

Urinary Imaging Findings in Young Infants With Bacteremic Urinary Tract Infection

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ABSTRACT

OBJECTIVES: To describe renal ultrasound (RUS) and voiding cystourethrogram (VCUG) findings and determine predictors of abnormal imaging in young infants with bacteremic urinary tract infection (UTI).

METHODS: We used retrospective data from a multicenter sample of infants younger than 3 months with bacteremic UTI, defined as the same pathogenic organism in blood and urine. Infants were excluded if they had any major comorbidities, known urologic abnormalities at time of presentation, required intensive unit care, or had no imaging performed. Imaging results as stated in the radiology reports were categorized by a pediatric urologist.

RESULTS: Of the 276 infants, 19 were excluded. Of the remaining 257 infants, 254 underwent a RUS and 224 underwent a VCUG. Fifty-five percent had ≥ 1 RUS abnormalities. Thirty-four percent had ≥ 1 VCUG abnormalities, including vesicoureteral reflux (VUR, 27%), duplication (1.3%), and infravesicular abnormality (0.9%). Age < 1 month, male sex, and non-*Escherichia coli* organism predicted an abnormal RUS, but only non-*E coli* organism predicted an abnormal VCUG. Seventeen of 96 infants (17.7%) with a normal RUS had an abnormal VCUG: 15 with VUR (Grade I–III = 13, Grade IV = 2), 2 with elevated postvoid residual, and 1 with infravesical abnormality.

CONCLUSIONS: Although RUS and VCUG abnormalities were common in this cohort, the frequency and severity were similar to previous studies of infants with UTIs in general. Our findings do not support special consideration of bacteremia in imaging decisions for otherwise well-appearing young infants with UTI.

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Infants and children with urinary tract infection (UTI) often undergo diagnostic imaging tests, including a renal ultrasound (RUS) and/or a voiding cystourethrogram (VCUG) to evaluate for underlying genitourinary abnormalities. There are currently conflicting guidelines about when to obtain a VCUG after a first-time UTI. The 2007 National Institute for Health and Care Excellence (NICE) guideline from the United Kingdom recommends a VCUG in infants <6 months old with an “atypical” UTI, where “atypical” is defined as a UTI that includes infection with a non-*Escherichia coli* organism or bacteremia.¹ These risk factors, which may be associated with an increased risk of urinary tract abnormalities,²⁻⁴ are not considerations in the American Academy of Pediatrics (AAP) 2011 guideline.⁵ However, the AAP guideline does not address infants <2 months of age. Consequently, there is lingering uncertainty over how to manage young infants with UTI and whether bacteremia in itself or other risk factors should be considered in decisions regarding diagnostic imaging.

Using data from multiple institutions on infants <3 months of age with bacteremic UTI, we aim to describe RUS and VCUG findings and determine predictors of abnormal imaging.

METHODS

Setting

A multicenter database of infants <3 months with bacteremic UTI was assembled to analyze management and outcomes for this condition. The original investigation included 276 infants from 20 hospitals at 11 hospital systems across the United States between 1998 and 2013 (listed in Acknowledgments).⁶ The central site for the study was Santa Clara Valley Medical Center in San Jose, California. All sites had existing databases of infants with bacteremic UTI. Each site obtained additional independent institutional review board approval for this study, and informed consent was waived.

Subjects

Infants were included if they were <3 months of age and had the same

pathogenic organism isolated from blood and urine, regardless of UTI history. The primary aim of the initial investigation was to examine parenteral antibiotics duration and outcomes.⁶ Infants in that investigation were excluded if they had major comorbidities (defined as neuromuscular conditions such as spina bifida, previous urologic surgery other than circumcision, or immunodeficiency), managed in the PICU or NICU, or had indwelling urinary or central venous catheters at the time cultures were drawn. For this secondary analysis, infants were also excluded if they had known urologic abnormalities at the time of presentation or had no record of any imaging performed. To avoid confirmation bias, infants who had only 1 of the 2 imaging studies were included.

Data Collection and Variables

Bacteremic UTIs at each site were originally identified using existing microbiology databases. Site investigators reviewed charts using a protocol specifically designed for this study. Data on RUSs and VCUGs were collected and recorded as normal (no relevant findings) or abnormal based on the official radiology report. The exact abnormalities stated in the radiology report were recorded as free text. Imaging findings were subsequently categorized by a pediatric urologist (J.A.), as described in Tables 1 and 3. For RUS findings, hydronephrosis (which included pelviectasis), described consistently as minimal, mild, moderate, or severe in the radiology reports, were then categorized as “mild” (which included minimal), “moderate,” or “severe” by our pediatric urologist (J.A.) based on this wording. When a range of findings was reported or if the degree of hydronephrosis differed between the left and right kidneys, the finding was categorized in the more severe end of the range (eg, “mild to moderate hydronephrosis” and “mild right and moderate left hydronephrosis” were categorized as moderate hydronephrosis). Similarly, VCUG findings for vesicoureteral reflux (VUR) were assigned to the higher end of reported ranges. The exact timing of imaging was not recorded.

TABLE 1 RUS Results in Infants <3 Months of Age With Bacteremic UTI (N = 254)

Finding	N (%)
Any abnormality	140 (55.1)
Hydronephrosis	
Any	108 (42.5)
Mild	84 (33.1)
Moderate	16 (6.3)
Severe	8 (3.2)
Hydroureter	12 (4.7)
Cortical abnormalities	28 (11.0)
Bladder thickening/debris	18 (7.1)
Duplication	6 (2.4)
Other ^a	6 (2.4)

^a Dysplasia, multicystic kidney, hutch diverticulum, ureterocele, dilated calyx, cystic lesion.

Statistical Analysis

To determine predictors of abnormal imaging, bivariate analysis was performed. Variables were included in multivariable analysis if the *P* value was <.10 on bivariate analysis. Multivariable logistic regression was used to identify independent predictors of imaging abnormalities, with adjustment for clustering by institution using the “cluster” modification. Calculations were performed using Stata V.13 (StataCorp, College Station, TX).

RESULTS

A total of 276 infants with bacteremic UTI were identified, from which 19 infants (6.9%) were excluded: 10 infants had known urologic abnormalities at the time of presentation, and 9 infants had no record of any imaging tests. Of the remaining 257 infants, 254 (98.8%) underwent an RUS, and 224 (87.2%; range by institution 66.7%–100%) underwent a VCUG. RUS abnormalities were common: 55.1% of RUS demonstrated at least 1 abnormality, the most common being hydronephrosis (42.5% of all RUS), cortical abnormalities (11.0%), and bladder thickening or debris (7.1%) (Table 1). RUS abnormalities (≥ 1) were more likely in male infants (adjusted odds ratio [aOR] 1.8, 95% confidence interval [CI] 1–3.1), infants age <1 month (aOR 1.8, 95% CI 1.2–2.7), and infants with non-*E coli* UTI (aOR 4.3, 95% CI 1.2–16.2) (Table 2). In infants aged <1 month, RUS abnormalities were found in 68.8% of male and 51.9% of

TABLE 2 Variables Associated With an Abnormal RUS

Variable	RUS Abnormal (%)	P	Adjusted OR (95% CI)
Age, mo			
1–3	62/134 (46.3)	Reference	Reference
<1	78/120 (65)	.003	1.8 (1.2–2.7)
Organism			
<i>E coli</i>	121/231 (52.4)	Reference	Reference
Non <i>E coli</i>	19/23 (82.6)	.005	4.3 (1.2–16.2)
Sex			
Female	44/100 (44.0)	Reference	Reference
Male	96/154 (62.3)	.004	1.8 (1–3.1)

female ($P = .10$) infants. In infants ≥ 1 month, RUS abnormalities were found in 52.5% of male and 41.1% of female infants ($P = .19$).

Of the 224 infants who underwent a VCUG, 33.5% had at least 1 abnormality, and 26.9% had VUR: 16.3% of all VCUGs demonstrated grade I to III VUR, 8.2% grade IV, and 2.3% grade V VUR (Table 3). The remaining abnormalities were duplication (1.3%), obstruction (0.9%), elevated postvoid residual (0.9%), infravesical abnormality (0.9%), and bladder dysfunction (0.4%) (Table 3). Of the 2 infants with obstruction, 1 was diagnosed with a duplicated collecting system and a ureterocele, and the other had posterior urethral valves (PUVs). The 2 infants with an “infravesical abnormality” included the 1 patient with PUVs and obstruction and a second with

TABLE 3 VCUG Results in Young Infants With Bacteremic UTI ($N = 224$)

Abnormality	n (%)
Any abnormality	75 (33.5)
Vesicoureteral reflux	
Any	69 (30.8)
Bilateral	31 (13.8)
Highest grade	
I–III	42 (18.8)
IV	21 (9.4)
V	6 (2.7)
Obstruction ^a	2 (0.9)
Other ^b	8 (3.6)

^a One infant with posterior urethral valves and the other with duplication and ureterocele.

^b One bladder dysfunction, 3 duplications, 2 elevated postvoid residual, 2 infravesical abnormality (both PUVs).

prostatic urethral narrowing who was confirmed to have PUVs on cystoscopy. VCUG abnormalities were more common in infants who had an abnormal RUS compared with infants with a normal RUS (46.4% vs 17.7%, $P < .001$; aOR 3.4, 95% CI 1.8–6.5) (Table 4). Non-*E coli* UTI was associated with an abnormal VCUG compared with *E coli* UTI (77.3% vs 28.7%, $P < .001$); aOR = 8, 95% CI 2.3–28). However, age and sex were not significantly associated with abnormal VCUGs (Table 4).

Of the 96 infants with a normal RUS who also underwent a VCUG, 17 (17.7%) had an abnormal VCUG: 13 with grade I to III VUR, 2 with grade IV VUR, 2 with elevated postvoid residuals (1 with grade IV VUR, 1 with no VUR), and 1 with an infravesical abnormality that was ultimately diagnosed as PUVs. This 60-day-old boy who was noted in the urologist’s history to have an “OK” urine stream was infected with *E coli* and had an initial RUS that was read as normal, although the ultrasound did not include the bladder. The infravesical abnormality was described as “abnormally dilated posterior-prostatic urethra; saccular contrast collection at the urogenital diaphragm as described questionably related to PUVs,” and this finding triggered referral to a urologist. The VCUG was repeated, demonstrated the same narrowing, and the patient underwent cystoscopy and was described to have PUVs, which were ablated.

DISCUSSION

This study characterizes RUS and VCUG abnormalities in infants < 3 months of age with bacteremic UTI. Bacteremic UTI is a unique condition in that it represents true

UTI, given that isolation of the same organism from the blood and urine renders contamination or asymptomatic bacteremia extremely unlikely. Whether bacteremic UTI represents a more severe form of UTI remains unclear.^{6–8} Nonetheless, the fact that the presence of bacteremia dictates the decision-making for imaging in some professional guidelines signifies the need for more comprehensive information on imaging findings in this subgroup, as well as in young infants with UTI in general. In our cohort, 55% of infants had ≥ 1 RUS abnormalities, and 34% of infants had ≥ 1 VCUG abnormalities. VCUG abnormalities were associated with non-*E coli* infection, but not with age or sex.

Previous studies of children < 2 to 3 months with febrile UTIs in general (bacteremic and nonbacteremic) have reported RUS abnormalities ranging from 21% to 62%.^{9–11} This wide range reflects differences in the criteria for “abnormal” and differing exclusion criteria (ie, abnormal prenatal imaging, which we were unable to ascertain reliably in our sample), and it may also reflect differences in the definition of UTI used as well as low interrater reliability on the part of the radiologists or urologists who are asked to interpret the images.^{12,13} In a large prospective study of 220 infants < 3 months of age by Tsai et al, 62% of RUS performed within 3 days of admission were characterized as abnormal, most commonly hydronephrosis or calyceal ectasia (39% of all RUS, 37.2% grade I–II, 1.8% grade III) and acute pyelonephritis (24.1%).¹⁰ In a smaller study by Ismaili et al of 43 infants < 3 months, 33% of RUS performed within 2 days of diagnosis were abnormal, defined as renal pelvic diameter > 7 mm, calyceal or ureteral dilatation, pelvic or ureteral wall thickening, and signs of renal dysplasia.⁹ Finally, Heldrich et al defined a positive RUS as dilatation of the renal pelvis, obstructive lesions, and absent kidney and found that 21% of ultrasounds performed 48 to 72 hours after diagnosis in their subset of 73 patients < 2 months old were abnormal.¹¹ In our cohort of infants with bacteremic UTIs, the prevalence of RUS abnormalities was 55% and fell toward the upper end of the range previously reported in infants with febrile UTIs. The

TABLE 4 Variables Associated With an Abnormal VCUG

Variable	VCUG Abnormal (%)	P	Adjusted OR (95% CI)
Age, mo			
1–3	43/118 (36.4)	Reference	Reference
<1	32/106 (30.2)	.32	NA
Organism			
<i>E coli</i>	58/202 (28.7)	Reference	Reference
Non- <i>E coli</i>	17/22 (77.3)	<.001	8 (2.3–28)
Gender			
Female	34/86 (39.5)	Reference	Reference
Male	41/138 (29.7)	.13	NA
RUS result			
Normal	17/96 (17.7)	Reference	Reference
Abnormal	58/125 (46.4)	<.001	3.4 (1.8–6.5)

NA, not applicable (not included in final model).

RUS screening in a potentially more targeted rather than universal approach.

For infants <2 months of age with UTI, there is no AAP guideline for imaging, whereas the NICE guideline recommends routine RUS and selective VCUG in this age range. If the AAP guideline for children aged 2 to 24 months were applied to our cohort, there would have been a small number of infants whose VCUG abnormalities would not have been detected after the first UTI (17 of 221 or 7.7% of infants who had both an US and VCUG, although this estimate may be biased by the fact that it does not include infants who only underwent 1 of the imaging procedures). Most of these infants had VUR, including 2 infants with grade IV VUR. However, the fact that the RUS is a poor screening test for the detection of VUR in infants with a first-time UTI is well established and is acknowledged in the AAP guideline,⁵ which accepts that some cases of VUR might be missed if VCUGs are not performed routinely after a first UTI. This acceptance is predicated on the fact that the majority of missed cases of VUR involve low-grade VUR and that early detection of VUR, especially low-grade VUR, may not benefit patients. In addition, infants with high-grade VUR are more likely to have a recurrent UTI, at which time the VUR would be identified on VCUG with a low likelihood of increased renal scarring compared with identification after the first UTI.¹⁵ Although 2 recent trials have demonstrated a modest effect of prophylactic antibiotics in preventing recurrent UTI, neither demonstrated any benefit in terms of reduction of future renal scarring.^{16,17} One of these trials was in children with and without VUR, and the number of doses of antibiotics needed to prevent 1 UTI in that trial (5110 doses, or 14 subjects treated daily for 1 year) was actually somewhat lower than the number needed in a more recent trial (5840 doses, or 8 subjects treated daily for 2 years), which only included subjects with VUR.^{16,17} Furthermore, in the latter trial, the efficacy of prophylactic antibiotics was actually slightly lower in children with higher grade VUR compared with lower grade VUR.¹⁶ These findings demonstrate that neither the

benefit of detection of the majority of these abnormalities remains unclear.

The prevalence of VCUG abnormalities in our cohort was 33.5% and within the range of 21% to 52% reported in previous studies of infants with febrile UTIs in general.^{3,9,10} In the aforementioned study by Tsai et al of 220 infants <3 months with UTI (bacteremic status not specified), VCUGs were performed after 7 to 10 days of antibiotic treatment, and the overall prevalence of VUR (27.3%) and distribution of grades of VUR was similar to that found in our study: 19% grade I–III, 5.9% grade IV, and 2.3% grade V VUR.¹⁰ The Ismaili et al study of 43 infants <3 months with UTI (with and without bacteremia) found that 21% of all VCUGs performed at least 1 month after the initial UTI diagnosis were abnormal, 15% grade I to III, and 7% grade IV or V VUR.⁹ Finally, in the 88 infants <3 months old with nonbacteremic UTIs in Honkinen et al's study, 52% had an abnormal VCUG: 45% of these infants had VUR (43% grade I–III, 2% grade 4–5), 2% with obstruction, and 4% with other abnormality.³ This study had a comparison group of 87 infants <3 months old with bacteremic UTI who had a similar prevalence of abnormal VCUGs (45%) but a higher prevalence of grade IV or V VUR (10%) and obstruction (7%) compared with their nonbacteremic counterparts.³ Although our study also had a higher prevalence of grade IV and V VUR (9.4 and 2.7%, respectively) compared with the

nonbacteremic infants in Honkinen et al's study, given the similar prevalence to the larger study by Tsai et al and the study by Ismaili et al, it remains inconclusive whether high-grade VUR is more common in infants with bacteremic UTI than infants with nonbacteremic UTI.

Because some imaging algorithms are predicated on the probability of detection of genitourinary abnormalities, we also assessed predictors of abnormal RUS and VCUGs. Although male sex and age <1 month were associated with an abnormal RUS, they were not significantly associated with an abnormal VCUG. We did find a significantly higher risk for both an abnormal RUS and VCUG in infants with non-*E coli* bacteremic UTIs, of which 82.6% had an abnormal RUS and 77.3% had an abnormal VCUG. The NICE guideline recommends a VCUG for infants <6 months with non-*E coli* UTI,¹ based on previous studies that found non-*E coli* UTI to be associated with a higher prevalence of urinary tract abnormalities,^{2–4} possibly because the abnormal anatomy makes it possible for non-*E coli* organisms with less virulence (such as *Klebsiella* and *Enterobacter*) to cause infection.¹⁴ Therefore, under the premise that detection of VCUG abnormalities is beneficial to patients, an imaging strategy that takes into account the type of organism responsible for the UTI would be justified. More research is needed to see if such risk factors should be considered in determining

presence nor grade of VUR modifies the effectiveness of prophylactic antibiotics in preventing recurrent UTI. While surgical correction of high-grade VUR is advocated by some, randomized trials have demonstrated no benefit of surgical correction over prophylactic antibiotics.¹⁸ Therefore, there is no established harm of non-detection of VUR after a first UTI.¹⁵ There is, however, potential harm in performing a VCUG, which is invasive and painful, expensive, and carries the malignancy concerns associated with ionizing radiation.^{19–21}

On the other hand, nondetection or delayed detection of PUVs is concerning, and there was 1 infant in our cohort who ultimately underwent surgical ablation of PUVs. This infant's RUS was read as normal, although it did not include bladder images, and the pediatric urologist who reviewed the images felt that the kidneys demonstrated mild hydronephrosis. There is a spectrum of severity for PUVs.^{22–24} Given this infant's reportedly normal urine stream and nondilated or minimally dilated kidneys, it is likely that his case was less severe and that a delay in detection would not have been as harmful as a case that involved severe obstruction. Nonetheless, a strategy that ensures bladder imaging in the United States, as recommended by the AAP, and close inspection of the images for obstruction, as well as close follow-up if a VCUG is not performed initially may be warranted in male patients.

Our study has several limitations. The study was retrospective and did not entail a specific imaging protocol. Therefore, not all infants had imaging studies performed, the ordering of VCUG was more selective than the ordering of RUS, and imaging patterns likely differed within and between hospitals. Unfortunately, such limitations are true of multiple other studies on which many guidelines are based, including the study referenced to support the NICE guideline's recommendation to obtain a VCUG in cases of bacteremic UTI.³ We excluded infants admitted to the ICU and those with significant comorbidities, and it is possible that children with more severe illnesses are

more likely to have clinically significant urologic abnormalities. In addition, there was no control group of infants with nonbacteremic UTIs who underwent imaging for comparison, so we relied on previously reported studies with similar age groups. Given that these studies generally define UTI by results from the urine culture and not the urinalysis, it is possible that a portion of the UTIs were not true UTIs,²⁵ in which case the studies may have underestimated the actual prevalence of genitourinary abnormalities. If true, our findings that abnormalities in infants with bacteremic UTI were no more common than those with UTI in general is even more reassuring that bacteremia does not necessarily warrant additional imaging consideration. On the other hand, at least 1 study has suggested that VCUG abnormalities are just as common in children with "false UTI" as they are in "true UTI,"²⁶ further muddling the debate about if and when it is important to detect VUR. Finally, because of the retrospective nature of our study, we do not know the exact timing of when imaging was performed and the outcomes of infants who had abnormal imaging.

CONCLUSIONS

Our findings do not support special consideration of bacteremia in imaging decisions of otherwise well-appearing young infants with UTI. Non-*E coli* infection was associated with both abnormal RUS and abnormal VCUG. Further studies are needed to analyze the relationship among bacteremic UTI, detection of VUR and outcomes, and the optimal imaging protocol for young infants with UTI.

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Urinary Imaging Findings in Young Infants With Bacteremic Urinary Tract Infection

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