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Neurodevelopmental Outcome of Extremely Low Birth Weight Infants with *Candida* Infection

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Abstract

Objective—*Candida* remains an important cause of late-onset infection in preterm infants. Mortality and neurodevelopmental outcome of extremely low birthweight (ELBW) infants enrolled in the *Candida* study was evaluated based on infection status.

Study design—ELBW infants born at NICHD Neonatal Research Network (NRN) centers between March 2004 and July 2007 screened for suspected sepsis were eligible for inclusion in the Candida study. Primary outcome data for neurodevelopmental impairment (NDI) or death were available for 1317/1515 (90%) of the infants enrolled in the Candida study. The Bayley Scales of Infant Development (BSID)-II or the BSID-III was administered at 18 months adjusted age. A secondary comparison with 864 infants registered with NRN enrolled during the same cohort never screened for sepsis and therefore not eligible for the Candida study was performed.

Results—Among ELBW infants enrolled in the Candida study, 31% with *Candida* and 31% with late-onset non-*Candida* sepsis had NDI at 18 months. Infants with *Candida* sepsis and/or meningitis had an increased risk of death and were more likely to have the composite outcome of death and/or NDI compared with uninfected infants in adjusted analysis. Compared with infants in the NRN registry never screened for sepsis, overall risk for death were similar but those with Candida infection were more likely to have NDI (OR 1.83 (1.01,3.33, p=0.047).

Conclusion—In this cohort of ELBW infants, those with infection and/or meningitis were at increased risk for death and/or NDI. This risk was highest among those with *Candida* sepsis and/or meningitis.

Keywords

Candida; Neonatal sepsis; Neurodevelopmental and Prematurity

Although premature infants remain at increased risk for adverse neurodevelopmental (ND) outcome, it is increasingly clear that this risk is modified by a variety of neonatal morbidities, including neonatal infection. *Candida* has consistently remained an important pathogen associated with late-onset neonatal sepsis (LOS), affecting approximately 7% of very low birthweight (VLBW) infants prior to hospital discharge.(1–4) Improved understanding of the morbidity and mortality associated with *Candida* infection is needed to interpret previous data and to consider new prevention and treatment strategies.

Adverse ND outcomes in preterm infants have been associated with LOS due to various bacterial pathogens (4, 5); however, data regarding outcome of infants with *Candida* infection have been somewhat variable. Friedman et al reported outcomes of 46 extremely low birthweight (ELBW) infants < 1000grams with *Candida* sepsis/meningitis compared

with ELBW peers.(6) Periventricular leukomalacia (PVL) (26% vs 12%; p=0.06), severe retinopathy of prematurity (22% vs 9%, p=0.04), chronic lung disease (CLD) (100% vs 34%; p=.0001), and adverse neurologic outcomes at 2 years of age (60% vs 35%, p=0.005) were more common among those with *Candida* infection.(6) Stoll et al compared ND outcomes of ELBW infants with *Candida* infection with those infected with bacterial pathogens and those who were uninfected.(4) The 105 infants with *Candida* were more likely to have moderate to severe cerebral palsy (CP) and neurodevelopmental impairment (NDI) compared with uninfected infants; however, these differences were not statistically significant after adjustment for other contributing variables. Benjamin et al reported ND outcome of 320 ELBW infants with *Candida* sepsis and/or meningitis, of whom 293 had sepsis only, 14 had sepsis and meningitis and 13 had meningitis only compared with peers without *Candida* infection. (7) *Candida* infected neonates had lower Bayley Scales of Infant Development-II (BSID-II) scores, were more likely to have moderate/severe CP, NDI, blindness and hearing impairment compared with those without *Candida* infection.(7)

The Neonatal Research Network (NRN) of the Eunice Kennedy Shiver National Institute of Child Health and Human Development (NICHD) performed a prospective observational study of ELBW infants evaluated for sepsis to develop predictive models for *Candida* infection.(8) This analysis evaluates mortality and neurodevelopmental outcome at 18–22 months adjusted age in ELBW infants from this cohort with *Candida* infection, compared with infants with other LOS pathogens and to uninfected infants.

Methods

Extremely low birthweight infants (401–1000 grams birthweight) born between March 2004 and July 2007 at participating NICHD NRN hospitals who were alive at 72 hours and subsequently screened for sepsis were eligible for inclusion in the Candida study which was a prospective observational study to develop predictive models to estimate the probability of invasive candidiasis based on laboratory and clinical variables.(8) This analysis evaluates the primary outcomes of death or NDI based on infection status for these infants. Infants with early onset sepsis (EOS), congenital anomalies, congenital infection and those lost to follow-up were excluded from analysis. Based on study design, the Candida study only included infants screened for sepsis, therefore to address potential bias introduced by using a higher at risk comparison group, we performed a secondary analysis comparing outcomes of uninfected ELBW infants enrolled during the same study period in the NRN registry. (9) IRB approval was obtained at each site and separate informed consents were obtained for the Candida Observational Study and the Neurodevelopmental Follow-Up Study.

Neonatal and maternal data were collected systematically from birth until hospital discharge, transfer, death or 120 days postnatal age and infant data were collected at the 18–22 month follow-up visit. Infection status was established based on positive cultures obtained at each study site. Additional clinical data were collected with each suspected episode of sepsis, including the use and timing of antibiotic and antifungal therapy.

Chronic Lung Disease was defined by the use of supplemental oxygen at 36 weeks postmenstrual age. Necrotizing enterocolitis (NEC) was defined by modified Bells Stage IIA or greater (10) and treated for ≥ 5 days. Early onset sepsis (EOS) within 72 hours of birth and late onset sepsis (LOS) after 72 hours were defined by a positive blood culture and antibiotic therapy for ≥ 5 days. Clinical infection was defined as suspected sepsis with negative cultures but administration of antibiotics for ≥ 5 days. Meningitis was defined as a positive cerebrospinal fluid (CSF) culture for *Candida* or bacterial organisms. Grades 3 and 4 intraventricular hemorrhage (IVH), as defined by Papile (11) were considered severe for

this analysis. Periventricular leukomalacia (PVL) was defined as the presence of cystic echolucencies in the periventricular white matter by ultrasonography.

Infants had a comprehensive neurodevelopmental evaluation at 18–22 months adjusted age. Certified examiners who were unaware of infection status performed a standardized neurosensory examination. Functional motor impairment was defined based on the Palisano Gross Motor Functional Classification score.(12) Children evaluated prior to October 1, 2007 (Epoch 1) were administered the cognitive and motor scales of the BSID-II Revised and those evaluated after this date (Epoch 2) were administered the cognitive and language scales of the BSID-III. Both instruments are normed based on a representative sample of children from the United States and standardized to a score of 100 ± 15 (mean ± standard deviation (SD).(13, 14) The composite language score is a sum of the receptive and expressive language scores on the BSID-III which are based on a scale of 1–19 and converted to a standardized score with a mean 100 ± 15 SD. Even though the fundamental structure of these two instruments is similar, changes in age adjusted item sets and instrument design limit the ability to combine or directly compare results from these two instruments. Therefore, categorical values of neurodevelopmental outcome based on these predefined definitions were used to compare patients in Epochs 1 and 2. Differences in the definition of neurodevelopmental impairment for the two epochs are outlined in Table I.

Patients in the *Candida* study were divided into four groups based on infection status: (1) Candida (blood or CSF culture positive for *Candida*); (2) LOS-Other (blood or CSF culture positive for bacterial pathogen but not Candida); (3) Clinical infection and (4) Uninfected (no history of infection or NEC) Additionally, ELBW infants enrolled in the NRN ELBW registry never treated for suspected or confirmed sepsis who were therefore ineligible for inclusion in the Candida study, comprised the NRN Registry-Uninfected group.

Statistical Analyses

Bivariate analyses were performed to compare demographic and morbidity profiles by infection status and epoch, using chi-square tests for categorical variables and analyses of variance for continuous variables. We estimated the incidence of three outcomes by infection status: (1) death, (2) NDI, and (3) death and/or NDI. We conducted multilevel logistic regression modeling to compare the risk of adverse outcomes (death and/or NDI) for children in each of the infection groups (Candida infection, LOS-Other, Clinical infection, Uninfected-Candida, and Uninfected NRN Registry) after adjusting for clustering of children within research centers and controlling for potential confounders including: epoch, sex, birth weight, race, maternal education, postnatal corticosteroids, NEC, and IVH/PVL. Five percent of children had missing data for maternal education, therefore multiple imputation was used to impute missing values for this variable to preserve the sample size for the regression models.

RESULTS

During the study period, 6,493 ELBW infants were born in 19 participating centers, of whom, 5,252 were alive at 72 hours. The Candida study included 1,515 ELBW infants who were screened for sepsis.(8) Data on the primary outcomes of death and/or neurodevelopmental impairment (NDI) were available for 1317 (90%) of the eligible infants enrolled in the Candida study (Figure; available at www.jpeds.com). Compared with children in the analyses, those who were lost to follow-up were less likely to have IVH/PVL and NEC, had higher gestational ages and birth weights, and were more likely to be in the uninfected infection group. There were no significant differences by sex, race, postnatal corticosteroid receipt, or CLD. From this same cohort of ELBW infants, there were 1,333 infants in the NRN ELBW registry who survived to 72 hours and were not screened or

treated for sepsis or meningitis. Among whom, 58 were excluded due to major congenital anomaly, 34 had incomplete data at follow-up, and 377 were lost to follow-up or ineligible for follow-up based on their gestational age. The remaining 864 infants (67% from Epoch 1 and 33% from Epoch 2) were included in our analyses as the GDB uninfected comparison group.

Bivariate analyses were conducted to compare *Candida*-infected children to those in the other infection groups based on epoch, sex, birth weight, maternal education, race, postnatal steroids, IVH/PVL, NEC, and CLD. (Table II) Compared with uninfected children in either the Candida study or the NRN registry, children with *Candida* infection were significantly more likely to be male, have lower birth weight, have lower maternal education, have received postnatal corticosteroids, have IVH/PVL, have NEC, and have CLD ($p < .05$; Table II)

Infection Incidence

Among infants in the Candida study, 123 infants (9%) developed *Candida* sepsis/meningitis, 533 infants (40%) had LOS associated with pathogens other than *Candida*, 381 (29%) had clinical infection, and 280 (21%) were uninfected. Among the infants with *Candida* sepsis/meningitis who survived and had repeated cultures from the same source, the median time to negative culture was 6 days (range 1–28 days); however, 25% of infants had positive cultures for ≥ 10 days.

A total of 55 (4.2%) of the infants in the Candida study had positive CSF cultures. The most common bacterial pathogens causing meningitis were: *Staphylococcus* sp. (coagulase-negative-*Staphylococcus* (N=28) and *S aureus* (N=4), *Klebsiella* sp (N=5) and *Steptococcus* sp (N=4). Positive CSF cultures due to *Candida* infection were due to *C albicans* (N=7) and *C parapsilosis* (N=1). Among those with a positive CSF culture for *Candida* only 50% also had a positive blood culture for *Candida* within 7 days.

Mortality by Infection Status

Two hundred and fifty-one infants (19%) enrolled in the Candida study died; of whom 51 (20%) had *Candida* sepsis/meningitis. Forty-one percent of *Candida* infected infants died (Table III). The death rate was similar between the two epochs; however, the risk was significantly higher among those infants who were male, of lower birth weight, with lower maternal education, and who developed severe IVH/PVL or NEC (Table IV).

Overall, when comparing infants enrolled in the Candida study, those with *Candida* sepsis/meningitis were more likely to die compared with both those infected with other pathogens and those who were uninfected (Table III). In adjusted analyses, these differences were statistically similar to those with other LOS infections; however, they were statistically different compared with uninfected infants in the Candida study (OR (95% CI) = 4.76 (2.24, 10.14), $p<.001$) (Table IV). Odds of death were similar compared with uninfected infants enrolled in the NRN registry; however, cause of death was most commonly attributed to proven or suspected sepsis (37%), NEC (16%), CLD (14%), and RDS (10%) among infants with *Candida* in contrast to those in the NRN Registry-Uninfected group where 50% of deaths were related to RDS or severe IVH.

Among infants with *Candida* dying before hospital discharge, the median number of days between first positive *Candida* culture and death was 13 days (range 0–283 days). Ninety-nine infants (80%) with *Candida* sepsis/meningitis had a catheter in place at the time of the initial infection. Death rates did not differ significantly between those with a catheter for ≤ one week and those with the catheter > one week (39% v 43%) after testing positive for *Candida*.

Neurodevelopmental Outcome

ND outcomes are reported by infection status and epoch (Tables I, III, and IV). In unadjusted comparison, *Candida* infected infants had similar rates of NDI to those infected with other LOS pathogens but higher rates compared with uninfected infants in both the Candida study and the NRN Registry Uninfected group (Table III). After controlling for other factors, these differences in NDI alone were no longer seen based on infection status for infants enrolled in the Candida study (Table IV). However, Candida infected had significantly higher odds of NDI compared with uninfected NRN registry infants with no history of suspected sepsis or proven sepsis (OR (95% CI) =1.83 (1.01,3.33, p=0.047) (Table IV). In unadjusted analyses, those with Candida infection were more likely to have a head circumference <3rd percentile for adjusted age at follow-up compared with those in the GDB Uninfected Group (Candida 21%; OR 5.42 (2.76, 10.66). Children with LOS (11% OR 2.55 (1.58, 4.14)) and Clinical Infection (13%; OR 2.97 (1.82,4.86)) were also more likely to have microcephaly than the GDB Uninfected Group. There was no difference between those in the two uninfected groups (Uninfected 5%; OR 0.97 (OR 0.49, 1.93).

Among infants in the Candida study, neurodevelopmental outcomes for the 544/688 (79%) infants enrolled in Epoch 1 and the 522/629 (83%) infants enrolled in Epoch 2 assessed at 18-month follow-up are outlined in Table I. The two groups were similar with respect to infection group, race, sex, gestational age, birth weight, IVH/PVL, CLD, and NEC. However, significantly more children in Epochs 1 received postnatal corticosteroids (13% vs. 9%; p=.023), and fewer had meningitis (3% vs. 5%; p=.033). Although children from the two study periods had similar mortality rates (Table IV), significant differences were noted in NDI at 18 months with 41% of children in Epoch 1 diagnosed with NDI compared with 11% in Epoch 2 (Table I). The rate of NDI increases from 11% to 30% in Epoch 2 if a cutoff of <85 is used to define NDI; however, the differences in rates of NDI remain significantly different between the two groups. Infants in Epoch 1 were significantly more likely to have moderate/severe CP than those in Epoch 2 (8% vs. 4%) (Table I).

Duration of positive cultures did not predict the risk for NDI. *Candida* infected infants with a catheter greater than or equal to one week after testing positive for *Candida* had significantly higher rates of NDI alone (50% vs. 19%) (OR (95% CI) = 4.37 (1.50, 12.77), p=.007) and the combined outcome of death/NDI (71% vs. 51%) (OR (95% CI) = 2.43 (1.12, 5.28), p= .025) compared with those with catheters less than or equal to one week after infection.

Composite Outcome of Death/NDI

Candida infected infants were significantly more likely to have death and/or NDI compared with all other infection groups. These differences were most striking among those infants < 750 grams and those who were uninfected.

Discussion

Infectious complications of prematurity, including late onset sepsis, have been associated with an increased mortality risk, adverse neurodevelopmental outcome and growth impairment.(4, 5, 15) In our study evaluating outcomes of a high risk group of infants who had clinical signs suggestive of sepsis, systemic candidiasis was associated with an increased risk of death and/or NDI compared with uninfected infants but similar outcome to those infected with other late onset pathogens.

Research suggests that the cytokine mediated inflammatory response generated in response to infection may be responsible for injury to the developing central nervous system secondary to activation of innate and adaptive immune responses resulting in direct and

downstream neurotoxic effects on developing neurons.(16, 17) Furthermore, the maturation dependent vulnerability of the developing white matter to cytokine induced injury creates a critical window of vulnerability for the ELBW infant which likely contributes to the adverse neurodevelopmental outcome of infected infants.(17–19) Clinical and animal studies evaluating cytokine response to specific pathogens are limited. (20, 21) The complexity of downstream activation and interaction makes it difficult to identify a direct causal relationship between a specific cytokine or pathogen and the resultant brain injury.(19, 22, 23) The number of children with a previous early onset pathogen was small therefore we were unable to evaluate any relationship between EOS and later risk of *Candida* infection or the impact on multiple infections on ND outcome.

In the current study, we evaluated differences in ND outcome between *Candida* infected infants to both those who were uninfected and those infected with other late onset pathogens to better understand the specific impact of *Candida* infection on ND outcome. Stoll et al evaluated ND outcome at 18 months in 6093 ELBW infants.(4) Compared with uninfected infants, those with infection had worse ND outcome; however, this risk did not vary based on pathogen except for an increased risk of hearing impairment among those with *Candida* infection. Similarly, in our study, survivors with systemic candidiasis had a similar risk of poor neurologic outcome as those infected with other pathogens, which suggests that the pathophysiologic pathways resulting in CNS injury in infected preterm neonates may not be pathogen specific. Additional research evaluating specific cytokine responses at the onset of infection are needed to better understand this relationship.

Our study is unique because only infants being evaluated for sepsis were eligible for inclusion in the Candida study. We speculated that the uninfected group in the Candida study was not representative of a more homogenous ELBW population because the overall rate of culture proven LOS in the Candida study cohort was significantly higher than previous reports of similar low birth weight populations. (3, 4) Therefore a significant percentage of infants would not be accounted for in the uninfected group based on our study design. How these findings affected our outcome are unclear; however, both represent potential bias and limit comparability with previous reports. Our results are consistent with this observation in that differences in ND outcome were seen between *Candida* infected infants compared with uninfected GDB infants but not with uninfected infants in the Candida study.

Approximately 7% of infants with *Candida* isolated from the blood culture also had a positive CSF culture; however, lumbar punctures were not systematically performed on infants with culture proven or suspected sepsis. The small number of infants with meningitis limits our ability to interpret these data. Furthermore, animal model and autopsy studies suggest that parenchymal involvement resulting in meningo-encephalitis is more common with *Candida* infection which may further underestimate the impact on CNS injury.(24)

The neurodevelopmental assessment tool changed during the study period due to the 2005 revision in the BSID. Even though there were similar demographic profiles and rates of *Candida* infection between both epochs, our study may not have been adequately powered to detect differences in NDI due to the unanticipated lower rate of NDI among infants evaluated using the BSID-III. We can only speculate about reasons for the significantly higher cognitive scores among children evaluated using the BSID-III. There are limited data regarding comparability of the two versions of the BSID, appropriate cutoffs to define impairment or the long term predictive validity of the BSID-III in a preterm population.(25) In our cohort, differences in NDI may be related to differences in rates of moderate/severe CP between the two epochs. Additional research is needed to explore the differences in these two instruments.

Interestingly, in this cohort neurodevelopmental outcome did not correlate with duration of positive cultures; however, these data were quite skewed and the number of patients with prolonged candidemia was small. However, similar to previous reports (26), we observed an association between delayed catheter removal and increased risk of death and/or NDI. Among *Candida* infected infants < 750 grams, 50% die, 33% survivors have NDI and 66% either die or have NDI. The dramatically increased mortality among infants infected with *Candida* emphasizes the need for development and implementation of multi-level strategies and guidelines to enhance prevention, early detection and treatment of these high risk infants. (7, 26–30)

Among infants enrolled in the Candida study, those with systemic candidiasis had the highest risk of death. Infected survivors had similar neurodevelopmental outcomes compared with other infants in this cohort but worse outcomes compared with peers with no history of suspected infection, particularly among those < 750 gram birthweight.

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Abbreviations

BSID	Bayley Scales of Infant Development
CLD	Chronic Lung Disease
CNS	Central Nervous System
CP	Cerebral Palsy
CSF	Cerebrospinal Fluid
ELBW	Extremely Low Birth Weight
EOS	Early Onset Sepsis
GA	Gestational Age
GDB	Generic Database
IVH	Intraventricular Hemorrhage
LOS	Late Onset Sepsis
ND	Neurodevelopmental
NDI	Neurodevelopmental Impairment
NEC	Necrotizing Enterocolitis
NICHD	National Institute of Child Health and Human Development
NRN	Neonatal Research Network
PVL	Periventricular Leukomalacia

RDS	Respiratory Distress Syndrome
VLBW	Very Low Birth Weight

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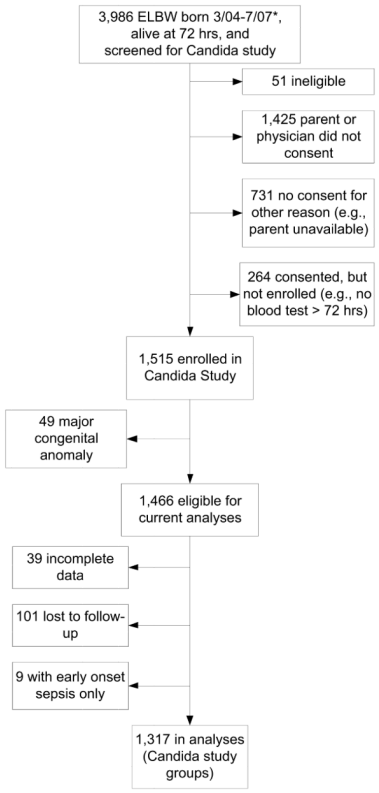

Figure 1. Candida Study Enrollment

* 2 infants in Candida study were born before 3/04 (birthdates 1/04 and 2/04)

Table 1

Neurodevelopmental Impairment Definitions and Outcomes by Epoch at 18 Months Adjusted Age of Children Enrolled in Candida Study who Survived to Follow-Up

Variable	Epoch 1 (N=544)	Epoch 2 (N=522)
Neurodevelopmental Impairment Definitions		
Child has any of the following:		
Neurological	Moderate to severe cerebral palsy with GMFCS level ≥ 2	Moderate to severe cerebral palsy with GMFCS level ≥ 2
Development	Bayley II MDI < 70 or PDI < 70	Bayley III cognitive < 70 or GMFCS level ≥ 2
Vision	Bilateral blindness with no functional vision	Visual acuity < 20–200 bilateral
Hearing	Bilateral amplification for permanent hearing loss	Permanent hearing loss that does not permit the child to understand directions of examiner and communicate despite amplification

Neurodevelopmental Outcomes	Epoch 1 N (%)	Epoch 2 N (%)	P
Neurodevelopmental Impairment	222 (41)	59 (11)	< .001
Visually impaired	5 (1)	5 (1)	.948
Hearing impaired	16 (3)	17 (3)	.783
Moderate/severe cerebral palsy	42 (8)	19 (4)	.004
Any cerebral palsy	85 (16)	49 (9)	.002
Gross motor function level ≥ 2	44 (8)	27 (5)	.056
MDI			
< 70	189 (35)	--	--
70–85	166 (31)	--	--
> 85	187 (35)	--	--
PDI			
< 70	127 (24)	--	--
70–85	136 (25)	--	--
> 85	277 (51)	--	--
Cognitive			
< 70	--	42 (8)	--
70–85	--	167 (32)	--
> 85	--	313 (60)	--
Language			
< 70	--	82 (16)	--
70–85	--	159 (31)	--
> 85	--	269 (53)	--

Table 2

Demographic and Medical Characteristics by Infection Status

Characteristic	Candida Study				GDB (Post hoc comparison group)
	Candida (N=123)	LOS (N=533)	Clinical infection (N=381)	Uninfected (N=280)	Uninfected (N=864)
	N (%)	N (%)	N (%)	N (%)	N (%)
Cohort 1	66 (54)	298 (56)	187 (49)	137 (49)	284 (33)
Male	70 (57)	286 (54)	191 (50)	123 (44)	362 (42)
Birth weight < 750g	83 (67)	257 (48)	194 (51)	82 (29)	295 (34)
High school or less education	70 (67)	255 (52)	176 (49)	139 (51)	388 (50)
Nonwhite race	56 (46)	245 (46)	158 (41)	111 (40)	387 (45)
Postnatal steroids	17 (14)	63 (12)	47 (12)	15 (5)	35 (4)
IVH/PVL	39 (32)	104 (20)	55 (14)	27 (10)	198 (23)
NEC	23 (19)	106 (20)	43 (11)	--	--
CLD	55 (63)	253 (58)	163 (48)	83 (31)	193 (29)
Early onset sepsis	3 (2)	13 (2)	9 (2)	--	--
Weight percentile at 18-month follow-up (kg)…mean (SD)	39 (30)	39 (30)	36 (29)	41 (28)	41 (30)
Length percentile at 18-month follow-up (cm)…mean (SD)	31 (30)	27 (28)	28 (28)	32 (27)	33 (29)
Head circumference percentile at 18-month follow-up (cm)…mean (SD)*	44 (36)	42 (31)	40 (32)	49 (30)	50 (30)
Head circumference at 18 mo <3rd percentile*	15 (21)	44 (11)	41 (13)	12 (5)	30 (5)

Note: The uninfected groups exclude infants with NEC by definition. Percentages for CLD and maternal education only include children with data on those variables.

*Head circumference data available on 1,715 children

Table 3

Death and Neurodevelopmental Impairment by Infection Status

Infection status	Death N/Total N (%)	NDI N/Total N (%)	Death/NDI N/Total N (%)
Candida Study			
Candida	51/123 (41)	22/72 (31)	73/123 (59)
LOS-Other	131/533 (25)	126/402 (31)	257/533 (48)
Clinical Infection	55/381 (14)	89/326 (27)	144/381 (38)
Uninfected	14/280 (5)	44/266 (17)	58/280 (21)
NRN Registry			
Uninfected	213/864 (25)	109/651 (17)	322/864 (37)

Note: Percentages for NDI include only children with NDI data at the follow-up visit.

Table 4

Logistic Regression Models of Death and NDI by Infection Status

Variable	Death		NDI		Death/NDI	
	Adj OR (95% CI)	p	Adj OR (95% CI)	P	Adj OR (95% CI)	p
Infection Status: Candida vs. Groups from Candida Study						
Candida vs. Uninfected (Candida study)	4.76 (2.24, 10.14)	< 0.001	1.37 (0.72, 2.63)	0.339	2.47 (1.47, 4.13)	0.001
Candida vs. LOS-Other	1.62 (0.96, 2.75)	0.073	0.79 (0.44, 1.43)	0.441	1.19 (0.76, 1.85)	0.457
Candida vs. Clinical infection	2.59 (1.47, 4.55)	0.001	0.83 (0.45, 1.53)	0.559	1.57 (0.99, 2.49)	0.057
Infection Status: Candida vs. Group from NRN registry						
Candida vs. Uninfected (NRN registry)	0.85 (0.51, 1.43)	0.545	1.83 (1.01, 3.33)	0.047	1.54 (0.99, 2.38)	0.054
Epoch 1	1.14 (0.88, 1.46)	0.325	6.22 (4.59, 8.43)	< 0.001	3.35 (2.69, 4.17)	< 0.001
Male	2.08 (1.62, 2.67)	< 0.001	1.54 (1.19, 1.99)	0.001	1.93 (1.57, 2.37)	< 0.001
Birth weight < 750g	5.41 (4.17, 7.02)	< 0.001	1.66 (1.27, 2.18)	< 0.001	3.20 (2.59, 3.95)	< 0.001
Nonwhite race	1.07 (0.84, 1.37)	0.587	1.56 (1.21, 2.01)	0.001	1.40 (1.14, 1.72)	0.001
High school or less	1.84 (1.35, 2.52)	< 0.001	1.44 (1.12, 1.86)	0.005	1.70 (1.35, 2.13)	< 0.001
Postnatal corticosteroids	1.19 (0.75, 1.89)	0.452	2.24 (1.45, 3.45)	< 0.001	2.00 (1.36, 2.93)	< 0.001
IVH/PVL	4.84 (3.70, 6.31)	< 0.001	3.08 (2.19, 4.33)	< 0.001	5.45 (4.17, 7.10)	< 0.001
NEC	5.20 (3.38, 8.02)	< 0.001	1.26 (0.75, 2.12)	0.377	2.82 (1.90, 4.18)	< 0.001

Note: Models also account for clustering of children within research centers. Model for NDI excludes children without data on NDI at follow-up. Reference categories are epoch 2, female, birth weight ≥ 750g, white race, more than high school education, did not receive postnatal steroids, did not have IVH/PVL, and did not have NEC. Areas under the ROC curve (AUC) for the models are: Death (AUC=0.83), NDI (AUC=0.77), and Death/NDI (AUC=0.80).