternal race/ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, other), antepartum hemorrhage, antenatal antibiotics, antenatal steroids, GA (22, 23, 24, 25, 26), BW (continuous), male sex, endotracheal intubation, highest respiratory support at 24 hours (HFV, CV, NSIMV, CPAP, other/no support), enteral feeds started in the first 3 days, infant temperature within 60 minutes of birth (≥96.5, <96.5, unknown/missing), prolonged early antibiotics (antibiotics for 5 or more days started within 72 hours of birth), and severe IVH diagnosed within 7 days of birth. Statistical significance was determined by the Wald chi-square test.

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[2] Unadjusted relative risks are reported for blindness and for hearing impairment due to small numbers.

[3] Due to small numbers, study center was not included in the model assessing this combined outcome and GA 22 and 23 weeks were combined.

Table 4.

Neurodevelopmental impairment (NDI) by number of infection episodes

Episodes	Infants, N	NDI, n (row %)	Comparisons	Adjusted RR[1] (95% CI)	p-value
LOS, 1	446	139 (31.2)			
2	107	37 (34.6)	LOS 2 vs 1 episode	1.06 (0.78–1.44)	0.72
3+	26	11 (42.3)	LOS 3+ vs 1 episode	1.10 (0.67–1.79)	0.71
LOCNC, 1	886	255 (28.8)			
2	330	131 (39.7)	LOCNC 2 vs 1 episode	1.35 (1.15–1.59)	<0.001
3+	179	70 (39.1)	LOCNC 3+ vs 1 episode	1.27 (1.02–1.56)	0.03

LOS, late-onset sepsis. LOCNC, late-onset blood culture-negative condition. NDI, neurodevelopmental impairment.

[1]Relative risks (RR) and confidence intervals (CI) adjusted for study center, maternal education (< high school degree, high school degree, > high school degree, unknown/missing), maternal medical insurance (private, public/self-pay/other), maternal race/ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, other), antepartum hemorrhage, antenatal antibiotics, antenatal steroids, GA (22, 23, 24, 25, 26), BW (continuous), male sex, endotracheal intubation, highest respiratory support at 24 hours (HFV, CV, NSIMV, CPAP, other/no support), enteral feeds started in the first 3 days, infant temperature within 60 minutes of birth (≥96.5, <96.5, unknown/missing), prolonged early antibiotics (antibiotics for 5 or more days started within 72 hours of birth), and severe IVH diagnosed within 7 days of birth. Statistical significance was determined by the Wald chi-square test.