Management and outcome of positive urine cultures in a neonatal intensive care unit

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Objectives: The aim of this study was to describe the management and outcome of positive urine cultures in a neonatal intensive care unit (NICU).

Study design: A chart review was completed of infants born October 1, 2004 to December 31, 2006 and admitted to the NICU at the Royal Alexandra Hospital, Edmonton, Alberta with any growth of bacteria or fungi in urine.

Results: Positive urine cultures were obtained in 64 of 2936 admissions (2%) and were classified as contaminated urines (n = 34), possible urinary tract infection (UTI) (n = 14), definite UTI (n = 10), and candidal UTI (n = 6). Management was inconsistent. Two children required new assisted ventilation but no other complications occurred.

Conclusions: The diagnosis of UTI in NICU is hampered by use of urine collection methods that are subject to contamination. Outcome is generally excellent, but there is a great need for guidelines on management of positive urine cultures in the NICU.

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1. Introduction

A urine culture is usually obtained when a septic work-up is performed on a term or preterm infant as the symptoms and signs of a urinary tract infection (UTI) are non-specific. Interpretation of results is complicated by the fact that contamination can occur with all methods of urine collection. There are no widely-accepted guidelines for the diagnosis and management of urinary tract infections in newborns in general and in the neonatal intensive care unit (NICU) in particular with American Academy of Pediatrics UTI guidelines being limited to children 2 months of age or older [1].
The objectives of this study were to describe the incidence and demographic features of infants with urine cultures growing bacteria or fungi in a tertiary care NICU and to analyze the treatments and renal investigations ordered and the outcome to help guide future diagnosis and management of UTI in the NICU.

2. Materials and methods

Approval to conduct this study was obtained from the Health Research Ethics Board of the University of Alberta.

2.1. Eligible patients

A retrospective chart review was completed of infants born October 1, 2004 through December 31, 2006 and admitted to the NICU at the Royal Alexandra Hospital (RAH), Edmonton, Alberta, Canada who had any growth of bacteria or fungi in their urine prior to NICU discharge. Infants were identified through the NICU database with cross-checking of microbiology laboratory records. Initial positive urine cultures were then classified as follows: (a) definite bacterial UTI ($\geq 10^8$ colony forming units/liter (CFU/L) in pure or mixed growth), (b) possible bacterial UTI ($10^7$ CFU/L pure or mixed growth), (c) Candida albicans, (d) mixed organisms, and (e) other organisms.

Table 1: Positive urine cultures obtained in a tertiary care NICU over a 26-month period.

<table>
<thead>
<tr>
<th></th>
<th>Contaminated urine ($N = 34$)</th>
<th>Possible bacterial UTI ($N = 14$)</th>
<th>Definite bacterial UTI ($N = 10$)</th>
<th>Candidal UTI ($N = 6$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collected by bladder catheterization (%)</td>
<td>26 (76%)</td>
<td>11 (79%)</td>
<td>9 (90%)</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>Rate per 100 NICU days</td>
<td>2.0</td>
<td>2.0</td>
<td>2.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Rate per 100 NICU admissions</td>
<td>1.2</td>
<td>0.5</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean gestational age (weeks)</td>
<td>29</td>
<td>31</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Mean birthweight (g)</td>
<td>1689</td>
<td>1964</td>
<td>2680</td>
<td>1263</td>
</tr>
<tr>
<td>Males:Females</td>
<td>19:15</td>
<td>8:6</td>
<td>5:5</td>
<td>5:1</td>
</tr>
</tbody>
</table>

Birthweight (rate per 100 NICU admissions in this weight category):

| Light | Rate per 100 NICU admissions | 1.2 | 0.5 | 0.3 | 0.2 |
| Medium | 0.5 | 0.3 | 0.2 | 0.1 |
| Heavy | 0.1 | 0.0 | 0.0 | 0.0 |

Organisms:

(i) *Escherichia coli*

(ii) *Coagulase-negative staphylococci*

(iii) *Klebsiella species*

(iv) *Mixed*

(v) *Others*

(vi) *Candida albicans*

Positive blood culture for same organism/blood cultures sent at time of diagnosis:

<table>
<thead>
<tr>
<th>Positive Blood Culture</th>
<th>4/33 (12%)</th>
<th>1/12 (8%)</th>
<th>4/10 (40%)</th>
<th>1/5 (20%)</th>
</tr>
</thead>
</table>

No antimicrobial therapy:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1 (3%)</th>
<th>2 (14%)</th>
<th>1 (10%)</th>
<th>0</th>
</tr>
</thead>
</table>

Treated for $\leq 48$ h antimicrobials:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>11 (32%)</th>
<th>3 (21%)</th>
<th>4 (40%)</th>
<th>3 (50%)</th>
</tr>
</thead>
</table>

Treated for $> 48$ h antimicrobials:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>22 (65%)</th>
<th>9 (64%)</th>
<th>5 (50%)</th>
<th>3 (50%)</th>
</tr>
</thead>
</table>

Renal ultrasound abnormal/number of renal ultrasound performed:

<table>
<thead>
<tr>
<th>Abnormal</th>
<th>0/14</th>
<th>1/8 (12.5%)</th>
<th>1/7 (14%)</th>
<th>1/4 (25%)</th>
</tr>
</thead>
</table>

Diagnosis of UCUG abnormal/Number of UCUGs performed:

<table>
<thead>
<tr>
<th>Abnormal</th>
<th>2/13 (15%)</th>
<th>2/5 (40%)</th>
<th>1/6 (17%)</th>
<th>1/2 (50%)</th>
</tr>
</thead>
</table>

Antibiotic prophylaxis ordered for UTI (%):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>11 (32%)</th>
<th>3 (30%)</th>
<th>4 (29%)</th>
<th>3 (50%)</th>
</tr>
</thead>
</table>
growth), (c) candidal UTI (growth of Candida at any colony count) or (d) contaminated urine (10^6 CFU/L pure or mixed growth). The definitions correspond closely to those commonly applied to bladder catheterization specimens in older children[1] to account for the fact that the method of urine collection was not uniformly documented in the charts, but was generally by bladder catheterization. Urine cultures are customarily obtained with septic work-ups but there is no written policy on this matter.

2.2. Data collection and definitions

In addition to demographic data, the following information relating to the positive urine culture was gathered: date of collection, possible associated signs and symptoms on the day the positive urine culture was obtained, and laboratory results including urinalysis and blood culture results. The presence of pyuria was defined as ≥1 white blood cell/high power field, and a significant rise in creatinine was defined as >25% increase from the closest previous result. Antimicrobial therapy and prophylaxis prescribed, renal diagnostic imaging (RDI) performed, and the rate of recurrence of positive urine cultures after treatment but prior to hospital discharge were also recorded. A positive urine culture was considered to be nosocomial if it occurred more than 48 h after birth.

2.3. Statistics

The rate of all four classifications of positive urine cultures per 100 hospital days and per 100 admissions in various birth weight (BW) categories was calculated. The association of UTI with BW categories was analyzed by binary logistic regression and the analysis of other categorical variables was performed using Chi square test.

3. Results

During this 26-month period, 2932 patients were admitted to the RAH NICU. Sixty-four infants (2%) had one or more positive urine cultures with the initial episodes of positive cultures being classified as 34 contaminated urines, 14 possible UTIs, 10 definite UTIs, and 6 candidal UTIs (Table 1). The majority of these initial positive urine specimens (50/64 or 80%) were obtained by bladder catheterization. For the remaining 14 samples, the method of collection was not recorded.

3.1. Demographics

The majority of positive urine cultures were from males (37/64 or 57%) with 49 of the 64 infants being <37 weeks gestational age (77%) and 44 having a BW <1500 g (69%) (Table 1). All infants with a candidal UTI were <37 weeks gestation. Combining possible and definite bacterial UTI with candidal UTI, there was a significant difference in the rate among the different birth weight categories with the highest rate being in infants with a BW of 750–999 g (P < 0.05, binary logistic regression).

The age of the infants with possible and definite UTI at the time of the first positive urine sample ranged from 1 to 30 days with 15 (50%) being 6–15 days of age. Candiduria was first documented at 6–10 days of age for two infants, 11–15 days of age for three infants, and 21–25 days of age for one infant. All urines that led to a diagnosis of definite bacterial or candidal UTI were collected after day 6 of life, but there were two possible UTIs with urine collected on days 3 and 5.

3.2. Clinical presentation

Clinical signs and symptoms at the time of the first positive urine culture were diverse and non-specific including temperature instability ($n = 19$; 30%), increased number of apneic, bradycardic and desaturation episodes ($n = 57$; 89%), lethargy or irritability ($n = 64$; 100%), feeding intolerance ($n = 20$; 31%), mottled appearance and/or pallor ($n = 14$; 22%). Two patients required initiation of mechanical ventilation at the time of the positive urine culture (one with a candidal UTI and one with a definite UTI with Escherichia coli), with the patient with E. coli also requiring initiation of inotropic support. Both had positive blood cultures for the urine isolate.

3.3. Laboratory data

The three most common organisms grown from the urines were E. coli, coagulase negative staphylococcus, and Klebsiella with the majority of definite UTIs being due to E. coli (Table 1). Only Gram positive organisms were isolated prior to day 6 of life. Bacteremia with the same organism was documented in 4 of 34 contaminated urines (12%) and in 5 of 22 possible or definite bacterial UTI (23%) while fungemia was documented in 1 of 6 candidal UTIs (20%).

Urinalysis was ordered for only 35 of the 64 infants with (55%) with 6 of 17 infants with contaminated urines (35%) and 16 of 18 infants with possible or definite bacterial or candidal
UTI (89%) having pyuria ($P < 0.05$, Chi square). No patient was documented as having a significant rise in serum creatinine associated with the UTI onset.

3.4. Treatment and outcome

Antimicrobials were administered for more than 48 h to 43 of the 64 infants (67%), with there being a trend towards more of the infants with possible or definite bacterial or candidal UTIs receiving >48 h antimicrobials (21/30; 70%) versus the infants with contaminated urines (22/34; 65%) ($P = 0.7$, Chi square) (Table 1). There were two deaths in study patients but neither was related to urosepsis.

Renal ultrasound was performed in 14 of 34 (41%) and voiding cystourethrogram (VCUG) in 13 of 34 (38%) infants with contaminated urines. All had normal ultrasound findings. VCUG was abnormal in 2 of 13 (15%) showing passive to grade 2–3 vesicoureteric reflux (VUR).

Renal ultrasound was performed in 19 of 30 (63%) and VCUG in 13 of 30 (43%) infants with possible or definite bacterial or candidal UTI. Abnormalities were detected in ultrasounds in three infants (16%) (multicystic dysplastic kidney, hydronephrosis and hydroureter, duplex collecting systems with unilateral dilatation) and in VCUGs in four infants (31%), showing Grades II–III reflux. This included one infant with a recurrent possible bacterial UTI who had Grade III reflux bilaterally.

Antibiotic prophylaxis was ordered following therapy for the positive urine culture in 11 of 34 infants with contaminated urines (32%) and in 10 of 30 infants with possible or definite bacterial or candidal UTI (33%). Recurrent possible or definite bacterial UTI was rare, occurring in only 1 of 34 infants with contaminated urines (3%) and in 2 of 24 infants with possible or definite bacterial UTI (8%). Likewise, only 1 of 6 infants with candidal UTI (17%) had a second urine culture that grew Candida (although clearance of candiduria was not documented during initial therapy).

4. Discussion

4.1. UTI definition

One of the goals of this study was to review the management of UTI in our NICU and identify factors that aid clinicians in the diagnosis of UTI. We applied the definition utilized for bladder catheter specimens in older children [1]. However, the universal presence of pyuria in the nine infants with possible bacterial UTI suggests that the majority of these infants had true UTI and that $10^7$ CFU/L (10^6 CFU/mL) pure or mixed growth should be considered diagnostic of a bacterial UTI in the NICU, although a prospective study would be required to prove this point. Our definition of pyuria (>1 WBC/HPF) was perhaps overly sensitive but there are no published standards for preterm neonates. The infants with $10^6$ CFU/L bacteria were classified as having contaminated urines but about one-third had pyuria, 4 of 34 had a positive blood culture for the same organism, 2 had recurrent possible or definite UTI, and 2 had VUR, suggesting that our definition was too strict and that at least some of these very low colony counts may represent true UTIs (although the ones with bacteremia could still be contaminated urines from a high concentration of organisms on the genitalia).

4.2. Incidence of UTI in NICUs

As explained, it seems that most of the infants we labeled as ‘possible UTI’ actually did have UTIs. The incidence of possible or definite UTI in our NICU with the usual mix of term and preterm infants was approximately 1% with all infections being nosocomial. An expected rate of UTI of 0.1–1% in all newborns but a much higher rate of 4–25% in preterm newborns has been quoted in previous studies [2]. Two recent studies looking at nosocomial UTI in NICU found highly variable rates of 0.7% (accepting only catheter urines with $\geq 10^8$ CFU/L) [3] and 6% (with the definition of UTI not being clear) [4]. When analyzing by specific birth weight categories, the rates of UTI in our study were lower than in most previous studies (Table 2). This could be because we used a stricter definition of UTI than did one previous study [7] or because the threshold for obtaining a urine sample was higher in the current study, resulting in incomplete UTI case-finding with some infants with UTI being cured by antibiotics given for other reasons without urine cultures being submitted. To establish the true expected rate, a prospective study should be done with culture of urine obtained by suprapubic aspiration with every septic work-up after the first day of life.

4.3. Need for urine cultures in the first 48 h of life

It remains controversial if urine cultures should be performed as part of a septic work-up in the
Table 2  Incidence of urinary tract infection and of structural renal abnormalities detected in neonatal intensive care unit studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Birthweight (g)</th>
<th>Incidence of UTI</th>
<th>Incidence of significant findings on renal ultrasound&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Incidence of VUR in infants with VCUG performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;sup&gt;[5]&lt;/sup&gt;</td>
<td>&lt;1000</td>
<td>3/55 = 5%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>&lt;sup&gt;[6]&lt;/sup&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≤ 1000</td>
<td>11/84 = 13%</td>
<td>4/11 = 36%</td>
<td>0</td>
</tr>
<tr>
<td>&lt;sup&gt;[2]&lt;/sup&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≤ 1000</td>
<td>34/279 = 12%</td>
<td>9/34 = 26%</td>
<td>2/26 = 8% (Grade II and Grade III)</td>
</tr>
<tr>
<td>Current study</td>
<td>≤ 1000</td>
<td>14/232 = 6%</td>
<td>0/10</td>
<td>1/8 = 13% (Bilat VUR)</td>
</tr>
<tr>
<td>&lt;sup&gt;[7]&lt;/sup&gt;&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;1500</td>
<td>48 /538 = 9%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>&lt;sup&gt;[5]&lt;/sup&gt;</td>
<td>1000—1499</td>
<td>2/149 = 1%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>&lt;sup&gt;[2]&lt;/sup&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1001—1500</td>
<td>28/483 = 6%</td>
<td>1/28 = 3.6%</td>
<td>4/17 = 24% (Grade I n = 2; Grade II n = 2)</td>
</tr>
<tr>
<td>&lt;sup&gt;[6]&lt;/sup&gt;&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1001—1749</td>
<td>16/253 = 6%</td>
<td>2/16 = 13%</td>
<td>3/16 = 19% (Grade II VUR)</td>
</tr>
<tr>
<td>Current study</td>
<td>1001—1500</td>
<td>6/340 = 1.8%</td>
<td>0/3</td>
<td>1/1 (Grades II—III VUR)</td>
</tr>
<tr>
<td>&lt;sup&gt;[5]&lt;/sup&gt;</td>
<td>1500—1999</td>
<td>1/160 = 1%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>&lt;sup&gt;[5]&lt;/sup&gt;</td>
<td>2000—2499</td>
<td>2/172 = 1%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>&lt;sup&gt;[5]&lt;/sup&gt;</td>
<td>≥2500</td>
<td>2/368 = 0.5%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Current study</td>
<td>All weights combined</td>
<td>30/2932 = 1%</td>
<td>4/19 = 21%</td>
<td>3/13 = 23%</td>
</tr>
</tbody>
</table>

NR — not reported; UTI — urinary tract infection; VCUG — voiding cystourethrogram; VUR — vesicoureteral reflux.

<sup>a</sup> Excludes mild renal pelvic dilatation, transient hydronephrosis, or nephrocalcinosis.

<sup>b</sup> Definition of UTI was >10<sup>5</sup> CFU/mL by suprapubic aspiration.

<sup>c</sup> Definition of UTI was >100 CFU/mL from a suprapublic aspiarate.

<sup>d</sup> Definition of UTI was any growth from a suprapubic aspirate (<sup>N</sup> = 5), >10<sup>7</sup> CFU/L from a catheter specimen (<sup>N</sup> = 25) or >5 × 10<sup>7</sup> CFU/L from a bag specimen (<sup>N</sup> = 18) with all cultures with mixed growth being considered contaminants.

The incidence of bacteremia with bacterial UTI was higher than anticipated in the current study (23%) with one previous study showing that although 2 of 5 infants with candiduria were candidemic (40%), only 2 of 61 infants with bacterial UTI (3%) were bacteremic [<sup>2</sup>]. Our observation could be due to a bias towards obtaining urine cultures only when a neonate presented with more severe illness.

### 4.4. Positive blood cultures in infants with UTI

The incidence of bacteremia with bacterial UTI was higher than anticipated in the current study. However, it is important to note that only severe cases were included in this study and other cases might have been missed. Further research is needed to determine the true incidence of bacteremia in infants with UTI.

### 4.5. Management of suspected or proven UTI

This study demonstrates the difficulty in interpreting positive urine cultures in neonates. It is clear that further efforts need to be made to obtain uncontaminated urines in NICU to improve the accuracy of diagnosis of UTI. A recent meta-analysis showed the paucity of data on direct comparison of catheterization versus suprapubic aspiration but suggested that suprapubic aspiration is more likely to yield uncontaminated urine samples [<sup>9</sup>]. A recent study suggested that suprapubic collection may be slightly more painful for the infant and that unless ultrasound is used, the success rate is lower than with bladder catheterization [<sup>10</sup>]. Therefore, we think suprapubic aspirates should be obtained...
when practical. Urinalysis should be performed on all specimens by a standard method to determine the sensitivity and specificity for diagnosis of UTI neonates.

Treatment of UTI was inconsistent in the current study. Excluding the 14 cases of possible UTI where management plans might have varied, there was no significant difference in the proportion of infants with contaminated urines being treated with greater than 48 h of antimicrobials versus infants with definite bacterial or candidal UTI (65% versus 75%; \( P = 0.47 \), Chi square), with it being concerning that 25% of the latter group received less than 48 h of antimicrobials. This is presumably due to confusion about the diagnostic criteria for bacterial or candidal UTI. This confusion is also supported by the observation that there was only a trend towards more infants with definite or candidal UTI (69%) having RDI performed as compared with infants with contaminated urines (41%; \( P = 0.07 \), Chi square). Almost all infants with positive urine cultures had prophylactic antibiotics ordered to follow their course of therapy. These findings suggest that clinicians were uncertain which positive urine cultures represented contamination, leading to inappropriate use of antimicrobials.

Since 37% of infants with possible or definite UTI did not have RDI performed for their first UTI, the true incidence of structural abnormalities or Grade II or higher VUR may be higher than 23%. The lack of RDI may be due to the conclusions of a recently published study suggesting that not all children require RDI with their first UTI [10]. However, the age range of the children in this previous study was one to 24 months which is markedly different from our study population. All other previous studies were small (Table 2) which makes it difficult to determine the expected rate of anomalies. Eliakim et al. suggest that RDI in infants with a BW less than 1000 g may not be warranted as these patients have a low incidence of underlying urinary tract abnormalities [6], but Table 2 demonstrates that this may not be the case. In a recent study, Miron et al reported complete concordance between prenatal and post first UTI renal ultrasound results in 96% of 209 children studied [12]. In addition, there have been reports of UTI precipitated by a VCUG. Considering this risk and the fact that the majority of women in North America undergo antenatal ultrasound examination, RDI may not be warranted in an infant with a possible or definite UTI who had a normal fetal ultrasound. Moreover, there remains debate about the value of long-term antibiotic prophylaxis for lower grades of reflux in all age groups [13], leading to uncertainty about the value of early detection of anomalies that predispose to UTI.

4.6. Outcome

Despite inconsistent management, the only major morbidity in this study was the need for new onset of assisted ventilation in two infants who also had bacteremia or fungemia. However, long-term renal function is the most important outcome and needs to be addressed by future studies.

4.7. Study limitations

The primary limitation of this study is that definitions of UTI have not been published or validated in preterm infants. Barely over half the infants in the current study had a urinalysis performed. Another major limitation of the study is that it is not known how often septic work-ups excluded a urine culture. A further limitation is that performance of RDI was not standardized. The duration of antimicrobials prescribed for a possible UTI may have been over-estimated if antibiotics were continued for other suspected sites of infection without this being recorded in the chart. It would have been ideal to have long-term follow-up regarding repeat UTI and results of any further RDI performed in the first few years of life in study infants.

5. Conclusions

Diagnosis and management of UTI in our NICU is inconsistent, yet short-term morbidity is minimal. The most important contributing factor to inconsistent management is likely the lack of validated diagnostic criteria, but there also is a great need for further studies on the role of RDI and the need for antimicrobial prophylaxis following a UTI in preterm infants. Pending definitive data, guidelines based on the minimal evidence that exists in the literature should be derived and prospectively studied.

Conflict of interest

I declare on behalf of all authors that we have no conflict of interest related to publication of this manuscript.

References


