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Do Infants in the Neonatal Intensive Care Unit Diagnosed with Urinary Tract Infection Need a Routine Voiding Cystourethrogram?

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Abstract

Objective—To determine if infants diagnosed with urinary tract infection (UTI) in the neonatal intensive care unit (NICU) require a routine voiding cystourethrogram (VCUG).

Study Design—Retrospective data analysis from three centers for infants admitted to the NICU born between 2000 and 2013 and diagnosed with UTI.

Results—126 infants from three centers were diagnosed with UTI during their hospitalization. Renal ultrasound (RUS) was performed in 115 infants (91.2%), of which 69 (60%) were abnormal. Mild to moderate hydronephrosis or pelviectasis were the most common abnormalities identified (n=34, 30%). There were 14 infants (12%) with severe abnormalities on RUS. VCUG was performed in 71 infants (56%), of which 3 (4%) were interpreted as abnormal with grade 2 vesicoureteral reflux (VUR) or less (2 infants normal RUS and 1 infant abnormal RUS).

Conclusion—More than 50% of infants with a UTI had an abnormal RUS but severe abnormalities were found only in 11% of infants. Only 4% of infants with UTI had VUR; none of these infants had severe VUR on VCUG. A routine VCUG after UTI in the NICU has a low yield and may be reserved for infants with severe or persistent abnormalities on RUS.

Keywords

neonate; urinary tract infection; vesicoureteral reflux; renal ultrasound; voiding cystourethrogram

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Introduction

There is uncertainty about the most appropriate and effective way to manage urinary tract infection (UTI) in children, and whether or not investigations and follow-up are justified. In 2011, the American Academy of Pediatrics (AAP) revised its guidelines for the diagnosis and management of initial UTI in febrile infants and children, which emphasized reducing the number of voiding cystourethrograms (VCUG).¹ These guidelines were reaffirmed by the AAP in 2016 and state that a VCUG is required in children aged 2–24 months only after a febrile UTI with abnormal renal ultrasound (RUS) findings, recurrent febrile UTI, or atypical/complex circumstances.² Recent guidelines from the National Institute for Health and Care Excellence (NICE) recommended that most infants and children with febrile UTI should have a RUS performed, but suggest restricting VCUG and antimicrobial prophylaxis for only certain circumstances.³ In the neonatal intensive care unit (NICU), where prevalence of UTI may range from 0.1% to 1% in all neonates and up to 25% in premature neonates, guidelines regarding management are essentially non-existent.^{4,5}

For patients admitted to the NICU and diagnosed with UTI, namely premature neonates and infants less than 2 months of age, there are limited data on the prevalence of urinary tract abnormalities, including vesicoureteral reflux (VUR). Existing evidence indicates that babies with the lowest birth weights may be at lower risk of underlying urinary tract abnormalities including VUR despite their higher risk of UTI.^{4,6,7} In addition, multiple studies have suggested that RUS is not a sensitive test to identify VUR in this population.^{4,8} Therefore, at present it is unclear whether patients in the NICU should have a routine VCUG after diagnosis of UTI.

A recent study described laboratory findings and imaging results for neonatal patients diagnosed with UTI in a single institution; they found that although renal pelvis dilation on RUS was common, it was not associated with VUR.⁹ Given that the AAP guidelines recommend omitting routine VCUG after the first UTI for older patients unless RUS is abnormal, these guidelines are clearly difficult to interpret for patients in the NICU. The objective of our study was to evaluate the utility of a VCUG in infants diagnosed with UTI in the NICU across three neonatal centers.

Methods

Centers

This study is a retrospective data analysis from three academic neonatal centers: Thomas Jefferson University Hospital in Philadelphia, Pennsylvania (level III, 40 beds and ~2,300 live births per year), Cooper University Hospital in Camden, New Jersey (level III, 35 beds and ~2,200 live births per year) and Christiana Care Health System in Newark, Delaware (level III, 60 beds and ~6,500 live births per year). All three units are staffed by attending neonatologists, pediatric residents, neonatal nurse practitioners and neonatal fellows, and the units serve primarily inborn infants. This study was approved by the Institutional Review Board at all three institutions (Thomas Jefferson University Hospital, Cooper University Hospital and Christiana Care Health System).

Study Population

Initial inclusion criteria included infants born between 2000 and 2013, admitted to one of the three participating NICUs and diagnosed with UTI during hospitalization. Infants without a positive urine culture (UC) were subsequently excluded from the study. Relevant demographic data were collected via chart review including date of birth, gestational age (GA), birth weight (BW), sex, race, and 5 minute Apgar score. Clinical information, laboratory data and imaging results were collected via chart review including UC results, RUS results, VCUG results and day of life for all studies.

Definitions

A positive UC was defined as any positive culture with at least one pathogenic organism that was treated with appropriate antibiotics based on reported sensitivities. A urine sample collected by catheterization is the gold standard for UC at all three institutions and method of collection was recorded when available. All RUS and VCUG studies were read by attending radiologists. RUS findings described as grade 1–2 hydronephrosis, “mild” or “moderate” pelviectasis or hydronephrosis, or “fullness of kidneys” were considered mild to moderate abnormalities. RUS findings described as grade 3–4 hydronephrosis or anatomic abnormalities were considered severe abnormalities. Any abnormality on VCUG was considered to be an abnormal finding. Infants born at less than 37 weeks’ gestation were considered premature.

Statistical Analysis

Descriptive analyses and statistical tests were performed as appropriate using the Sigma plot version 13 (Systat Software, Inc., Point Richmond, CA). A subgroup analysis of premature versus term infants was performed. The groups were compared by Student t-tests, Mann-Whitney U-tests or chi-square tests as appropriate. The difference was considered significant for $p < 0.05$.

Results

Characteristics of the Study Subjects

A total of 148 infants were diagnosed with UTI between all three centers during the study period. Of these, 22 infants were subsequently excluded after chart review for never having a documented positive urine culture. Therefore 126 infants were diagnosed with a UTI with a positive UC, treated with antibiotics during hospitalization and were included in the analysis. The breakdown of patients contributed by each center was as follows: Thomas Jefferson University Hospital (35 infants, 27.8%, incidence 7/1,000 NICU admissions), Cooper University Hospital (41 infants, 32.5%, incidence 6.6/1,000 NICU admissions) and Christiana Care Health System (50 infants, 39.7%, incidence 3/1,000 NICU admissions).

The majority of patients were premature and male; other demographics and clinical characteristics of the study population are shown in Table 1. None of the infants had major prenatally diagnosed renal or urethral abnormalities; 15/126 (11.9%) had reported mild pyelectasis on prenatal ultrasound. There were no infants with reported postnatal diagnosis of major congenital abnormality.

Urine specimens were obtained due to suspected sepsis and the median duration of antibiotic treatment was 7 days (range 5–20 days). The median age of first UTI diagnosis was 37 days of life (interquartile range (IQR) 19–63 days), the median age when first RUS was performed was 41 days of life (IQR 19–68 days) and the median age of when VCUG was performed was 82 days of life (IQR 42–117). *Escherichia coli* was the most common organism (27%) identified on first positive urine culture, and 19% of positive cultures grew mixed organisms. Table 2 shows the breakdown of organisms causing UTI. Seven infants had a positive blood culture at the time of UTI diagnosis, and most of these (6 of 7) grew the same organism from both sites. No infants had documented concurrent meningitis at the time of UTI diagnosis. Only three infants underwent circumcision before diagnosis of UTI.

RUS was performed in 115 of 126 infants (91%), of which 69 (60%) were reported as abnormal and 46 (40%) were reported as normal (Figure 1). Mild to moderate hydronephrosis or pelviectasis were the most common abnormalities identified by RUS (n=34, 30%). There were 55 infants (48%) with mild to moderate abnormalities on RUS and 14 infants (12%) with severe abnormalities.

VCUG results were available for 71 infants (56%), of which 3 (4%) were interpreted as abnormal (Figure 1). None reported VUR of grade 3 or higher. Of the 3 infants with an abnormal VCUG, 2 had a normal RUS and 1 had an abnormal RUS. The first infant (male, GA 41 weeks) with an abnormal VCUG (right sided grade 2 VUR, left sided grade 1 VUR, and duplicate collecting system) had a previously normal RUS. The second infant (female, GA 38 weeks) with an abnormal VCUG (complex cloacal congenital anomaly, right sided VUR without reportable grade) had a previously abnormal RUS (fetal lobulation of kidneys, bilateral cortical renal cysts). The third infant (female, GA 25 weeks) with an abnormal VCUG (bilateral grade 2 VUR) had a previously normal RUS. There were no significant differences in BW, GA, sex, race, 5-minute Apgar scores, day of UTI diagnosis and number of infants with abnormal RUS between infants with and without VCUG results available (data not shown). Of the 15 infants with prenatal diagnosis of mild pyelectasis, none of the had an abnormal postnatal VCUG.

Of the 126 infants, 85 (67.5%) had a documented method of urine collection as catheterization; the remaining infants did not have a documented method of collection or were not obtained via catheterization. Infants with urine samples obtained via catheterization were analyzed separately and there were no significant differences in the baseline demographics or the number of infants with abnormal RUS or VCUG in the total cohort or this subgroup with urine samples obtained via catheterization (Table 1).

Male infants were more likely to develop UTI during their NICU stay than were females ($p<0.001$). Of the infants diagnosed with UTI, 57% of males and 64% of females had an abnormal RUS ($p=0.5$). VCUG results were available for 54 of 89 males with UTI with 1 reported as abnormal, and were available for 17 of 37 females with UTI with 2 reported as abnormal ($p=0.14$). Of the 126 infants diagnosed with UTI, 105 (83.3%) were premature and 21 (16.7%) were term ($p<0.001$). Premature infants with UTI, compared to term counterparts, were just as likely to be male and to have abnormal RUS or abnormal VCUG

(Table 3). There were 10 infants with recurrent UTI before VCUG was performed, and all of them had a normal VCUG.

Discussion

The main finding of this study, from a population of three neonatal centers, was that more than half of the infants in the NICU diagnosed with UTI had an abnormal RUS. However, severe abnormalities on RUS were uncommon. Only one infant with a severe abnormality on RUS had a documented abnormal VCUG, and of the 3 total infants that had an abnormal VCUG, 2 had a previously normal RUS. None of the studied infants had severe VUR (grade 3 or higher) on VCUG. These results suggest that a routine VCUG after the first UTI in the NICU has a low yield and may potentially be reserved for infants with severe or persistent abnormalities on RUS, and support previous findings that RUS doesn't correlate with VCUG in this population.

Recently, the AAP and other organizations have released or updated guidelines regarding the diagnosis and management of UTI and VUR in the pediatric population. As discussed earlier in this paper, these 2016 guidelines² suggest that a VCUG should be performed in children aged 2–24 months only after a febrile UTI with abnormal RUS findings, recurrent febrile UTI, or atypical/complex circumstances. Based on one retrospective study, these guidelines seem applicable to clinical practice.¹⁰ The American Urological Association has released guidelines on the management of primary VUR in children, most recently in 2010.¹¹ These guidelines do not address screening for VUR after UTI but focus instead on management of VUR after diagnosis. The NICE issued recommendations on the diagnosis, treatment and long-term management of UTI in children in 2007.³ These guidelines recommend that most infants and children with febrile UTI should have RUS performed, but suggest restricting VCUG and antimicrobial prophylaxis for only certain circumstances. Follow-up studies assessing the applicability of these changes are conflicting. Schroeder *et al* found a decrease in VCUG studies and prophylactic antibiotic use without increasing the risk of UTI and without an apparent decrease in detection of high grade VUR following the NICE recommendations, and concluded that clinicians can be more judicious in their use of urinary tract imaging.¹² Ristola *et al*, on the contrary, concluded that based on their retrospective cohort study that the NICE guidelines for imaging studies in children younger than 3 years old with UTI cannot be recommended.¹³ Despite the numerous pediatric guidelines and follow up studies, UTI in the population of the NICU has not been extensively studied and presently published guidelines are difficult to apply to this unique patient population. Data from the current study suggest that severe renal abnormalities and/or VUR are not common in the NICU population and therefore support the practice of not performing a routine VCUG in this setting.

A previous study reported that the prevalence of UTI was significantly higher in infants with extremely low-birth-weight (BW less than 1000 grams) (ELBW) compared with that in premature infants with birth weight greater than 1000 grams.⁶ The authors also found that premature ELBW infants diagnosed with UTI were less likely to have an abnormal VCUG than were infants with birth weight greater than 1000 grams, and that the few infants that had an abnormal VCUG all had an abnormal RUS previously. Another study reported that

UTI was more common in infants weighing 1000–1500 grams, however the overall rate of VUR in that cohort of low birth weight infants with UTI who had VCUG performed was low (13.9%), and even lower in the ELBW babies compared to the infants weighing 1000–1500g (7.7% vs. 23% respectively).⁴ None of the premature infants with VUR had higher than grade 3 VUR, and the majority had a normal RUS (83%). This discordance between RUS and VCUG has been reported previously, and the findings of the current study support the notion that RUS is a poor screening test for VUR.⁸ In 2016, a retrospective analysis of infants diagnosed with UTI in the NICU found that urinary tract abnormalities were uncommon, and the rate of high-grade VUR was exceedingly low.⁷ While VCUG is considered a relatively safe study with patient and parent anxiety as the main complication, in addition to the cost and radiation exposure, rare complications have been reported, including bladder rupture in children and infants.^{14,15}

The major strength of this study is the large sample size of infants diagnosed with UTI across three neonatal centers. Our results add to the existing, albeit limited, literature on management of infants in the NICU with UTI. A recent study also found a low incidence of urinary tract abnormalities and VUR in a cohort of very low birth weight infants.¹⁶ The AAP guidelines for diagnosis and management of UTI only apply to infants age 2–24 months, and do not apply to hospitalized infants in the NICU.¹ To our knowledge, there are no formal guidelines on diagnosis and management of UTI in patients admitted to the NICU, namely premature infants and infants less than 2 months of age. Therefore, given the retrospective nature of our study, we decided to include infants with a positive urine culture and diagnosed by the provider with UTI and treated with appropriate antibiotics. While this is clearly not a perfect method, it does capture infants diagnosed “clinically” with UTI and therefore may be relevant/generalizable to providers.

This study has several limitations, namely inherent biases related to the retrospective design. The VCUG rate of the study population was low; 55 of 126 (44%) infants diagnosed with UTI did not have documented VCUG results available. As a result, our study may have underestimated the prevalence of VUR in the population. This may be due to patient transfers to other facilities, VCUG performed after discharge at other facilities, or incomplete records. However, it is unlikely that we missed severe abnormalities on VCUG, as the demographics of infants with VCUG were similar to the infants without VCUG. In addition, although urine collection via sterile catheterization is standard of care in the participating centers, some urine samples may have been collected by alternative methods such as bag collection and could have been contaminated. Lastly, we did not account for colony forming units per milliliter of urine in the diagnosis of UTI as recommended by the AAP given significant practice variation. Instead we included infants with growth on UC and treated with appropriate antimicrobials by the provider, as this signaled a clinically significant UTI.

In conclusion, based on these results, a routine VCUG after the first UTI in the NICU has a low yield and may potentially be reserved for infants with severe or persistent abnormalities on RUS or other risk factors such as recurrent or atypical UTIs. More population-based studies are needed to definitively evaluate the utility of obtaining a routine VCUG after UTI in infants in the NICU.

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Abbreviations

AAP	American Academy of Pediatrics
BW	birth weight
ELBW	extremely low birth weight
GA	gestational age
NICE	National Institute for Health and Care Excellence
NICU	neonatal intensive care unit
RUS	renal ultrasound
UA	urinalysis
UC	urine culture
UTI	urinary tract infection
VCUG	voiding cystourethrogram
VUR	vesicoureteral reflux

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[urinary tract infection (UTI); renal ultrasound (RUS); voiding cystourethrogram (VCUG)]

Figure 1.

Renal ultrasound and voiding cystourethrogram results

[urinary tract infection (UTI); renal ultrasound (RUS); voiding cystourethrogram (VCUG)]

Table 1

Demographics of the study population (n=126)

	All infants (n=126)	Infants with documented catheterized samples (n=85)
Gestational age (weeks) (mean±SD)	29.1±5.6	29.7±5.9
Birth weight (grams) (mean±SD)	1376±974	1499±1067
Preterm	105 (83%)	68 (80%)
Male gender (n) (%)	89 (71)	61 (72)
APGAR 5 minutes (median, range)	7 (1–9)	7 (1–9)
Race		
White (n) (%)	47 (37)	33 (39)
Black (n) (%)	54 (43)	35 (41)
Hispanic (n) (%)	16 (13)	12 (14)
Other (n) (%)	9 (7)	5 (6)
RUS performed (n) (%)	115 (91)	76 (89)
Abnormal RUS (n) (%)	69/115 (60)	47/76 (62)
Severely abnormal RUS (n) (%)	14/115 (12)	10/76 (13)
VCUG performed (n) (%)	71 (56)	45 (53)
Abnormal VCUG (n) (%)	3/71 (4)	2/45 (4)

Table 2

Infectious organisms identified on urine culture (n, %)

<i>Escherichia coli</i>	34 (27)
<i>Klebsiella spp.</i>	15 (11.9)
<i>K. pneumoniae</i>	11 (8.7)
<i>K. oxytoca</i>	4 (3.2)
<i>Enterobacter spp.</i>	12 (9.5)
<i>E. aerogenes</i>	9 (7.1)
<i>E. cloacae</i>	3 (2.4)
Coagulase-negative staphylococcus	12 (9.5)
<i>Enterococcus faecalis</i>	10 (7.9)
<i>Candida spp.</i>	8 (6.3)
<i>Pseudomonas aeruginosa</i>	5 (4)
<i>Streptococcus agalactiae</i>	3 (2.4)
Methicillin-resistant <i>Staphylococcus aureus</i>	1 (0.8)
<i>Serratia marcescens</i>	1 (0.8)
<i>Citrobacter spp.</i>	1 (0.8)
Mixed organisms	24 (19)

Table 3

Premature and term infants with urinary tract infection (n=126)

	Premature (n=105)	Term (n=21)	p-value
Birthweight (grams) (mean±SD)	1042±598	3053±728	<0.001
Gestational age (weeks) (mean±SD)	27.1±3.6	39.0±1.5	<0.001
Male (n, %)	77 (73)	12 (57)	0.2
Abnormal RUS (n, %)	58/96 (60)	11/19 (58)	1.0
Severe abnormal RUS (n, %)	10/96 (10)	4/19 (21)	0.24
Abnormal VCUG (n, %)	1/57 (1.8)	2/14 (14)	0.097

[standard deviation (SD); renal ultrasound (RUS); voiding cystourethrogram (VCUG)]