Empiric Antifungal Therapy and Outcomes in Extremely Low Birth Weight Infants with Invasive Candidiasis

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Objective To assess the impact of empiric antifungal therapy for invasive candidiasis on subsequent outcomes in premature infants.

Study design This was a cohort study of infants with a birth weight ≤1000 g receiving care at Neonatal Research Network sites. All infants had at least one positive culture for *Candida*. Empiric antifungal therapy was defined as receipt of a systemic antifungal on the day of or the day before the first positive culture for *Candida* was drawn. We created Cox proportional hazards and logistic regression models stratified on propensity score quartiles to determine the effect of empiric antifungal therapy on survival, time to clearance of infection, retinopathy of prematurity, bronchopulmonary dysplasia, end-organ damage, and neurodevelopmental impairment (NDI).

Results A total of 136 infants developed invasive candidiasis. The incidence of death or NDI was lower in infants who received empiric antifungal therapy (19 of 38; 50%) compared with those who had not (55 of 86; 64%; OR, 0.27; 95% CI, 0.08-0.86). There was no significant difference between the groups for any single outcome or other combined outcomes.

Conclusion Empiric antifungal therapy was associated with increased survival without NDI. A prospective randomized trial of this strategy is warranted. *(J Pediatr 2012;161:264-9)*.

Candida species are a leading cause of mortality in the neonatal intensive care unit (NICU).[1] The incidence of candidemia in extremely low birth weight (ELBW) infants ranges from 2% to 20%.[1-3] *Candida* bloodstream infections are associated with poor outcomes, including a 25%-40% mortality rate and a 73% rate of death or neurodevelopmental impairment (NDI; a composite of blindness, deafness, neurodevelopmental delay, or cerebral palsy).[1,2,4,5] Prompt diagnosis of candidemia and initiation of antifungal therapy are crucial to survival in infants and older patient populations.[2,6-8]

The standard method for diagnosing candidemia is blood culture; however, blood culture has poor sensitivity for invasive fungal infections.[9-13] Based on adult autopsy studies, the sensitivity of the blood culture for diagnosing invasive candidiasis is 29%.[9] These data are based on multiple blood cultures with

BPD	Bronchopulmonary dysplasia
ELBW	Extremely low birth weight
EOD	End-organ damage
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit
ROP	Retinopathy of prematurity

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volumes ≥10 mL; sensitivity is likely to be worse in ELBW infants, in whom blood culture volumes often range from 0.5 to 1 mL.[14] Thus, reliance on blood culture results can result in underdiagnosis of *Candida* infection and delays in antifungal therapy.

Empiric antifungal therapy involves the receipt of an effective antimicrobial regimen early in the workup of a patient with suspected fungal infection, before the availability of culture results and regardless of negative culture results. In certain high-risk patients, empiric antifungal therapy has been shown to improve outcomes. Empiric antifungal therapy in adult patients with fever and neutropenia has been associated with prevention of invasive fungal infections and improved survival.[7,15-18] In addition, empiric antifungal therapy in neonatal candidemia has been linked to a decreased incidence of disseminated infection and reduced mortality.[2,19,20] However, previous studies in infants were small and did not address secondary outcomes, such as duration of candidemia, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), end-organ damage (EOD), and NDI. There have been no reports of randomized trials evaluating empiric antifungal therapy in ELBW infants. The purpose of the present study was to determine whether empiric antifungal therapy is associated with lower mortality and morbidity in ELBW infants with fungal infection, and to provide the epidemiology necessary for a future randomized trial.

Methods

This study was a retrospective analysis of demographic, clinical, and microbiological data collected from infants receiving care at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network sites. The infants were enrolled in Generic Database and Early Diagnosis of Nosocomial Candidiasis and Neurodevelopmental Follow-Up studies. All infants had a birth weight ≤1000 g, were age <120 days, received care between March 2004 and July 2007 at one of 17 Neonatal Research Network sites, were alive at 72 hours, and had at least 1 positive culture for *Candida* from blood, urine, cerebrospinal fluid, and/or other sterile body source. Clinical data for these infants were recorded and processed as described previously.[21] The Institutional Review Board at each center approved participation in the registry and the follow-up studies. Written informed consent for participation in the study was obtained from parents or legal guardians.

The primary outcomes of our analysis included survival to discharge or transfer and time to clearance of *Candida* from culture. Clearance of *Candida* was defined as the presence of a negative culture from the same source from which the positive culture was obtained. Secondary outcomes included surgery for ROP, BPD, EOD, and NDI. Surgery for ROP included laser surgery, cryotherapy, and vitrectomy. BPD was defined as receipt of supplemental oxygen at 36 weeks postmenstrual age. EOD was defined as endophthalmitis, endocarditis, brain parenchyma invasion, renal abscess, or hepatosplenic abscess. NDI was assessed during a comprehensive neurodevelopmental evaluation at 18-22 months adjusted age, which included an interview with the infant's primary caretaker, psychometric assessments of mental and motor skills, neurologic examination, and testing for hearing and vision impairment. During the study period, the Network Follow-Up study changed the psychometric instrument used to evaluate neurocognitive functioning from the Bayley Scales of Infant Development, Second Edition[22] to the Bayley Scales of Infant and Toddler Development, Third Edition.[23] For children evaluated with the Bayley Scales of Infant Development, Second Edition (those born before 2006), NDI was defined by a Bayley Scale score of <70 (>2 SD below the mean) in either the Mental Developmental Index or the Psychomotor Developmental Index, moderate or severe cerebral palsy, blindness with no functional vision in either eye, or deafness requiring bilateral hearing aids. For children evaluated with the Bayley Scales of Infant and Toddler Development, Third Edition (those born in 2006 or after), NDI was defined as a Bayley Scale Cognitive Composite score of <70, a Gross Motor Function score of level II or above, moderate or severe cerebral palsy, <20-200 vision bilaterally (defined as requiring that an object be held directly in front of the child's face for him or her to see it), or permanent hearing loss that did not permit the child to understand the directions of the examiner and communicate despite amplification. For all children, cerebral palsy was defined as a moderate or severe nonprogressive disorder characterized by abnormal tone in at least one extremity and abnormal control of movement and posture.

We also analyzed several combined outcomes, including surgery for ROP or death by discharge or transfer, BPD or death by 36 weeks postmenstrual age, EOD or death by discharge or transfer, and NDI or death by 18-22 months adjusted age. Empiric antifungal therapy was defined as receipt of a systemic antifungal on the day of or the day before the first positive culture for *Candida*. Systemic antifungal medications included fluconazole, amphotericin B deoxycholate, amphotericin B lipid preparations, 5-flucytosine, and echinocandins (anidulafungin, micafungin, and caspofungin).

We compared the demographic characteristics of infants who received empiric antifungal therapy and those who did not using the Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables. We also compared the *Candida* organisms isolated in each group. We then performed adjusted analyses to assess for differences in outcomes between infants who received empiric antifungal therapy and those who did not. Because the physician's decision to administer empiric antifungal therapy might have been affected by a range of variables reflecting individual physician practices, severity of presentation, and likelihood of fungal infection, we created propensity scores for the likelihood of empiric antifungal therapy. The propensity score (ie, the propensity for an infant to receive or not receive empiric antifungal therapy) is the summary predictor derived from the collection of potentially confounding covariates. Each infant's propensity score is an estimated probability of being