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

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

Study design ELBW infants born at *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) centers between March 2004 and July 2007 who were 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 of the 1515 infants (87%) enrolled in the *Candida* study. The *Bayley Scales of Infant Development*-II or -III was administered at 18 months' adjusted age. A secondary comparison was performed with 864 infants enrolled in the NRN Generic Database during the same cohort who were never screened for sepsis and therefore not eligible for the *Candida* study.

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, 95% CI 1.01-3.33, $P = .047$).

Conclusions 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. *(J Pediatr 2013;163:961-67)*.

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.

BSID	*Bayley Scales of Infant Development*	LOS	Late-onset sepsis
CLD	Chronic lung disease	ND	Neurodevelopmental
CNS	Central nervous system	NDI	Neurodevelopmental impairment
CP	Cerebral palsy	NEC	Necrotizing enterocolitis
CSF	Cerebrospinal fluid	NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
ELBW	Extremely low birth weight		
EOS	Early-onset sepsis		
GA	Gestational age	NRN	Neonatal Research Network
GDB	Generic database	PVL	Periventricular leukomalacia
IVH	Intraventricular hemorrhage		

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Candida has consistently remained an important pathogen associated with neonatal late-onset sepsis (LOS), affecting approximately 7% of very low birth weight infants before 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[6] reported outcomes of 46 extremely low birth weight (ELBW) infants <1000 g with *Candida* sepsis and/or meningitis compared with the outcomes of ELBW peers. Periventricular leukomalacia (PVL) (26% vs 12%, $P = .06$), severe retinopathy of prematurity (22% vs 9%, $P = .04$), chronic lung disease (CLD) (100% vs 34%, $P = .0001$), and adverse neurologic outcomes at 2 years of age (60% vs 35%, $P = .005$) were more common among those with *Candida* infection.[6] Stoll et al[4] compared ND outcomes of ELBW infants with *Candida* infection with those infected with bacterial pathogens and those who were uninfected. 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[7] 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. Neonates infected with *Candida* had lower *Bayley Scales of Infant Development* (BSID)-II scores and were more likely to have moderate or severe CP, NDI, blindness, and hearing impairment compared with those without *Candida* infection.[7]

The Neonatal Research Network (NRN) of the *Eunice Kennedy Shriver* 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 ND outcome at 18-22 months' adjusted age in ELBW infants from this cohort with *Candida* infection, compared with infants with other LOS pathogens and compared with uninfected infants.

Methods

The ELBW infants (401-1000 g birth weight) 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 conducted 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, or 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] Institutional review board approval was obtained at each site, and separate informed consents were obtained for the *Candida* observational study and the ND 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- to 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.

CLD was defined by the use of supplemental oxygen at 36 weeks' postmenstrual age. Necrotizing enterocolitis (NEC) was defined as being of modified Bells stage IIA or greater[10] and treated for ≥5 days. EOS (within 72 hours of birth) and LOS (after 72 hours of birth) 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 et al,[11] were considered severe for this analysis. PVL was defined as the presence of cystic echolucencies in the periventricular white matter on ultrasonography.

Infants had a comprehensive ND 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 before 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 US and standardized to a score of 100 ± 15 (mean ± 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 2 instruments is similar, changes in age-adjusted item sets and instrument design limit the ability to combine or directly compare results from these 2 instruments. Therefore, categorical values of ND outcome based on these predefined definitions were used to compare patients in epochs 1 and 2. Differences in the definition of NDI for the 2 epochs are outlined in **Table I**.

Patients in the *Candida* study were divided into 4 groups based on infection status: (1) *Candida* (blood or CSF culture