Outcomes Following Candiduria in Extremely Low Birth Weight Infants

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Background. Candidiasis carries a significant risk of death or neurodevelopmental impairment (NDI) in extremely low birth weight infants (ELBW; <1000 g). We sought to determine the impact of candiduria in ELBW preterm infants.

Methods. Our study was a secondary analysis of the Neonatal Research Network study Early Diagnosis of Nosocomial Candidiasis. Follow-up assessments included Bayley Scales of Infant Development examinations at 18–22 months of corrected age. Risk factors were compared between groups using exact tests and general linear modeling. Death, NDI, and death or NDI were compared using generalized linear mixed modeling.

Results. Of 1515 infants enrolled, 34 (2.2%) had candiduria only. Candida was isolated from blood only (69 of 1515 [4.6%]), cerebrospinal fluid (CSF) only (2 of 1515 [0.1%]), other sterile site only (not urine, blood, or CSF; 4 of 1515 [0.3%]), or multiple sources (28 of 1515 [2%]). Eleven infants had the same Candida species isolated in blood and urine within 3 days; 3 (27%) had a positive urine culture result first. Most urine isolates were Candida albicans (21 of 34 [62%]) or Candida parapsilosis (7 of 34 [29%]). Rate of death or NDI was greater among those with candiduria (50%) than among those with suspected but not proven infection (32%; odds ratio, 2.5 [95% confidence interval, 1.2–5.3]) after adjustment. No difference in death and death or NDI was noted between infants with candiduria and those with candidemia.

Conclusions. These findings provide compelling evidence that ELBW infants with candiduria are at substantial risk of death or NDI. Candiduria in ELBW preterm infants should prompt a systemic evaluation (blood, CSF, and abdominal ultrasound) for disseminated Candida infection and warrants treatment.

Invasive candidiasis is a leading cause of infectious mortality in the neonatal intensive care unit. The incidence in ELBW infants is 7%–8% [1–3], and neurodevelopmental impairment (NDI) is common among survivors [4]. Candida species invade virtually all tissues, including the retina, brain, heart, lung, liver, spleen, and joints [4, 5].

Data from animal and small single-center observational human studies suggest that candiduria in the premature infant is synonymous with disseminated Candida infection, results in high mortality, and should prompt a systemic evaluation (blood culture, cerebrospinal fluid [CSF] examination, and abdominal ultrasound) in premature infants [6–8]. However, some clinicians view Candida isolated from the urine of an infant as a contaminant. The epidemiology, risk factors for infection, and predictive capabilities of clinical judgment for the diagnosis of neonatal candidiasis were recently evaluated by the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network.
(NRN) Candida study [9]. In that cohort of ELBW infants suspected of having infection, mortality among infants with Candida isolated from urine only was similar to mortality among infants with Candida isolated from blood only. Mortality and NDI associated with candiduria in ELBW infants are unknown. In the current analysis, we compared mortality and NDI among infants in the NRN Candida study with candiduria only with those with candidemia and with ELBW infants with suspected, but not proven, infection to determine the impact of candiduria in ELBW infants.

**METHODS**

**Patients**
We performed a cohort study involving infants enrolled in the NRN Candida study [9]. The initial study identified risk factors for Candida infection and evaluated predictive models [9]. In this analysis, our primary goal was to determine the relationship between candiduria and death and/or NDI, and secondary goals were to determine the extent of sepsis evaluation in ELBW infants and the Candida species associated with candiduria. Infants with a birth weight <1000 g were evaluated for possible sepsis after 72 postnatal hours (late-onset sepsis [LOS] [3]) and <120 days of age and were treated from March 2004 through July 2007 at NRN sites. Two centers routinely used antifungal prophylaxis: 1 site used fluconazole (n = 56), and 1 site used nystatin (n = 104). None of the centers routinely used empirical antifungal therapy for infants undergoing an evaluation for possible LOS.

**Definitions**
Urine specimens obtained by suprapubic aspiration or in/out catheterization were evaluated in this analysis. Cultures deemed to be contaminants by the clinician were excluded (3 of 72 [4.2%] Candida-positive urine cultures). “Candiduria only” was defined as Candida isolated from urine during hospitalization (not from blood, CSF, or other sterile site), “Candidemia only” was defined as Candida isolated only from blood during hospitalization. Infants who were evaluated for sepsis but had no positive culture results (with bacteria or Candida) from a normally sterile site were classified as “no proven infection.” Sterile body fluid cultures positive for Candida were subcultured locally and shipped to Duke University for independent confirmation by the Duke University Mycology Research Unit. Antifungal therapy was prescribed at the discretion of the attending neonatologist; amphotericin B deoxycholate, lipid complex amphotericin, and fluconazole were the antifungal agents prescribed most frequently. Because the primary study was focused on risk and diagnosis, dosing was not recorded.

Concordance of culture results was determined at 2 levels: organism and timing. Organism concordance required isolation of the same Candida species in a normally sterile site (blood, urine, or CSF). Timing of concordance required at least 1 pair of positive urine and blood culture results within 72 hours of each other during the Candida infection. All reported concordant results met criteria for both organism and timing. Infants with isolation of the same organism in cultures obtained >72 hours apart were classified as having persistent infection. Positive culture results that occurred >2 weeks apart and/or were due to different Candida species were classified as separate infections. Prolonged initial empirical antibiotic therapy was defined as broad-spectrum antimicrobial use >5 days from birth in the absence of a positive blood culture result. Medicaid or uninsured status was used as a proxy for socioeconomic status. Insurance data were obtained from the discharge questionnaire or 18-month follow-up questionnaire if the discharge questionnaire was missing. Insurance data from the most proximal follow-up questionnaires were substituted for missing data at baseline. Necrotizing enterocolitis, periventricular leukomalacia, intraventricular hemorrhage, and postnatal steroids for bronchopulmonary dysplasia were defined as previously described [10]. NDI at 18–22 months of age was defined as any impairment in Table 1; evaluation included the Bayley Scales of Infant Development (BSID) II (for infants born before 2006) or III.

**Statistical Analysis**
All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute). All results are reported at the infant level. For analyses that are necessarily culture-specific (eg, entry blood and first positive result), the earliest culture is referenced. Extent of sepsis evaluation was assessed as (1) the frequency of

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic impairment</td>
<td>Moderate to severe cerebral palsy with GMFCS level ≥2</td>
<td>Moderate to severe cerebral palsy with GMFCS level ≥2</td>
</tr>
<tr>
<td>Development</td>
<td>Bayley II MDI &lt;70 or PDI &lt;70</td>
<td>Bayley III cognitive &lt;70 or GMFCS level ≥2</td>
</tr>
<tr>
<td>Vision</td>
<td>Bilateral blindness with no functional vision</td>
<td>&lt;20–200 bilateral</td>
</tr>
<tr>
<td>Hearing</td>
<td>Bilateral amplification for permanent hearing loss</td>
<td>Permanent hearing loss that does not permit the child to understand directions of examiner and communicate despite amplification</td>
</tr>
</tbody>
</table>

Abbreviations: GMFCS, gross motor function classification system; MDI, mental development index; PDI, psychomotor development index.
blood, urine, and CSF samples sent for culture within 72 hours after the entry blood culture; (2) the frequency of blood, urine, and CSF samples sent for culture within 72 hours after the first culture positive for any bacteria or Candida; and (3) the frequency of blood, urine, and CSF samples sent for culture within 72 hours after the first culture positive for Candida for infants with candiduria or candidemia. Infants who died within 72 hours after the index culture were excluded only from the analysis of extent of evaluation.

Demographic characteristics and risk factors were contrasted between infection groups using Fisher exact tests and logistic regression for binary measures and general linear models for continuous measures. These characteristics and risk factors included gestational age at birth, birth weight, sex, ethnicity/race, premature rupture of membranes, vaginal or Cesarean delivery, Medicaid or uninsured status, antenatal antibiotic or steroid exposure, enteral feeding, presence of a central catheter, antibiotics, and prolonged initial empirical antibiotic therapy.

The prevalence of the following 4 adverse outcomes was calculated by infection group: (1) death by hospital discharge, (2) death by 18-month follow-up, (3) NDI at 18-month follow-up, and (4) death or NDI at 18-month follow-up (death/NDI). Associated odds ratios (ORs), confidence intervals (CIs), and P values were based on generalized linear mixed models, adjusting for clustering of children in research centers. Modeling of NDI outcomes was also adjusted for Bayley cohort (BSID II vs BSID III). Factors associated with Candida infection in unadjusted analyses were assessed in generalized linear mixed models models as potential confounders with death/NDI. A final model was fit to assess for the relationship of infection group status with death/NDI after adjusting for all potential confounders.

RESULTS

The NRN Candida study enrolled 1515 infants (Figure 1). An evaluation for LOS was a criterion for enrollment in the primary study and included a blood culture for all 1515 infants enrolled: 604 of 1515 had bacterial infection only, 92 of 1515 had an episode of both Candida and bacterial infection, 45 had Candida infection only, and 774 had no proven infection. Twenty-three of 34 infants (68%) with candiduria and 44 of 69 (64%) with candidemia also had bacterial infection. Twenty-eight of 1515 (2%) enrolled infants died within 72 hours after enrollment; 33 of 696

*Figure 1. Consort diagram of the cohort. *Groups of any infection (candidiasis or bacterial) are not mutually exclusive. Specifically, of 1515 enrolled infants, 604 had bacterial infection only, 92 had both Candida and bacterial infection, 45 had Candida infection only, and 774 had no proven infection. Infants with candiduria, candidemia, meningitis, or other sterile site had Candida isolated from that source alone. Abbreviations: ELBW, extremely low birth weight; NRN, neonatal research network.
Five of the 34 infants (15%) with candiduria had an episode of candiduria, and 2 of 69 (3%) with candidemia had Candida albicans frequently isolated species from the first positive culture result. The first Candida albicans-positive culture result was followed by Candida parapsilosis in approximately half of the survivors: 26 of 39 (67%) with candidemia, 9 of 22 (41%) with candiduria, and 290 of 599 (48%) with no proven infection. No statistically significant adjusted difference in death and the composite of death or NDI was noted between infants with candiduria and those with candidemia after adjustment for center and BSID cohort.

Outcomes Following Candiduria
Of the 764 infants alive at discharge in our study cohorts (candiduria [n = 25], candidemia [n = 50], or no proven infection [n = 689]), 13 (2%) died before follow-up and 91 (12%) were lost to follow-up or had incomplete NDI information available.

Outcomes (adjusting for center and Bayley cohort, as appropriate) after candiduria or candidemia, compared with infants with no proven infection, are shown in Table 4. Death before discharge was more frequent in infants with candiduria (9 of 34 [26%]) or candidemia (19 of 69 [28%]), compared with those with no proven infection (85 of 774 [11%]) (OR, 2.7 [95% CI, 1.2–6.1], for candiduria vs no proven infection). Death by 18 months was more frequent in infants with candiduria (10 of 33 [30%]) or candidemia (22 of 61 [36%]), compared with infants with no proven infection (94 of 725 [13%]) (OR, 2.8 [95% CI, 1.3–6.1], for candiduria vs no proven infection). The BSID II examination was used for follow-up evaluation at 18–22 months in approximately half of the survivors: 26 of 39 (67%) with candidemia, 9 of 22 (41%) with candiduria, and 290 of 599 (48%) with no proven infection. No statistically significant adjusted difference in death and the composite of death or NDI was noted between infants with candiduria and those with candidemia after adjustment for center and BSID cohort.

| Table 2. Late-Onset Sepsis Evaluation in Extremely Low Birth Weight Infants | Depth of Evaluation Within 72 Hours of Reference Culture* |
|---|---|---|---|---|---|
| **Reference Culture** | **Total Cohort** (N = 1487) | **Any Bacterial Infection** (n = 663) | **Any Candidiasis** (n = 127) | **Candiduria** (n = 34) | **Candidemia** (n = 62) |
| **Depth of Evaluation** | **Entry Blood** | **First Bacterial Positive** | **First Candida Positive** | **First Candida-Positive Urine** | **First Candida-Positive Blood** |
| Blood + urine | No. (%), % Male | No. (%), % Male | No. (%), % Male | No. (%), % Male | No. (%), % Male |
| 197 (13%), 51% | 95 (14%), 61% | 30 (24%), 67% | 12 (35%), 67% | 11 (18%), 91% |
| Blood + CSF | 219 (15%), 53% | 98 (15%), 48% | 23 (18%), 35% | 16 (26%), 25% |
| Urine + CSF | 35 (5%), 66% | 4 (3%), 100% | 4 (12%), 100% |
| Blood + urine + CSF | 217 (15%), 56% | 111 (17%), 51% | 20 (16%), 65% | 3 (9%), 67% | 12 (19%), 58% |

Abbreviation: CSF, cerebrospinal fluid.

* Fifty-six infants (4%) were excluded from at least 1 analysis of evaluation depth because they died within 72 hours of a reference culture.

**Evaluation categories are mutually exclusive.**

Blood, urine, CSF, or other normally sterile source.

(5%) infants with any bacterial infection, 10 of 137 (7%) with any candidiasis, 7 of 69 (10%) with candidemia, and 0 of 34 with candiduria died within 72 hours after the first positive reference culture result. Infants who died within 72 hours after the reference culture were excluded only from relevant analyses in Table 2.

Infants with candiduria were more likely to have prolonged rupture of membranes, be delivered vaginally, have lower mean birth weight and mean gestational age, be male (71% vs 46%), and have prolonged initial empirical antibiotic therapy (Table 3), compared with those without infection. No differences were observed between infants with candiduria and infants with candidemia for the presence of a central venous line within 3 days after discharge, and 7 (23%) were Candida-positive by repeat testing. Renal ultrasound was performed in 23 of 34 (68%) with candiduria; no abscesses were identified in these patients. Nine of the 11 infants with concordant Candida infection had a renal ultrasound, and 2 had renal abscesses.

Timing, Etiology, and Persistence of Infection
The first Candida-positive urine culture result occurred on median postnatal day 29.5 (5th–95th percentile, 8–73). The most frequently isolated species from the first positive culture result was *Candida albicans* (blood: 36 of 69 [52%]; urine: 21 of 34 [62%]), followed by *Candida parapsilosis* (blood: 25 of 69 [36%]; urine: 7 of 34 [21%]). Organism-associated mortality was similar for candiduria and candidemia. *C. parapsilosis* was associated with the greatest mortality (blood: 6 of 25 [24%]; urine: 2 of 7 [29%]), followed by *C. albicans* (blood: 8 of 36 [22%]; urine: 5 of 21 [24%]). Five of the 34 infants (15%) with candiduria had >1 episode of candiduria, and 2 of 69 (3%) with candidemia had a second Candida infection. In total, 7 of 34 (21%) infants with candiduria and 20 of 69 (29%) infants with candidemia had persistent or multiple infections.

Follow-up urine culture was performed for 30 of 34 infants with candiduria (2 infants without repeat testing died before discharge), and 7 (23%) were Candida-positive by repeat testing. Renal ultrasound was performed in 23 of 34 (68%) with candiduria; no abscesses were identified in these patients. Nine of the 11 infants with concordant Candida infection had a renal ultrasound, and 2 had renal abscesses.
The combined rate of death or NDI at 18–22 months was 50% among infants with candiduria, 61% among those with candidemia, and 32% among those with no proven infection. In a model adjusting for center and Bayley cohort, the risk of death or NDI was increased among infants with candiduria, compared with those with no proven infection (OR, 2.5 [95% CI, 1.2–5.3]), and among those with candidemia, compared with those with no proven infection (OR, 3.0 [95% CI, 1.7–5.3]) (Table 5). There was no statistically significant difference in the adjusted risk of death/NDI between infants with candiduria and those with candidemia (OR, 0.8 [95% CI, 0.3–2.2]).

**DISCUSSION**

The goal of this analysis was to determine the incidence and impact of candiduria on death and NDI among ELBW infants. The NRN *Candida* study is the largest cohort of comprehensively studied ELBW infants with candiduria and includes follow-up evaluation at 18 months. Our findings underscore the clinical importance of a *Candida*-positive urine culture result in ELBW infants and support the need for clinical and laboratory evaluation and treatment.

The clinical risk factors and specific pathogen frequency and mortality did not differ between infants with candiduria and those with candidemia in this cohort and in comparison with a previous NRN study cohort [4]. No differences were present between infants with candiduria and those with candidemia with respect to initiation of early feeding (by day of life 3) and use of cephalosporins in close proximity to infection. The only potentially modifiable risk factor for candiduria that we identified was the use of prolonged initial empirical antibiotic therapy in the absence of a positive blood culture result. Specific *Candida* species frequency and organism-associated mortality were similar among infants with candiduria and candidemia.
Candiduria in this cohort of comprehensively studied ELBW infants significantly increased the risk of death (by discharge or by 18 months) and death or NDI at 18 months, compared with no proven infection. Adjusted analyses showed no difference in death or NDI at 18 months between infants with candiduria and those with candidemia or between infants with candiduria and those with no proven infection. This may be a reflection of the small sample size of infants with \textit{Candida} infection seen at 18 months, because the positive ORs demonstrated an increased risk of death or NDI. Our cohort consisted of 22 ELBW infants with candiduria who were evaluated for NDI at 18–22 months. Of note, rate of NDI was not statistically different among the 3 groups (suspected infection, not proven; candiduria; and candidemia) (Table 4). Our findings are in contrast to the findings of a previous NRN article based on a different cohort of infants [4]. We believe that this is a reflection of the smaller sample size in the current cohort. Outcome information on ELBW infants who were not evaluated for infection was not available to permit comparison with a group of infants without suspected sepsis. In the previous NRN study, >300 infants developed invasive candidiasis, with 178 evaluated for NDI at 18–22 months [4]. Data on the frequency and impact of

### Table 4. Outcomes Following Candiduria in Extremely Low Birth Weight Infants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Proven Infection (n = 774)</th>
<th>Candiduria (n = 34)</th>
<th>Candidemia (n = 69)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death by discharge&lt;sup&gt;c&lt;/sup&gt;</td>
<td>85/774 (11%)</td>
<td>9/34 (26%)</td>
<td>19/69 (28%)</td>
<td>2.69 (1.18–6.13)</td>
</tr>
<tr>
<td>Death by 18 months&lt;sup&gt;c&lt;/sup&gt;</td>
<td>94/725 (13%)</td>
<td>10/33 (30%)</td>
<td>22/61 (36%)</td>
<td>2.77 (1.25–6.14)</td>
</tr>
<tr>
<td>NDI by 18 months&lt;sup&gt;d&lt;/sup&gt;</td>
<td>130/599 (22%)</td>
<td>6/22 (27%)</td>
<td>15/39 (38%)</td>
<td>1.62 (.57–4.59)</td>
</tr>
<tr>
<td>Death or NDI by 18 months&lt;sup&gt;d&lt;/sup&gt;</td>
<td>224/693 (32%)</td>
<td>16/32 (50%)</td>
<td>37/61 (61%)</td>
<td>2.49 (1.16–5.33)</td>
</tr>
</tbody>
</table>

Reasons NDI could be missing: child died, child was not present at the 18-month follow-up, or not enough information was available to determine NDI. Number of children with complete NDI data: no infection (Bayley II [n = 290], Bayley III [n = 309]), candidia (Bayley II [n = 9], Bayley III [n = 13]), candidemia (Bayley II [n = 26], Bayley III [n = 13]).

**Abbreviations:** CI, confidence interval; CSF, cerebrospinal fluid; NDI, neurodevelopmental impairment; OR, odds ratio.

<sup>a</sup> At least 1 urine culture positive during hospitalization. Infants who had multiple episodes of infection from the same organism are included. Infants who also had \textit{Candida} in blood/CSF/other sterile source at any time during hospitalization are excluded.

<sup>b</sup> At least 1 blood culture positive during hospitalization. Infants who had multiple episodes of infection from the same organism are included. Infants who also had \textit{Candida} in urine/CSF/other sterile source at any time during hospitalization are excluded.

<sup>c</sup> Analyses of death by discharge and death by 18 months are adjusted for clustering of children within center.

<sup>d</sup> Analyses of NDI by 18 months or death/NDI by 18 months are adjusted for clustering of children within center and Bayley cohort.

<sup>e</sup> OR (95% CI) is for no proven infection versus candiduria.

### Table 5. Predictors of Neurodevelopmental Impairment and Death in Extremely Low Birth Weight Infants Before and After Adjustment

<table>
<thead>
<tr>
<th>Predictor of Death or NDI by 18 Months</th>
<th>Adjusted for Bayley Cohort and Center&lt;sup&gt;a&lt;/sup&gt; OR (95% CI)</th>
<th>Adjusted for All Covariates&lt;sup&gt;b&lt;/sup&gt; OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Candidiasis group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candiduria vs no proven infection</td>
<td>2.49 (1.16–5.33)</td>
<td>1.73 (0.75–3.96)</td>
</tr>
<tr>
<td>Candidemia vs no proven infection</td>
<td>2.97 (1.67–5.28)</td>
<td>2.20 (1.13–4.26)</td>
</tr>
<tr>
<td>Candidia vs candidemia</td>
<td>0.84 (0.33–2.12)</td>
<td>0.79 (0.28–2.17)</td>
</tr>
<tr>
<td>GA at birth, decreasing weeks</td>
<td>1.27 (1.15–1.40)</td>
<td>1.13 (1.00–1.28)</td>
</tr>
<tr>
<td><strong>Birth weight (grams)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>750–1000</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>500–749</td>
<td>2.03 (1.47–2.80)</td>
<td>1.75 (1.18–2.58)</td>
</tr>
<tr>
<td>&lt;500</td>
<td>9.88 (3.00–32.51)</td>
<td>8.24 (2.45–27.72)</td>
</tr>
<tr>
<td>Male</td>
<td>1.78 (1.30–2.43)</td>
<td>1.86 (1.32–2.64)</td>
</tr>
<tr>
<td>ROM &gt;18 hours</td>
<td>1.10 (.75–1.62)</td>
<td>1.13 (.73–1.74)</td>
</tr>
<tr>
<td>Caesarean delivery</td>
<td>1.24 (.89–1.73)</td>
<td>1.54 (1.03–2.28)</td>
</tr>
<tr>
<td>Medicaid or uninsured&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.53 (1.10–2.14)</td>
<td>1.56 (1.09–2.25)</td>
</tr>
<tr>
<td>Prolonged initial empirical antibiotic therapy&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.36 (.98–1.88)</td>
<td>1.24 (.87–1.78)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; GA, gestational age; NDI, neurodevelopmental impairment; OR, odds ratio ROM, rupture of membranes.

<sup>a</sup> Maximum n = 786.

<sup>b</sup> Maximum n = 726.

<sup>c</sup> Medicaid/uninsured indicates that insurance is from public sources, a mix of public and private sources, or that the infant was uninsured.

<sup>d</sup> More than 5 days of broad-spectrum antimicrobial treatment in the absence of a positive blood culture.
candiduria were not collected as part of that investigation. In the current cohort, we evaluated 103 infants with invasive candidiasis (69 with candidemia and 34 with candiduria) and collected NDI information on 61 (59% of those with invasive candidiasis: 39 with candidemia and 22 with candiduria). In addition, 18–22-month follow-up evaluation included BSID II examination in approximately half of the cohort.

Candiduria, which may precede a Candida-positive blood culture result, is likely to be underdiagnosed because of failure to evaluate urine samples from ELBW infants with suspected infection and the bias of some clinicians that Candida in the urine is likely to be a contaminant. In addition, in some cases, there may be negative blood culture results with the presence of invasive disease in the urinary tract [11, 12]. Infants who receive a diagnosis of candiduria may have a higher risk (30%–50%) of developing subsequent candidemia [8, 13, 14]. In this cohort, urine samples were evaluated within 72 hours in only 11 of 62 (18%) of infants with candidemia. In addition, infants with Candida-positive blood and urine culture results represented the largest group of those with multisource Candida infection in this cohort (11 of 28 [39%]). Of note, 7 of 11 (64%) infants with concordant candiduria and candidemia died.

Some clinicians view Candida isolated from the urine of an infant as a likely contaminant, particularly if from a catheterized specimen in an uncircumcised male infant. Although this approach may be reasonable in the older patient with an indwelling catheter in the intensive care setting [15], our data suggest that it is not appropriate for the ELBW infant. The current Infectious Diseases Society of America guidelines for the treatment of invasive candidiasis support aggressive universal antifungal therapy for neonatal candiduria is weak [15]. Evaluation in very low birth weight infants (birth weight <1500 g) showed that candiduria significantly increased the risk of invasive candidiasis [16]. Taken together with our current findings, these data reinforce the need for a systemic evaluation for disseminated infection and initiation of antifungal treatment in ELBW infants with isolated candiduria.

Urine cultures were included in the LOS evaluation (≥72 hours of life) for 197 of 1515 (13%) infants in this cohort at enrollment in the primary study. Although studies involving preterm infants have suggested that urine cultures are of limited value as part of a sepsis evaluation on the first day of life, inclusion of a urine culture in the LOS evaluation is important [17]. The frequency of urinary tract infection (bacterial or fungal etiology) in this cohort was 11.4%, consistent with other epidemiologic reports in this age group [17, 18]. Urinary tract infection–associated mortality (bacterial or fungal) is not trivial (23%) in the preterm infant [8]. Very low rates of concurrent blood and urine assessment, combined with the limited sensitivity of diagnostic testing for Candida (21% with candidemia have false-negative blood culture results while receiving antifungal therapy) suggests that the actual rate of candiduria may be higher than found in this study. In addition, the frequency of performing a lumbar puncture for CSF culture was also low and concerning in light of the frequency of blood culture–negative bacterial meningitis (30% of CSF culture positive) or Candida meningitis (up to 50%) [4, 19, 20]. The clinician’s perception of the risk of lumbar puncture (“too sick to tap”) is often cited as the reason for deferral. Stoll et al [20] reported that performing a lumbar puncture in very low birth weight infants did not alter the risk of death, in stark contrast to meningitis, which increased the risk of death by >2.5-fold. Thus, barring clinical instability that might delay obtaining a CSF sample, an LOS evaluation in the preterm infant should include an attempt to perform cultures of urine, blood, and CSF samples.

Our study has several limitations. The number of candiduria observations (despite being the largest cohort of infants with candiduria and follow-up) is small. Another limitation is the change in the BSID testing used to assess neurodevelopment midway through follow-up of study participants. Some experts have expressed concern that the BSID III underestimates disabilities [21], but the BSID III includes separate assessments for language and cognition. For this analysis, with the small numbers of infants with the conditions of concern who were seen during follow-up, we did not perform separate analyses for each of the BSID cohorts but included testing of the 2 testing regimens in risk-adjusted analyses.

CONCLUSIONS

Urine cultures were included in the LOS evaluations of only a minority of ELBW infants in our study cohort. Because of adverse outcomes among ELBW infants with candiduria, we strongly suggest that urine, blood, and CSF samples be obtained when evaluating an ELBW for LOS. These findings provide compelling evidence that ELBW infants with candiduria are at substantial risk of death or NDI. Therefore, identification of candiduria should prompt a systemic evaluation for disseminated Candida infection and initiation of treatment in all ELBW infants.

Notes

Acknowledgments. The funding agencies provided overall oversight for study conduct, but all data analyses and interpretation were independent of the funding agencies.

Data collected at participating sites of the NICHD NRN were transmitted to RTI International, the data-coordinating center (DCC) for the network, which stored, managed, and analyzed the data for this study. On behalf of the NRN, Dr Abhik Das (DCC principal investigator), Dr Marie Gantz, and Ms Sylvia Tan (DCC statisticians) had full access to all the data in
the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study: [List of names and affiliations]

Conflicts of Interest. Conflicts that the editors consider relevant to the manuscript have been disclosed.

All authors: No reported conflicts.

Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the manuscript have been disclosed.

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