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

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Abstract

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

Study design—This was a cohort study of infants <1000 g birth weight cared for at Neonatal Research Network sites. All infants had at least 1 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—136 infants developed invasive candidiasis. The incidence of death or NDI was lower for infants who received empiric antifungal therapy (19/38, 50%) compared with those who had not (55/86, 64%; odds ratio=0.27 [95% confidence interval 0.08–0.86]). There was no significant difference between the groups for any single outcome or other combined outcomes.

Conclusions—Empiric antifungal therapy was associated with increased survival without NDI. A prospective randomized trial of this strategy is warranted.

Keywords

Candida; neonate; mortality; neurodevelopmental impairment

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% incidence of mortality and a 73% incidence 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 for the diagnosis of candidemia is the blood culture. However, blood culture has poor sensitivity for invasive fungal infections.^{9–13} On the basis of adult autopsy studies, the sensitivity of the blood culture to diagnose invasive candidiasis is 29%.⁹ These data are based on multiple blood cultures with volumes >10 mL; sensitivity is likely to be worse in ELBW infants where blood culture volumes often range from 0.5–1 mL.¹⁴ Reliance on blood culture results, therefore, can result in under-diagnosis of *Candida* infection and delay in antifungal therapy.

Empiric antifungal therapy is the receipt of an effective antimicrobial regimen early in the work-up of a patient with suspected fungal infection, prior to the availability of culture results or regardless of negative culture results. In certain high-risk patients, empiric antifungal therapy has been shown to improve outcomes. Empiric antifungal treatment in adult patients with fever and neutropenia has been shown to result in prevention of invasive fungal infections and improved survival.^{7,15–18} In addition, empiric antifungal therapy in neonatal candidemia has been linked to 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 our study was to determine whether empiric antifungal therapy is associated with lower mortality and morbidity among ELBW infants with fungal infection, and to provide the epidemiology necessary for a future randomized trial.

METHODS

We performed a retrospective analysis of demographic, clinical, and microbiological data collected from infants cared for 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 were 1000 g birth weight and <120 days of age, were cared for between March 2004 and July 2007 at 1 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 (CSF), 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 was obtained from parents or legal guardians for participation in the study.

The primary outcomes of this analysis included survival to discharge or transfer and time to clearance of *Candida* from culture. Clearance of *Candida* from culture 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, or vitrectomy. BPD was defined as receipt of supplemental oxygen at 36 weeks postmenstrual age (PMA). 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 primary caretaker for the infant, psychometric assessments of mental and motor skills, a neurologic examination, and ascertainment of 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 II²² to the Bayley Scales of Infant and Toddler Development III.²³ For children evaluated with the Bayley II (those born prior to 2006), NDI was defined by a Bayley Scale score of <70 (>2 standard deviations below the mean) in either the Mental Developmental Index (MDI) or the Psychomotor Developmental Index (PDI), 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 III (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 a condition that requires the child to have an object held directly in front of his/her face in order 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 non-progressive disorder characterized by abnormal tone in at least 1 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 PMA, 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* was drawn. 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 infants who did not receive empiric antifungal therapy using the Wilcoxon rank sum test for continuous variables and the chi-square 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 did and did not receive empiric antifungal therapy. Because the physician's decision to administer empiric antifungal therapy may have been affected by a variety of variables reflecting physician practice, severity of presentation, and likelihood of fungal infection, we created propensity scores for the likelihood of empiric antifungal therapy. The propensity score (i.e., the propensity for an infant to receive empiric antifungal therapy or not) is the summary predictor derived from the collection of potentially confounding covariates. Each infant's propensity score is an estimated probability of being exposed to empiric antifungal therapy.²⁴ The propensity scores were created from a logistic regression model that predicted antifungal use based on center, gestational age, birth weight, postnatal age at first positive culture, sex, race, prior surgical necrotizing enterocolitis or intestinal perforation, presence of central catheter, hyperglycemia, hypoglycemia, presence of endotracheal tube, use of systemic steroids, platelet count, days of antibiotic exposure, and amount of enteral fluid received in the previous 24 hours. Clinical data used as predictors in the model to create propensity scores were collected on the day of or in the week prior to the first positive culture for *Candida*.

We then created models with and without stratification by propensity score quartiles to predict each of the outcome variables. Cox proportional hazards regression models were created for days until clearance of *Candida*, and logistic regression models were created to predict all categorical outcomes. Birth weight, age, sex, and use of empiric antifungal therapy were included in the models as covariates. For the composite outcome of death or NDI, Bayley exam cohort (born prior to 2006 vs. born in 2006 or later) was an additional covariate. Because of the small number of infants with NDI, empiric antifungal therapy and Bayley exam cohort were the only covariates included in that model. Likewise, for the outcome of EOD, the use of empiric antifungal therapy was the only covariate used in the logistic regression model for this outcome. Cox regression models produced hazard ratios (HRs) and associated 95% confidence intervals (CI) for each covariate, and logistic regression models were used to generate odds ratios (ORs) and 95% confidence intervals. *P* values <0.05 were considered statistically significant. All analyses were conducted using SAS version 9 (SAS Institute Inc, Cary, NC).

RESULTS

Of a total of 1515 ELBW infants enrolled at Neonatal Research Network sites, 136 infants met the inclusion criteria and were included in the study. The median gestational age at birth was 24.9 weeks (interquartile range [IQR] 24.0–25.9), the median birth weight was 683 g (615–820), the median age at first positive culture was 20 days (12–33), and 59/136 (43%) of the subjects were female (Table 1). There was no difference in gestational age at birth, age at first positive culture, birth weight, sex, or race between infants who received empiric antifungal therapy and infants who did not receive empiric antifungal therapy. Of the infants who received empiric antifungal therapy, 24/39 (62%) received amphotericin B, 9/39 (23%) received amphotericin B lipid preparations, 5/39 (13%) received fluconazole, and 1/39 (3%) received 5-flucytosine. These medications represented the empiric therapy; most infants also received other antifungal agents throughout their treatment courses. The median number of days between the start of empiric therapy and the day that the culture was reported positive for *Candida* was 2 days (1–4). Of the 136 infants, 9/136 (7%) received fluconazole prophylaxis at some point during the study; only 3/9 (33%) started prophylaxis prior to or on the day of the first positive culture and were still receiving it on the day of the first positive culture, and none of these 3 infants received empiric antifungal therapy.

A total of 139 organisms were isolated from the 136 infants (Table 1). *Candida* species were isolated from the blood only in 69/136 (51%), the urine only in 33/136 (24%), the CSF only in 2/136 (1%), another sterile body source only in 4/136 (3%), and multiple sources in 28/136 (21%). The most commonly isolated pathogens were *C. albicans* (86/139, 62%) and *C. parapsilosis* (41/139, 29%). Three infants had positive cultures for both *C. albicans* and *C. parapsilosis*. There was no difference in the proportion of organisms classified into each of these groups between infants who received empiric antifungal therapy and infants who did not receive empiric antifungal therapy ($P=0.33$).

Overall, death occurred in 47/136 (35%) infants (Table 2). The incidence of NDI was 32% (23/73). Death or NDI at 18–22 months adjusted age occurred in 60% of infants (74/124). The median (IQR) time until clearance of infection was 6 (4–14) days for the 95 infants who attained clearance. The incidence of surgery for ROP was 29/90 (32%), and the incidence of BPD was 64/101 (63%). EOD occurred in 8/131 (6%) infants.

Propensity scores for empiric antifungal therapy were created for the 116 infants with complete data for all predictors in the propensity score model. In 105/116 cases, the clinical predictors in the model used to create the propensity score were collected on the day of the first positive culture; in 11/116 cases, the clinical data were from the week prior to the first positive culture. Twenty infants were missing at least 1 variable used to calculate the propensity score and were excluded from subsequent models stratified by quartile of propensity score.

Models with and without stratification by propensity score quartile produced similar results. There was no difference in death, time until clearance, surgery for ROP, BPD, EOD, or NDI between infants who received empiric antifungal therapy and infants who did not receive empiric antifungal therapy (Table 3). For the combined outcomes of EOD or death, surgery for ROP or death, and BPD or death, there was also no difference between groups. However, for the composite outcome of NDI or death by 18–22 months corrected age, the incidence was lower for infants who received empiric antifungal therapy (19/38, 50%) compared with infants who had not received empiric antifungal therapy (55/86, 64%; OR=0.27 [95% CI 0.08–0.86]; $P=0.03$). This result was unchanged when the 3 infants receiving fluconazole prophylaxis at the time of the first positive culture were excluded from analysis (OR=0.25 [95% CI 0.08–0.82]; $P=0.02$).

DISCUSSION

Although guidelines exist for empiric therapy for other infections in infants, such as group B *Streptococcus* infections,²⁵ no such recommendations are available for the empiric treatment of fungal infections. The most recent guidelines by the Infectious Diseases Society of America on the management of adult and pediatric patients with invasive and mucosal candidiasis do not address the issue of empiric therapy in infants.²⁶ We therefore sought to determine whether empiric antifungal therapy was associated with higher survival, shorter time to clearance of *Candida*, and lower incidence of NDI in a large group of infants with documented *Candida* infections. Although there were no differences in these single outcomes between infants who did and did not receive empiric antifungal therapy, we found that infants who received empiric antifungal therapy had improved survival without NDI at 18–22 months adjusted age.

Randomized studies in adults and children with cancer, fever, and neutropenia have shown a clear clinical benefit of empiric antifungal therapy, without proof of survival benefit.^{16, 7, 27} In addition to these randomized trials, several retrospective studies have analyzed outcomes of patients with documented invasive *Candida* infection to determine the effect of empiric

antifungal therapy on mortality. Adequate antifungal therapy administered prior to the reporting of blood culture results was associated with improved survival in a cohort of 199 patients (including 29 children and 11 premature infants) with invasive *Candida* infection.¹⁸ In a study of 157 adults with candidemia, delay of therapy for >12 hours was an independent risk factor for mortality.²⁸

Although fewer data examining empiric antifungal therapy in infants are available, several prior small studies suggest a possible benefit. In a report of 13 patients weighing <2000 g with *Candida* infection, 10/13 (77%) received inadequate empiric therapy.²⁹ The study did not address the effect of antifungal therapy alone; however, mortality was found to be higher in patients who had received inadequate empiric therapy for any bacterial or fungal organism, 9/21 (43%), than in patients who received adequate therapy, 3/24 (13%). A retrospective study of 51 infants with candidiasis found an absolute mortality reduction of 12% when patients were started on appropriate antifungal therapy <2 days after the blood culture was drawn.² In a single-center, retrospective study, empiric antifungal therapy was initiated at the time of sepsis evaluation in infants <1500 g who had clinical signs of infection or neutropenia, had been exposed to broad-spectrum antibiotics for at least 7 days, and had at least 1 of the following additional risk factors: total parenteral nutrition, mechanical ventilation, postnatal corticosteroid therapy, exposure to an histamine-2 receptor blocker, or signs of mucocutaneous *Candida* infection.²⁰ Death occurred in 11/18 (61%) infants with *Candida* sepsis prior to the institution of the empiric antifungal therapy. After institution of empiric antifungal therapy guidelines, none of the 6 infants with *Candida* sepsis died. The results of these studies are consistent with our finding of possible benefit from empiric antifungal therapy.

Mortality in our cohort (35%) and the incidence of death or NDI (60%) are consistent with previous studies of infants with *Candida* infection.^{4,30} With such a high incidence of adverse outcomes, it is essential to identify affected infants early in order to initiate therapy. However, blood culture take an average of 2 days to become positive for *Candida* and can be falsely negative. Over-reliance on blood cultures may lead to significant delay in therapy; other methods to diagnose invasive candidiasis (e.g., polymerase chain reaction) have not been validated in infants.⁹

In addition to poor performance of laboratory assays to detect invasive candidiasis, we have shown previously that NICU clinicians are not able to diagnose the infection clinically.²¹ The use of empiric antifungal therapy in infants at risk for fungal infections could eliminate these delays and lead to lower mortality and improved neurodevelopmental outcomes. Routine use of empiric antifungal therapy, however, will also increase exposure to systemic antifungal agents and thus exposure to possible side effects. Given the poor sensitivity of laboratory methods for detection of invasive candidiasis, duration of therapy in infants with negative cultures remains a matter of debate. We suggest that although antifungal therapy can be discontinued in infants with negative cultures, these infants should be monitored closely for deterioration following cessation of therapy. Cultures should be repeated promptly at any subsequent signs of clinical decompensation. Repeated cultures increase the likelihood that invasive candidiasis will be detected.

The use of fluconazole prophylaxis to prevent invasive fungal infection was not evaluated in our study. Excluding from analysis infants receiving prophylactic fluconazole at the time of culture did not change our results. Although several randomized trials in infants have demonstrated the efficacy of fluconazole prophylaxis in reducing colonization and preventing invasive fungal infection,^{3,31} because of concerns regarding the development of resistance and drug side effects, routine prophylaxis is not recommended for all at-risk infants.³² Several retrospective studies have evaluated the use of oral nystatin prophylaxis in

premature infants and suggest a possible decrease in fungal infection, but no randomized studies have been reported.^{33,34} Even if prophylaxis is provided to the most premature infants (e.g., <750 g birth weight), invasive candidiasis will remain a concern for more mature preterm infants, young infants who have undergone surgery, and infants who receive prophylaxis and suffer from breakthrough infections. Antifungal prophylaxis in populations in which it is currently indicated (e.g., patients who have received stem cell transplantation) reduces but does not eliminate invasive fungal infections.³⁵ Likewise, invasive fungal infections can occur in infants who are receiving antifungal prophylaxis. Therefore, regardless of whether antifungal prophylaxis is being employed, clinicians should consider the use of empiric antifungal therapy in infants undergoing evaluations for sepsis due to clinical decompensation.

This study has several limitations. The primary limitation is that the study is a pre-specified secondary analysis of a prospective observational study and is not a randomized trial. Regression models and propensity scores in cohort studies may overlook significant covariables that influence outcomes, which are more likely to be balanced in randomized studies. We were also limited in our analysis of the secondary outcome EOD by the small numbers of infants who exhibited this outcome. The outcome of days until clearance of infection may also be unreliable because the date of the first negative blood culture is not always consistent with the exact time of clearance. An additional limitation to our study is that neurodevelopmental status was assessed by a single follow-up visit. As children grow older, neurodevelopmental outcomes often evolve.³⁶

As NICUs are faced with caring for increasing numbers of extremely premature infants, guidelines for empiric antifungal therapy will be essential. The utility of empiric antifungal therapy will be best addressed with an adequately powered randomized controlled trial.

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LIST OF ABBREVIATIONS

BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CSF	Cerebrospinal fluid
ELBW	Extremely low birth weight
EOD	End-organ damage
IQR	Interquartile range
HR	Hazard ratio
MDI	Mental Developmental Index
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit
OR	Odds ratio
PDI	Psychomotor Developmental Index

PMA	Postmenstrual age
ROP	Retinopathy of prematurity

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Table I

Demographics and organisms

	Received empiric antifungal therapy N=39 (%)	Did not receive empiric antifungal therapy N=97 (%)	P value
Gestational age (weeks)			0.33
22–24	23 (59)	51 (53)	
25–27	16 (41)	41 (42)	
28–29	0 (0)	5 (5)	
Sex			0.73
Female	16 (41)	43 (44)	
Race			0.93
Non-Hispanic white	10 (26)	28 (29)	
Non-Hispanic black	17 (44)	40 (41)	
Other/unknown	12 (31)	29 (30)	
Birth weight (g)			0.87
<500	2 (5)	2 (2)	
500–599	6 (15)	14 (14)	
600–699	16 (41)	34 (35)	
700–799	6 (15)	18 (19)	
800–899	5 (13)	15 (15)	
900–999	4 (10)	14 (14)	
Day of life at time of 1 st positive culture			0.87
7	2 (5)	8 (8)	
8–14	11 (28)	22 (23)	
15–28	13 (33)	38 (39)	
29–63	11 (28)	23 (24)	
>63	2 (5)	6 (6)	
Organism			0.33
<i>C. albicans</i>	27 (69)	59 (61)*	
<i>C. parapsilosis</i>	10 (26)	28 (29)	
<i>C. glabrata</i>	1 (3)	4 (4)	
Other†	1 (3)	6 (6)	

* Includes 3 infants with both *C. albicans* and *C. parapsilosis*.

† Includes unknown (4 who did not receive empirical therapy), *C. tropicalis* and *C. guilliermondii* (1 each in those who did not receive empirical therapy), and *C. lusitanae* (1 who received empirical therapy).

Table II**Outcomes**

Outcome	Received empiric antifungal therapy (n=39)	Did not receive empiric antifungal therapy (n=97)
Death, N (%)	13/39 (33)	34/97 (35)
Days until clearance, median (IQR)	7 (4–10)	6 (4–14)
End-organ damage, N (%)	2/36 (6)	6/95 (6)
End-organ damage or death, N (%)	15/39 (38)	37/96 (39)
Surgery for retinopathy of prematurity, N (%)	9/28 (32)	20/62 (32)
Surgery for retinopathy of prematurity or death, N (%)	20/38 (53)	51/88 (58)
Bronchopulmonary dysplasia, N (%)	17/29 (59)	47/72 (65)
Bronchopulmonary dysplasia or death, N (%)	27/39 (69)	71/96 (74)
Neurodevelopmental impairment, N (%)	5/24 (21)	18/49 (37)
Neurodevelopmental impairment or death, N (%)	19/38 (50)	55/86 (64)

Table III

Effect of empiric antifungal therapy on outcomes

Outcome	Model without stratification on propensity score quartile OR or HR (95% CI)	Model with stratification on propensity score quartile OR or HR (95% CI)	Stratified model P value
Death (OR)	0.75 (0.32–1.75)	0.58 (0.20–1.66)	0.31
Days until clearance (HR)	1.43 (0.92–2.23)	1.55 (0.88–2.72)	0.13
End-organ damage (OR)	0.87 (0.17–4.54)	2.49 (0.33–18.9)	0.38
End-organ damage or death (OR)	0.84 (0.37–1.92)	0.80 (0.29–2.22)	0.67
Surgery for retinopathy of prematurity (OR)	0.99 (0.36–2.77)	0.56 (0.16–1.99)	0.37
Surgery for retinopathy of prematurity or death (OR)	0.65 (0.28–1.45)	0.41 (0.15–1.14)	0.09
Bronchopulmonary dysplasia (OR)	0.70 (0.28–1.74)	1.09 (0.34–3.45)	0.89
Bronchopulmonary dysplasia or death (OR)	0.63 (0.27–1.52)	0.91 (0.31–2.71)	0.87
Neurodevelopmental impairment (OR)	0.34 (0.09–1.21)	0.40 (0.07–2.17)	0.29
Neurodevelopmental impairment or death (OR)	0.36 (0.15–0.88)	0.27 (0.08–0.86)	0.03

Referent: no empiric therapy. Logistic and Cox proportional hazards regression models included the following covariates: birth weight, age, sex, and use of empirical antifungal therapy. For the composite outcome of death or NDI, Bayley exam cohort (born prior to 2006 vs. born in 2006 or later) was an additional covariate. For NDI, the only covariates included were empiric antifungal therapy and Bayley exam cohort. For end-organ damage, the only covariate included was the use of empiric antifungal therapy. Models were created with and without stratification on propensity score quartile.