Neonatal Candiduria: Does it Jeopardize the Outcome of Infants at Risk in Cairo University Neonatal Intensive Care Units?

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Abstract

Background: There is limited information on neonatal candidal urinary tract infection (UTI). Predisposing factors are prematurity, antimicrobial agents, and prolonged hospital stay.

Objectives: To discuss the prevalence of candiduria among the risky neonates, to evaluate which of the predisposing factors has the highest risk of candiduria in Cairo University NICUs. We also tried to figure out the incidence of early complications (candidiasis and renal candidiasis) among candiduric neonates.

Patients and Methods: We prospectively studied 50 neonates at risk [with gestational age (GA) 30-39 weeks] from Neonatal Intensive Care Units NICUs of Cairo University between January 2009 and September 2009. Urine samples were collected by sterile urethral catheterization under complete aseptic precautions. Studied cases were divided according to presence of candida in urine into two main groups:
1- Group I (with candiduria) (n=16) [10 fullterm (FT) and 6 preterm (PT)].
2- Group II (without candiduria) (n=34).

Blood cultures, Kidney function tests and renal ultrasound were ordered for certain cases to exclude candidiasis.

Results: The incidence of candiduria among neonates at risk was 32% of case.

There was no significant difference between the two groups as regard GA sex, duration of either hospital stay, or antibiotic therapy. However, certain antibiotic combinations were associated with higher incidence of candiduria.

Conclusion: Neonatal candidal UTI may be associated with morbidity and mortality. Routine urine analysis (especially for neonates with risk factors) is recommended to start antifungal therapy. Periodic re-evaluation of the feedback of antibiotic therapy protocols-in NICUs- is mandatory.

Key Words: Candiduria – Neonatal Intensive Care Units (NICUs) – Antibiotics – Urinary tract infections.

Introduction

ISOLATION of Candida from the urine of newborns can be indicative of contamination or of urinary tract infection. Although bacteremia is a complication of less than 3% of pediatric nosocomial bacterial urinary tract infections (UTIs) it is not clear how often candidal UTI is a precursor to candidemia or to candidal infection at other sites [1]. Candidal UTI in the Neonatal Intensive Care Units (NICU) population occurs both in term infants with congenital abnormalities and in preterm infants, and is associated with renal parenchymal disease and extra-renal dissemination. A wide variation in clinical approach was documented. Factors which predispose to candiduria include: Prematurity, prior use of antimicrobial agents, indwelling urinary catheters and prolonged hospital stay [2].

Candidal urinary tract infection may be associated with candidemia in high risk newborn, and in advanced cases may be complicated by renal candidiasis (manifested by “fungus balls” in renal sonography or renal parenchymal infiltration) [3].

The overall mortality rate in those infants was significant (30%). In one third of the deaths, Candida infection was deemed to be a contributing factor, suggesting the need for antifungal therapy with repeat evaluation for dissemination in infants who are slow to respond to therapy [4].

The primary purpose of this study is to describe the prevalence, presentation, and clinical outcome of candidal UTIs in infants in the neonatal intensive care unit (NICU) of Cairo University Hospitals. Also we aimed to assess which of the studied risk factors carries the highest risk among our NICU patients.
Patients and Methods

This prospective study was performed in NICUs in Kasr El-Aini Obstetrics and Children hospitals of Cairo University. The study protocol was approved by the University ethics review board. Neonates ≤28 days of postnatal age were prospectively enrolled between Jan., 2009 and Sep. 2009 if they met one of three criteria:

1) Prematurity, 2) Extended hospital stay ≥7 day, or 3) they receive double or more antibiotic course for ≥7 days. Neonates receiving antifungal therapy were excluded as this might affect the results of urine culture. All neonates were submitted to full antenatal, natal and postnatal history taking including mode of delivery, gender, birth weight and assessed gestational age using the New Ballard Score [5]. Complications during hospital stay were recorded. Neonatal sepsis was diagnosed on clinical basis and laboratory data fulfilling 2 out of the following criteria: Positive blood culture, positive CRP value >1 0mg/L or immature: Total neutrophil (I/T) ratio >0.25 [6].

In our unit we assess respiratory distress severity using the Downes' score [7] and diagnose respiratory distress syndrome (RDS) radiologically together with arterial blood gases. Diagnosis of hypoxic ischemic encephalopathy (HIE) was based on history of labour and low apgar score together with clinical manifestations. Grading of HIE was done according to Sarnat and Sarnat [8]. For all included study subjects (50 at risk neonates), urine samples were collected by sterile urethral catheterization under complete aseptic precautions. Collected urine samples were sent immediately to the hospital microbiology lab. [9]. Blood cultures, Kidney function tests and renal ultrasound were ordered for certain cases with deterioration or slow response to treatment to exclude candidemia and renal candidiasis.

Urine analysis and culture methods:

In the microbiology lab, urine samples were microscopically examined and then cultured using a calibrated platinum loop (0.001ml) onto CLED (Cystine lactose electrolyte deficient) agar plates. Yeasts were identified by colony morphology and Gram stain. Colony counts of yeasts per one mL of urine were calculated by multiplying the number of yeast colonies on the culture plate by 1000. The detection level for quantitative cultures used in this study was 1000 CFU/ml, represented by a single colony of yeast on a plate [10].

Candida species identification: Candida species were identified by germ tube formation [11] and by Chromogenic media, CandiSelectTM 4 (Bio-Rad Laboratories, France).

Blood culture: When the patient showed bad general condition or on total parental nutrition (TPN) as risk factor of candidemia, blood culture was done to detect Candida in blood using the automated blood culture system BACTEC 9050. After overnight incubation at 37 °C, the resulting yeasts (if present) were identified as mentioned above to compare the Candida species in blood with that of urine [12].

Statistical methods:

Data were analyzed using SPSS program version 10. Numerical data were expressed as mean ± SD. t-test was used for comparison between means. Pearson correlation was used to correlate numerical values. Categorical data were summarized as number and percentages. Categorical data were compared using chi square test. For all tests $p$-value was considered significant if less than 0.05.

Results

Fifty infants (28 males, 22 females) met the study inclusion criteria whose median gestational age was 35.8 weeks (range 30-39 weeks) and median birth weight is 1354 (range 1250-4880) grams.

The studied cases were divided according to presence of candida in urine into two main groups (Fig. 1).

1- Group I (with candida in urine) (n=16) [10 fullterm (FT) and 6 preterm (PT)].
2- Group II (without candiduria) (n=34) [17 (50%) PT].

![Fig. (1): Results of urine culture for Candida.](image)
Table (1) shows demographic data of both groups. There was no statistical significant difference between both groups as regard gestational age, postnatal age, birth weight, durations of NICU stay and antibiotic regimens. Candidal UTI was diagnosed at a mean age of 15.75 (±5.5) days. Clinical findings on the day of diagnosis included fever of 38.0°C (n=3, 19%), feeding intolerance (n=2, 12.5%), and respiratory deterioration (n=3, 19%). Total study mortality was 12 cases (24%), out of which 5 cases were among group I (31%) versus 7 cases among group II (20.5%). Death was mainly due to sepsis or respiratory failure.

On comparing incidence of candiduria among fullterm (10) and preterm (6) studied cases, there was no statistically significant difference. (p-value: 0.408) (Table 2).

The primary reasons for NICU admission are demonstrated in Table (3). There was no statistical significant difference between the two studied groups (candida +ve or –ve) as regards diagnosis on NICU admission. (p =: 0.09).

Out of the 16 cases with candiduria, two infants (12.5%) showed bad general condition, so blood cultures were ordered and candidemia was excluded.

Three of them (19%) showed impaired kidney functions, with creatinine levels around 2.8mg% so abdominal US was done to exclude renal candidiasis as a complication of candiduria with negative results for renal fungal balls but one of which had polycystic kidney.

Table (4) demonstrates the comparison of antibiotic combinations between both groups where patients on antibiotic combination (group E) of Amoxicillin/sulbactam and 3rd generation cephalosporin showed higher incidence of candiduria (p-value: 0.004); and patients on Amoxicillin/sulbactam, aminoglycosides and 3rd generation cephalosporin (group C) showed lower incidence of candiduria.

There was no statistically significant difference between the two main groups as regard numbers of pus cells (p-value: 0.9) and RBCs (p-value: 0.4) in urine analysis Table (5).

Results of epithelial cells in urine analysis may be accompanied by significant increase incidence of candida in urine (p-value: ≤0.04) but there is no significant increase in crystals (oxalates, urates in urine in cases with candiduria (p = ≥0.77).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I N=16</th>
<th>Group II N=34</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weeks</td>
<td>37.56 ±3.52</td>
<td>37.08 ±3.03</td>
<td>0.62</td>
</tr>
<tr>
<td>Postnatal age</td>
<td>15.75 ±5.50</td>
<td>16.47 ±6.52</td>
<td>0.71</td>
</tr>
<tr>
<td>Birth weight (Kg)</td>
<td>2.52 ±0.76</td>
<td>2.37 ±0.84</td>
<td>0.55</td>
</tr>
<tr>
<td>Days in NICU</td>
<td>12.50 ±3.98</td>
<td>12.29 ±4.06</td>
<td>0.86</td>
</tr>
<tr>
<td>Antibiotic Duration (In days)</td>
<td>11.68 ±3.41</td>
<td>11.02 ±3.63</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Table (2): Comparison between the studied groups as regards gestational age.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (Candida positive)</th>
<th>Group II (Candida negative)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full term N (27)</td>
<td>10</td>
<td>17</td>
<td>0.408</td>
</tr>
<tr>
<td>Preterm N (23)</td>
<td>6</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

Table (3): Comparison between studied groups as regards diagnosis on NICU admission.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>4</td>
<td>5</td>
<td>0.09</td>
</tr>
<tr>
<td>Pneumonia/MAS</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>RDS</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>HIE</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Surgical conditions</td>
<td>2</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Grower</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Renal problems</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

RDS : Respiratory distress syndrome.
HIE : Hypoxic ischemic encephalopathy.
MAS : Meconium aspiration syndrome.
Grower : Preterms admitted for weight gain.
Table (4): Comparison between antibiotics used in Candida Positive and Candida negative cases.

<table>
<thead>
<tr>
<th>Antibiotic types</th>
<th>Group I N=16</th>
<th>Group I N=34</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A Ampcillin/Sulbactam and aminoglycosides</td>
<td>6 (37.5%)</td>
<td>11 (32.35%</td>
<td>0.7 (NS)</td>
</tr>
<tr>
<td>Group B Vancomycin and Imipenem</td>
<td>1 (6.2%)</td>
<td>1 (2.94%)</td>
<td>0.5 (NS)</td>
</tr>
<tr>
<td>Group C Ampcillin/sulbactam, aminoglycosides &amp; 3rd generation cephalosporin</td>
<td>2 (12.5%)</td>
<td>15 (44.11%)</td>
<td>0.02 (significant)</td>
</tr>
<tr>
<td>Group D Vancomycin and Imipenem &amp; 3rd gen cephalosporins</td>
<td>1 (6.2%)</td>
<td>5 (14.7%)</td>
<td>0.3 (NS)</td>
</tr>
<tr>
<td>Group E Ampcillin/sulbactam &amp; 3rd generation cephalosporin</td>
<td>6 (37.2%)</td>
<td>2 (5.88%)</td>
<td>0.004 (highly significant)</td>
</tr>
</tbody>
</table>

Pearson Chi-square

<table>
<thead>
<tr>
<th>p value</th>
<th>11.028</th>
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</thead>
</table>

Fig. (2): Types of Candida species among Group I.

Fig. (3): Sex distribution of candiduria in the studied neonates.

Fig. (4): C. albicans case 13.

Fig. (5): C. tropicalis case 6.
Table (5): Comparison between urine analysis (pus cells, RBCs) among studied groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I</th>
<th>Group II</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 16</td>
<td>N = 34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (±SD)</td>
<td>Median (range)</td>
<td>Mean (±SD)</td>
</tr>
<tr>
<td>Pus cells / HPF</td>
<td>6.06 (8.18)</td>
<td>4 (1-35)</td>
<td>6.08 (8.74)</td>
</tr>
<tr>
<td>RBCs / HPF</td>
<td>2.06 (2.08)</td>
<td>1 (1-8)</td>
<td>3.41 (6.29)</td>
</tr>
</tbody>
</table>

Discussion

Candida infections have become an increasingly frequent problem in neonatal intensive care units, particularly among extremely low birth weight infants. Multiple risk factors have been identified with prior antibiotic exposure, presence of a central line, endotracheal intubation, and prior fungal colonization reported most frequently. The primary site of infection can involve the bloodstream, meninges, or urinary tract, but disease is frequently disseminated to multiple organ systems [13]. Physicians often do not follow-up a positive urine analysis results for Candida. Efforts to increase clinician awareness of current recommendations for managing candiduria and further studies to elucidate specific risk factors in defined patient populations are warranted [14].

We studied fifty cases with two or more risk factors for candiduria in NICU. Sixteen of them (32%) were positive and thirty four (68%) were negative. Among positive cases, only two positive cases had risk factor for candidiasis (bad general condition) and needed blood culture to detect Candida in blood. Three positive cases had impaired kidney function and abdominal U.S was ordered to detect renal fungus of renal candidiasis.

The present study results agreed with Phillips et al. (1997) [15] who reported that Candida spp. were the pathogens identified in 42% of hospital-acquired urinary tract infections in a neonatal intensive care unit. However our results regarding incidence of candidemia tends to oppose the above study as no cases showed positive blood culture for Candida and renal US of the selected cases showed no renal fungus. This discrepancy may be attributed to the few number of cases, early blood sampling before the spread of Candida to blood to show candidemia or due to starting antifungal therapy when Candida have been detected in urine as a part of our units’ protocols.

Meanwhile, Bougnoux et al., 2008 [16] reported that, Candidemia is late-onset ICU-acquired infection associated with high mortality. No difference in susceptibility and genetic background were found between blood and urine strains of Candida species. Moreover, it was previously recommended that serial renal ultrasounds are required to reliably detect late appearing renal fungus balls in neonates with candiduria [17].

The current study comes in agreement with Devile et al., 1992 [18] who reported, long ago, that Candida albicans was the most commonly isolated organism in candiduria of term and preterm patients followed by C. tropicalis. Our results were also validated by Chen et al., (2008) [14] and Robinson et al., 2009 [4] who proved no significant influence for gestational age on the types of Candida isolated from urine.

Gender variation among neonates showed no significant difference as regards occurrence of Candiduria. A result which opposes Spahiu et al., 2010 [19] who revealed that, neonatal UTI revealed male predominance.

Our results revealed that congenital renal anomalies or surgical procedure have no effect on occurrence of candiduria. On the other hand, these conditions have been identified as major risk factors for UTI including candidal UTI in infants and older children [20]. This difference may be attributed to few numbers of cases with congenital renal anomalies or surgical cases among the studied cases. Results revealed that, cases on antibiotic combination of (Ampcillin/Sulbactam & 3rd generation Cephalosporin) have high incidence of urinary Candidiasis while those on (Ampcillin/Sulbactam, Aminoglycosides & 3rd generation Cephalosporin) have low incidence of urinary Candidiasis. These results need to be well investigated to detect whether or not aminoglycosides affect candidal colonization so as to explain the marked difference in incidence of candiduria between neonates receiving groups A and C of antibiotics.

Although Triolo et al., 2002 [21] reported that, neonatal Candiduria is rare but occur most often in patients with prolonged hospital stays and combined antibiotic therapy, our results showed that they have no effect on development of Candiduria. Although we excluded cases on antifungal therapy we couldn’t interrupt protocol of vitamins or tonics (that enhance the immune system) in NICU. This might explain the non significant candiduria in cases with prolonged hospital stay or extended antibiotic regimens. Regarding urine
analysis, our results agree with Robinson et al., 2009 [4] who stated that there was no relation between presence of Candida in urine and pyuria.

Primary Limitation to reach conclusion from this study was that, although patients were enrolled prospectively, investigations for dissemination were limited to the cases with clinical or laboratory signs so complication could not be precisely recognized. Moreover, we studied the incidence of candiduria among neonates with risk factors not among the whole NICU population.

Although, the need for full investigation of infants with candiduria in the absence of candidemia is less clear from the previous literature, it was suggested that extrarenal candidal infection should be sought even in infants on treatment with a slow response to therapy.

**Conclusion:**

Neonates presenting as candidal UTI, within the NICU population irrespective of gestational age, may be associated with morbidity and mortality.

Further studies are needed to highlight the percentage of candiduric patients complicated by candidemia or renal candidiasis and to determine the optimal therapy and duration of treatment for this relatively rare entity. Repeated revisions for combined antibiotic therapy protocols in NICUs is recommended to outweigh their benefits against side effects.

**References**