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Prevalence of Renal Anomalies Following Urinary Tract Infections in Hospitalized Infants Less Than Two Months of Age

Lisa Nowell, MD[a], **Cassandra Moran, DO**[b], **P. Brian Smith, MD, PhD**[b,c], **Patrick Seed, MD, PhD**[b], **Barbara D. Alexander, MD**[c,d], **C. Michael Cotten, MD**[b], **John S. Wiener, MD**[b,e], and **Daniel K Benjamin Jr, MD, MPH, PhD**[b,c]

[a]Duke University School of Medicine, Durham, NC

[b]Department of Pediatrics, Duke University Medical Center, Durham, NC

[c]Duke University Clinical Research Institute, Durham, NC

[d]Department of Medicine and Pathology, Duke University Medical Center, Durham, NC

[e]Department of Surgery, Duke University Medical Center, Durham NC

Abstract

Objective—Our aim was to determine the incidence of anatomic abnormalities following a urinary tract infection in infants < 2 months of age hospitalized in the neonatal intensive care unit.

Study Design—This was a retrospective, single center cohort study of infants < 2 months of age in the neonatal intensive care unit with a urinary tract infection and documented renal imaging.

Results—We identified 141 infants with urinary tract infections. The mean gestational age and birth weight were 28 weeks and 1254 g, respectively. The most commonly identified pathogen was coagulase negative *Staphylococcus* (28%, 44/156). A major abnormality was found on at least one imaging study for 4% (5/118) of infants. Major abnormalities were noted on 4% (5/114) of renal ultrasounds and 2% (2/82) of voiding cystourethrography examinations.

Conclusions—Among infants in the neonatal intensive care unit < 2 months of age at the time of a urinary tract infection the prevalence of major anatomic abnormalities is < 5%.

Keywords

renal abnormalities; renal ultrasound; voiding cystourethrography

INTRODUCTION

Urinary tract infections (UTIs) are common in children, occurring in up to 1% of all infants and 8% of infants <1500 g birth weight.1, 2, 3, 4, 5 Recurrent UTIs of the upper tract

Corresponding author: P Brian Smith MD MHS Duke Clinical Research Institute PO Box 17969 Durham NC 27715 Ph: 919-668-8951 Fax: 919-668-7058 brian.smith@duke.edu.

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(pyelonephritis) are associated with renal scarring, defined by perfusion defects and loss of kidney contours or cortical thinning with volume loss.[6] Such scarring may lead to end stage renal disease. In order to prevent these sequelae, the American Academy of Pediatrics recommends a renal bladder ultrasound (RUS) and either a voiding cystourethrography (VCUG) or radionuclide cystography to detect the presence of vesicoureteral reflux (VUR) following an initial febrile UTI in children 2 to 24 months of age.[7] However, recent data suggest that VUR may not be an independent predictor of recurrent UTIs or new renal scarring.[8] A recent randomized controlled trial demonstrated that mild-moderate reflux did not increase the incidence of recurrent UTIs and scarring in children.[6]

Although there are no current recommendations for infants < 2 months of age, the current practice at Duke University Medical Center, like many medical centers, has been to extend the radiographic recommendations to infants < 2 months of age and to screen infants with both a RUS and a VCUG following a UTI. However, there are concerns about unnecessarily exposing infants to invasive procedures and to the radiation involved with a VCUG.[9, 10, 11] Furthermore, the lack of consensus regarding the utility of VCUG to prevent renal scarring and end stage renal disease makes this concern even more relevant.

We sought to identify the prevalence of reflux and other functional and structural abnormalities identified on urinary tract imaging following UTIs in infants hospitalized in the Duke University Medical Center neonatal intensive care unit (NICU). Due to the increased length of hospitalization and immature immune status predisposing these infants to UTIs, we hypothesized that the incidence of major structural abnormalities would be uncommon in hospitalized infants compared to estimates in older infants and children.

METHODS

We identified all infants < 2 months of age in the Duke University Medical Center NICU with a positive urine culture for a single organism from January 1996 to August 2006 from the Clinical Microbiology Laboratory database. RUS and VCUG results were obtained from the patient's medical records.

Urine cultures were obtained as part of sepsis evaluations. This cohort contained all the UTI cases in the NICU during this time period. We defined a UTI as isolation of ≥ 1000 colony forming units of a single organism from a specimen obtained by either suprapubic aspiration or in and out catheterization. If mixed organisms were isolated from a urine culture or the infant's antibiotic treatment was stopped when culture results were reported, the episode was not considered a UTI. UTIs were classified as separate infections for the same infant if: 1) > 14 days had elapsed between cultures and there was at least 1 negative urine culture between two positive cultures; 2) > 30 days had elapsed between two urine cultures with the same organism; or 3) a different organism was isolated.

Demographic information (age, birth weight, gender, and race) was collected for each infant. Method of urine collection (suprapubic aspiration or catheterization) and organism cultured were recorded. In cases where the collection method was unknown, the samples were treated as bag collections and not included in the analysis. Results from cerebrospinal fluid (CSF) and blood cultures obtained within 72 hours of the positive urine culture were recorded. We reviewed the most recent RUS and VCUG for each infant. The NICU practice was typically to obtain the RUS at least 1 week after completing UTI treatment and a VCUG when the patient attained a weight ≥ 1500 g and was deemed to be clinically stable.

The degree of hydronephrosis and/or VUR was recorded. The classification systems used to describe the degrees of severity by VCUG and RUS were 1) the International system of radiographic grading of vesicoureteric reflux; International Reflux Study in Children and 2) Ultrasound grading of hydronephrosis: Introduction to the system used by the Society for Fetal Urology, respectively.12 13 If VUR was bilateral, the higher grade was recorded. If any radiographic study had abnormalities other than hydronephrosis or VUR, a pediatric urologist was consulted to determine which abnormalities were significant. Renal agenesis, posterior urethral valves, horseshoe kidneys, dysplastic kidneys, VUR ≥3, and hydronephrosis ≥3 were considered major abnormalities.

Our NICU practice is to obtain repeat urine cultures after an initial positive urine culture until negative. A RUS and VCUG is obtained for all infants with a documented UTI. Although a RUS is performed at any point, the VCUG is generally delayed until after the UTI treatment is complete and the infant is >1500 g. Indications to begin UTI prophylaxis for infants are as follows: 1) 2 UTIs, 2) UTI and any abnormality on RUS, and 3) any infant regardless of UTI status with ≥ grade 3 hydronephrosis on RUS, until a VCUG is performed.

We used STATA 10 (College Station, TX) to analyze the data. Fisher's exact tests were used where appropriate. The Duke University Medical Center Institutional Review Board approved this study.

RESULTS

We identified 141 infants with at least one UTI. Of the 141 infants, 9% (13/141) had multiple UTIs (Table 1). The mean gestational age, birth weight, and day of life of first UTI were 28 weeks [95% confidence interval; 24, 38], 1254 g [610, 2670], and 29 days [8, 56], respectively. Males represented 65% (91/141) of the infants with a UTI.

The organisms most commonly isolated were coagulase negative *Staphylococcus* (CoNS) (28%, 44/156), *Escherichia coli* (17%, 27/156), *Enterococcus sp*. (12%, 18/156), and *Klebsiella* species (11%, 17/156) (Table 2). Mortality following Gram-positive UTIs was 6% (4/72) compared with 9% (6/70) following Gram-negative UTIs (P=0.49). Mortality following *Candida* UTIs was 21% (3/14) compared to bacterial UTIs, 7% (10/142) (P=0.06).

There were 134 blood cultures obtained within 72 hours of the initial diagnostic urine culture, and 92% (123/134) were negative (Table 3). The organisms isolated in the urine with the highest concordance with a positive blood culture were *Staphylococcus aureus* (20%, 2/10) and coagulase negative *Staphylococcus* (19%, 8/42). We identified 38 CSF cultures obtained within 72 hours of the diagnostic urine culture, and 97% (37/38) were negative. There was one concordant urine and CSF CoNS culture.

The majority of infants, 84% (118/141), diagnosed with UTIs had one or more urologic imaging procedures performed. A RUS was performed in 81% (114/141) and a VCUG in 58% (82/141) of infants. Both imaging studies were obtained in 55% (78/141) of infants. Major abnormalities were noted on 4% (5/114) of RUS and 2% (2/82) of VCUGs (Table 4). Overall, a major abnormality was identified in 4% (5/118) of infants who had at least one imaging study obtained and 2 of these infants had been previously diagnosed on prenatal ultrasound (Table 5). Among the 78 infants that underwent a RUS and VCUG, 4% (3/78) had a major abnormality noted.

Infant birth weight, occurrence of second UTI, gender, and infecting species were not associated with the presence of major structural abnormalities. There was no difference in the incidence of major abnormalities in infants with a birth weight < 1500 g (2%, 2/91) and infants ≥1500 g (11%, 3/27, P=0.08). The prevalence of major abnormalities in infants with one UTI and multiple UTIs was 5% (5/106) and 0% (0/12), respectively (P=0.56). Similarly, no difference in prevalence of major abnormalities was found between males (5%, 4/76) and females (2%, 1/42) (P=0.60). Causative organism did not predict the presence of structural abnormalities: Gram-negative rods 6% (4/64), Gram-positive cocci 2% (1/55), and *Candida* 0% (0/13) (P=0.5.).

DISCUSSION

The usefulness of renal imaging studies to predict future kidney disease is unclear. Therefore, imaging in routine follow-up must be weighed in relation to the number of infants who receive the studies with normal results, especially for the VCUG which is an invasive procedure requiring catheterization and radiation.[14] Evidence for radiographic imaging following infection in young infants is scarce,[15] and this study is one of the largest studies to date examining renal imaging in hospitalized infants after UTIs.

VUR has been reported in up to 33% of all children diagnosed with a UTI.[16] Kanellopoulos et al. found 24% (15/62) of infants less than 1 month and 21% (47/234) of infants 1–12 months of age had VUR after a first UTI.[17] Furthermore, in that study 8% (5/57) of infants less than 1 month and 9% (20/214) of infants 1–12 months had other structural abnormalities, such as hydronephrosis and posterior valves.[17] The incidence of structural anomalies found by renal imaging in other groups has ranged from 35% in febrile infants presenting to the emergency department to 55% in asymptomatic jaundiced newborns with a UTI.[18, 19] Our results demonstrated the presence of VUR in 7% (1% grade III) and hydronephrosis in 30% (2% grade III) of infants in the NICU with a first UTI. Other anomalies included echogenic foci/stones, bladder diverticulum, duplication, renal agenesis, dysplasia, horseshoe kidney, and posterior urethral valves. However, only 4% (5/118) of the cohort had major structural abnormalities. This is similar to Cleper et al. who found that only 6.3% (4/64) of infants followed for a neonatal UTI had VUR of grade 3 or higher.[20] Meanwhile, a study of infants up to eight months of age presenting to the inpatient setting for an initial UTI found that 20.9% (18/86) had structural abnormalities, but only 10.5% (9/86) were severe VUR grade 3 or 4.[21] Blickman et al. found that 29.3% (39/133) of children under the age of 6 had VUR grade 3 or higher on renal imaging.[16] Our data support our hypothesis that structural anomalies, especially severe cases warranting further treatment, are lower in young hospitalized infants when compared to older infants and children in the outpatient setting.

In our cohort, there was no difference in the prevalence of major structural anomalies between infants with birth weights < 1500 g and those with birth weights ≥1500 g. In contrast, a study of 62 infants < 1500 g found that VUR was less frequent in infants < 1000 g birth weight (7.7%, 2/26) than those between 1001 to 1500 g birth weight (23%, 4/17).[1] The difference in findings may be due to the relatively small sample size of the most premature infants in both studies.

It has been suggested that radiographic imaging, particularly RUS, following a UTI in infants may not be useful due to the use of ultrasounds during routine prenatal care and the diagnosis of major structural anomalies.[11] However, it has also been suggested based on a study of 179 infants 1–24 months of age, that RUS should be used for infants with persistent fever or abdominal findings or no prenatal ultrasound.[22] Goldman et al. found that intrauterine ultrasound performed poorly in detecting urinary tract abnormalities that were subsequently found on RUS after birth.[4] This finding is consistent with our data, where abnormal prenatal ultrasound evidence was present only in those infants with severe structural abnormalities. These data would suggest that normal prenatal ultrasounds should not influence radiographic imaging following a UTI.

Escherichia coli is the most common pathogen isolated in UTIs. However, our analysis revealed a higher incidence of CoNS (28%) relative to *Escherichia coli* (17%). Although *Escherichia coli* has been shown to be associated with fewer renal abnormalities when compared to *Klebsiella*, *Enterococcus*, and CoNS infections,[23] our study did not demonstrate a difference in renal abnormalities between species. We observed a high mortality for infants with *Candida* UTIs, 21% (3/14), when compared to other species.

This single-center study is limited by its retrospective design and lack of documentation of urinalysis results or UTI prophylaxis. Since outcomes were evaluated after the first positive urine culture, our study could have missed an infant who never developed a UTI while receiving UTI prophylaxis for abnormalities identified on prenatal imaging. Additionally, 23 infants in this UTI cohort did not have a documented VCUG or RUS, 2 of whom died of unknown causes. The most common urine culture species for this cohort was CoNS (52%, 12/23), followed by *Enterococcus* (17%, 4/23), and *Klebsiella* (13%, 3/23). It is possible that a major anomaly was missed in these children. Because only 55% of the cohort underwent both RUS and VCUG and 16% had no imaging, the frequency of anatomical abnormalities may have been underestimated.

Current guidelines recommend a suprapubic aspirate or catheterization specimen to diagnose a UTI. Although a suprapubic aspiration remains the gold standard for diagnosing a UTI, it was not obtained for the majority of patients included in this study for various reasons including: caregiver perception that urine cultures were not indicated and inability to obtain samples because of lack of bladder distention. Eliminating UTI episodes in our analysis when cultures revealed mixed flora or when antibiotic treatment was stopped when culture results were reported may have underrepresented the true number of UTIs. In young infants, the definition of UTI is often dependent on collection method and clinical status of the patient. Our definition of a UTI and our methods for urine collection are not identical to those in previously published reports potentially limiting comparison. Urine samples obtained via catheterization, as opposed to a suprapubic tap, may have overestimated the frequency of a UTI and contributed to the high number of CoNS UTIs from contamination.

The total number of neonates admitted to the NICU during the study period was 8755. However, the number of infants admitted to the NICU with a primary diagnosis of a UTI is unknown but no infants were identified in the 1st 3 days of life. Some infants with UTIs may not have been identified if urine cultures were not obtained as part of the sepsis evaluation or cultures were drawn after administration of empirical antibiotic. The greatest strength of this study was the large number of hospitalized infants with UTIs identified.

Early identification of children with urologic abnormalities that may predispose them to recurrent infections and renal scarring is critical. However, imaging recommendations following UTIs in very young infants are based on limited evidence. We found that the incidence of major urologic abnormalities among neonates in the NICU with UTIs was < 5%. All major anomalies were detected by RUS; these findings would suggest that RUS alone may serve as an appropriate initial imaging study in this population. However, most children with VUR have a normal RUS. For this reason, we continue to obtain both RUS and VCUG in all infants after an initial UTI and await further studies of larger cohorts and assessments of risks and benefits of invasive diagnostic tests in this population.

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Abbreviations

UTI	urinary tract infection
NICU	neonatal intensive care nursery
VCUG	voiding cystourethrography
VUR	vesicoureteral reflux
RUS	renal bladder ultrasound
CI	confidence interval
CoNS	coagulase negative *Staphylococcus*

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Table 1

Demographics

Demographics	Total (%)
Gender	
Male	91 (64)
Female	50 (35)
Ethnicity	
African American	75 (53)
Caucasian	53 (38)
Hispanic	11 (8)
Indian	2 (1)
Gestational Age	
<28 weeks	76 (54)
28–33 weeks	43 (31)
>33 weeks	21 (15)
Birth Weight	
<1000g	65 (46)
1000–1499 g	43 (31)
≥1500g	33 (23)
Day of Life of UTI	
0–3 days	1 (0.7)
4–7 days	3 (2)
8–30 days	76 (54)
31–60 days	61 (43)
Outcome	
Lived/transferred	128 (91)
Died	13 (9)
Infection Status	
Single UTI	128/141 (91)
Multiple UTIs	13/141 (9)*
Total	141

*11 infants had 2 UTIs. 2 infants had 3 UTIs.

Table 2

Organisms identified by urine culture.

Organism	Total (%)
Gram-positive	
CoNS.	44 (28)
Enterococcus sp.	18 (12)
Staphylococcus aureus	10 (6)
Gram-negative	
Escherichia coli	27 (17)
Klebsiella sp.	17 (11)
Enterobacter sp.	14 (9)
Citrobacter sp.	5 (3)
Proteus sp.	4 (3)
Pseudomonas sp.	2 (1)
Gram-negative rods unspeciated	1 (0.6)
Candida sp.	14 (9)
Total	156

Table 3

Concordance of blood and urine cultures per organism isolated.

Organism	**Concordant Samples Blood & Urine Positive / Total # Patients with Blood & Urine Collected (%)**
Gram-positive	
CoNS	8/42 (19)
Enterococcus sp.	0/16 (0)
Staphylococcus aureus	2/10 (20)
Gram-negative	
Enterobacter	0/12 (0)
Klebsiella sp.	1/16 (6)
Escherichia coli	0/24 (0)
Candida sp.	0/14 (0)
Total	11/134 (8.2)

Table 4

Results of renal ultrasound (n=114) and VCUG (n=82) following UTI.

	Total (%)
Renal Ultrasound Study Results	114
Hydronephrosis	
Hydronephrosis grade I	27 (24)
Hydronephrosis grade II	5 (4)
Hydronephrosis grade III	2 (2)*
Other findings	
Echogenic foci/stones	9 (8)
Duplication	0 (0)
Unilateral agenesis	1 (1)*
Dysplastic	1 (1)*
Horseshoe	1 (1)*
VCUG Study Results	82
Reflux	
VUR grade I	3 (3)
VUR grade II	2 (2)
VUR grade III	1 (1)*
Other findings	
Bladder diverticulum	2 (2)
Posterior urethral valves	1 (1)*

*Major abnormality.

Table 5

Demographics for 5 infants with severe structural abnormalities noted on radiographic imaging that required further treatment.

						Abnormality on Imaging	
Gest Age (weeks)	**BW (g)**	**Sex**	**DOL**	**Urine Culture**	**Prenatal Diagnosis**	**RUS**	**VCUG**
26	810	M	8	*Proteus* sp.	No	Renal agenesis	Not done
40	3665	M	23	*Escherichia coli*	No	Grade 3 Hydronephrosis	Grade1 Hydronephrosis
32	2580	M	21	*Citrobacter* sp.	Yes	Grade 3 Hydronephrosis	Posterior Urethral Valves
27	800	M	49	*Enterococcus* sp.	No	Horseshoe Kidney	Grade 3 VUR
35	1855	F	2	*Escherichia coli*	Yes	Dysplastic Kidneys	Not done