The Role of Renal Ultrasound in Children With Febrile Urinary Tract Infection

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Abstract

Background: This study was designed to examine the capability of renal ultrasonography (US) for predicting vesicoureteral reflux (VUR) and renal scarring (RS), and to assess, using initial US, the significant urologic abnormalities that impact on management of children hospitalized with the first febrile urinary tract infection (UTI).

Methods: Hospitalized children aged ≤ 2 years with the first febrile UTI were prospectively evaluated using imaging studies, including 99mTc dimercaptosuccinic acid (DMSA) scan, US, and voiding cystourethrography.

Results: Of the 310 children analyzed (195 boys and 115 girls), 105 (33.9%) had abnormal US. Acute DMSA scans were abnormal in 194 children (62.6%), including 89 (45.9%) with concomitant abnormal US. There was VUR in 107 children (34.5%), including 79 (25.5%) with grades III-V VUR. The sensitivity and negative predictive values of US were 52.3% and 75.1%, respectively, for grades I-V VUR; and 68.4% and 87.8%, respectively, for grades III-V VUR. Eighty-five children (27.4%) had RS, including 55 (64.7%) with abnormal US. Of the 105 children with abnormal US, 33 (31.4%) needed subsequent management (surgical intervention, parental counseling, or follow-up of renal function). Nephromegaly on initial US and grades III-V VUR were risk factors of RS.

Conclusions: Abnormal US may carry a higher probability of grades III-V VUR and RS, and can affect subsequent management in a significant number of children. Nephromegaly on initial US and grades III-V VUR are strongly associated with an increased risk for RS. Thus, US should be performed on children after the first febrile UTI and children with normal US may not require voiding cystourethrography.

Keywords: Children; Renal scarring; Renal ultrasonography; Urinary tract infection; Vesicoureteral reflux

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Introduction

Urinary tract infection (UTI) is one of the leading causes of bacterial infections in febrile children aged ≤ 2 years [1]. The association between UTI and congenital abnormalities like vesicoureteral reflux (VUR) may put children at high risk of acute pyelonephritis (APN) and subsequent renal scarring (RS) [1, 2]. Although the long term medical problems of VUR and infection-related renal damage are being questioned [3, 4], it is believed that postpyelonephritic RS with recurrences, especially in the presence of high grade VUR, may cause future medical problems like hypertension and/or impaired kidney function [5-8]. This is the major driving force for further investigations and treatment of the first UTI.

The goal of imaging in children after the first UTI is the early detection of congenital abnormalities of the urinary tract like obstructive uropathy and VUR that may predispose the child to additional persistent or recurrent infections and renal damage. Although the noninvasive nature, lack of radiation, and relatively lower cost of ultrasonography (US) have made it an ideal initial screening tool in children after the first UTI, its accuracy is highly dependent on the experience of the operator. The value of US in evaluating children at the time of the first UTI remains contentious. The widespread use of maternal-fetal US that frequently identifies children with congenital obstructive uropathy prenatally has been suggested to lessen the need for US later in childhood [9, 10].

Moreover, recent studies have shown the limited value of US for children after the first UTI because of its poor ability in detecting VUR and RS, as well as its lack of impact on subsequent management or care [9-15]. By contrast, other authors claim that US can accurately detect obstructive uropathy, kidney size, renal abscess, and ureterocele in hospitalized children, thereby directly influencing subsequent management based primarily on US examination and suggesting that US should be carried out routinely in children with the first UTI [16-20].

Children hospitalized with a febrile UTI are a distinct subgroup that is more clinically ill and at higher risk of renal damage. The aim of this study was to examine the ability of US for predicting VUR and RS, as well as to evaluate significant urologic abnormalities that impact on subsequent management with a change of therapy or investigations based on initial US in children hospitalized with the first febrile UTI.

Methods

Patients and study design

This prospective cohort study evaluated children aged ≤ 2 years who were admitted to an urban tertiary referral center and academic teaching hospital for the first febrile UTI. The hospital's Institutional Review Board approved the study protocol and the parents of all participants provided informed consent.

The diagnosis of the first febrile UTI was based on the presence of fever with a body temperature ≥ 38 °C, pyuria (≥ five white blood cells per high-power field) and/or positive nitrite or leukocyte esterase tests, and presence of positive urine culture, defined as any growth of a single bacterium in urine from a suprapubic bladder aspiration, or growth of a single microorganism from ≥ 10^5 colony-forming units/mL collected from the midstream clean-void urine specimen of toilet-trained young children, or ≥ 5×10^4 colony-forming units/mL collected from a transurethral catheterized specimen [1]. Children with a history of antenatal hydronephrosis, known urogenital or anorectal malformations, neurogenic disease, or previous UTI episodes were excluded.

All of the children were treated empirically with combined intravenous cefazolin (100 mg/kg/d) and gentamicin (7.5 mg/kg/d) for at least 3 days after admission according to the hospital's antibiotic policy. This regimen was later adjusted according to results of the antimicrobial susceptibility tests for overall treatment duration of 7 - 21 days.

Renal and bladder US examinations

All of the children underwent US to detect urinary tract abnormalities within the first 2 days of admission using an SSD-4000SV (ALOKA Co., Ltd., Tokyo, Japan) with a sector or linear 5.0 MHz probe. All abnormal US findings were recorded, including ≥ 7-mm anteroposterior diameter of the renal pelvis, and/or any grade of dilatation of the calyces or ureters irrespective of anteroposterior diameter; pelvic or ureteral wall thickening; absence of cortico-medullary differentiation; irregular renal outline and signs of renal hypoplasia (i.e., small kidney and thinned or hyperechoic cortex); duplicated renal collecting system, abnormal kidney size, renal cysts, dysplastic kidney, stenosis of the ureteropelvic junction, or ureterovesical junction and ureterocele [21].

Renal hypoplasia was defined as a longitudinal length of kidney less than two standard deviations for age; and nephromegaly as a renal length greater than two standard deviations for age [22]. Examination of the bladder was also performed to detect dilatation of the distal ureters, bladder wall hypertrophy, and presence of ureterocele. Significant urologic abnormalities were defined as those that impacted on subsequent management with a change of therapy, investigations, or follow-up (e.g., surgical intervention, parental counseling, and need for follow-up of renal function) based on initial US findings. Parental counseling was defined as specified for children with hypoplastic kidney, solitary kidney, and multicystic dysplastic kidney, which needed long term follow-up of renal function and growth of the kidneys, and counseling for avoidance of potential nephrotoxic agents or factors.

Significant urologic abnormalities included ureteropelvic junction obstruction (UPJO), ureterovesical junction obstruction (UVJO), hypoplastic kidney, duplex kidney, ureterocele, solitary kidney, and cystic kidney disease that were usually not visualized by voiding cystourethrography (VCUG) examination. At least two investigators reviewed all US reports to ensure uniform findings.

99mTc-dimercaptosuccinic acid renal scan and VCUG examinations

A 99mTc-dimercaptosuccinic acid (DMSA) scan was performed within the first 5 days of admission to verify the presence of renal lesions. An abnormal acute DMSA scan suggesting APN was defined as the presence of focal or diffuse areas of decreased uptake, with preservation of the renal contour [23, 24]. If there was an abnormal acute DMSA scan, a late DMSA scan was performed at least 6 months after the acute infection to evaluate the presence of late RS [10]. RS was defined as the occurrence of focal or generalized areas of diminished uptake of the isotope at the same locations as in the acute DMSA scan and/or associated loss of the kidney contour or cortical thinning with reduced volume [23, 24].

A VCUG was performed 1 - 3 weeks after diagnosis and control of the acute infection. The VUR was graded I-V according to the International Reflux Study in children [25]. A single experienced nuclear medicine physician and a single experienced pediatric radiologist, both of whom were unaware of the patient's clinical and laboratory findings and blinded to the study, interpreted the DMSA and VCUG.

Statistical analyses

Chi-square test was used to compare group proportions with qualitative data. The diagnostic values of sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios were all calculated. Multivariate logistic regression was used to identify potential predictors of RS. Results were expressed as odds ratio, 95% confidence interval, and P value. Statistical significance was set at P < 0.05. All statistical analyses were performed using the SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL, USA).

Results

Demographic and population characteristics

A total of 310 children aged ≤ 2 years old were admitted for the first febrile UTI during the 5-year study period. There were 195 (62.9%) boys and 115 (37.1%) girls, with a median age of 5 months (range: 0.5 - 24 months) and a male/female ratio of 1.7:1. Of the 310 children, 267 (86.1%) were aged < 1

Table 1. Ultrasonography Findings and Vesicoureteral Reflux in Children With the First Febrile UTI

	US findings (n = 310)		Odds ratio (95% CI)		P
No VUR	154	49	3.454	2.096 - 5.692	< 0.001
VUR	51	56			
Grade I	1	1			
Grade II	25	1	28.080	6.174 - 127.710	< 0.001
Grade III	21	12			
Grade IV	4	28			
Grade V	0	14			
Acute DMSA scan					
Abnormal	105	89	5.298	2.911 - 9.640	< 0.001
Normal	100	16			

year, including 175 (89.7%) boys and 92 (80.0%) girls, with a male/female ratio of 1.9:1. Forty-three (13.9%) children were aged 1 - 2 years, with a male/female ratio of 0.87:1. All of the boys in the study were uncircumcised, as is customary in Taiwan. The most common causative microorganism isolated was *Escherichia coli*, isolated in 263 children (84.8%), and 47 (15.2%) children had other bacteria, including Klebsiella, Proteus, Citrobacter, Pseudomonas, and Enterococcus species.

There were abnormal acute DMSA scans suggesting APN in 194 (62.6%) children (118 boys, 60.8%; 76 girls, 39.2%), and 89 (45.9%) had an abnormal US (Table 1). The remaining 116 children (37.1%; 77 boys, 66.4%; 39 girls, 33.6%) had normal acute DMSA scans suggesting lower UTI.

US findings

Of the 310 children, 105 (33.9%) had abnormal US, including 49 (46.7%) with normal VCUG and 56 (53.3%) with demonstrable VUR (Table 1). There were significant differences between children with and those without VUR (P < 0.001), and between grades I and II and grades III-V VUR (P < 0.001). There was also a significant difference in abnormal US between children with APN and UTI (P < 0.001).

The most common abnormal US findings were various grades of hydronephrosis, seen in 54 children, including UPJO in three and UVJO in two. Other abnormal US findings were renal hypoplasia in 16 children, nephromegaly in 16, thickened bladder wall in seven, uncomplicated duplex kidney in three, duplex kidney with obstructive ureterocele in three, solitary kidney in three, bilateral duplex kidney with right obstructive upper pole moiety in one, simple ureterocele in one, and multicystic dysplastic kidney in one.

Of the 33 children with significant urologic abnormalities who needed further investigations to determine management, seven (21.2%) with normal VCUG underwent non-antireflux surgery, including UPJO in one, VUJO in one, duplex kidney with obstructive ureterocele in three, simple ureterocele in one, and bilateral duplex kidney with the right poorly functioning upper pole moiety in one.

The remaining 26 children were subsequently managed by parental counseling and/or further follow-up of renal function. Sixteen children with nephromegaly (suggestive of acute lobar nephronia) were treated with antibiotic therapy for 3 weeks [26, 27].

VCUG findings

The VCUG was abnormal in 107 children (34.5%). The presence of VUR, graded using US findings (the maximum degree of reflux given if bilateral, Table 1), revealed no difference in the incidence of VUR between boys and girls (P = 0.679). Grades III-V VUR was present in 79 children (25.5%; 55 boys and 24 girls). The rate of APN in children with VUR was significantly higher than that in children without VUR (81.3% vs. 52.7%, P < 0.001). There was a significant association between APN and the presence and severity of VUR (P < 0.001).

Diagnostic performances of US for revealing grades I-V and grades III-V VUR

The diagnostic characteristics of US for predicting VUR (Table 2) demonstrated that the sensitivity and NPV of US for grades I-V VUR were 52.3% and 75.1%, respectively. However, 51 of 107 (47.7%) children with grades I-V VUR had normal US, which would have been missed if US was the only screening test used. The sensitivity and NPV of US for grades III-V VUR were 68.4% and 87.8%, respectively. Twenty-five (31.6%) of the 79 children with grades III-V VUR had normal US (grade III in 21 and grade IV in four). No case of grade V VUR was missed by the US screening. Grades III-V VUR had 25.5% prevalence in the study population, with a post-test probability of 50% for a positive test and 10% for a negative test.

Diagnostic ability of US for predicting RS and risk factors for RS

Of the 310 children, 85 (27.4%) had RS, including 55 (64.7%) with abnormal US. The sensitivity and NPV of US for predict-

Table 2. Diagnostic Performances of Renal Ultrasonography

Parameter	Grades I-V VUR	Grades III-V VUR	RS
N	56/107	54/79	55/85
Sensitivity (%)	52.3	68.4	64.7
Specificity (%)	75.9	77.9	77.8
PPV (%)	53.3	51.4	52.4
NPV (%)	75.14	87.8	85.4
LR+	2.17	3.10	2.91
LR-	0.63	0.41	0.45

ing RS were 64.7% and 85.4%, respectively (Table 2). The correlations between the presence of RS and different variables of interest were also evaluated (Table 3). Using bivariate analysis, RS was significantly more frequent in children with VUR, in children with abnormal US and significant urologic abnormalities, and when initial US examination showed nephromegaly. The presence of RS was independent of age and sex.

Multivariate analysis confirmed that the incidence of RS significantly correlated with the presence of VUR (Table 4). The risk was significantly increased with higher grade. Nephromegaly on initial US also significantly correlated with the risk for RS. However, abnormal US and significant urologic abnormalities no longer appeared as risk factors for RS.

Discussion

Although US can disclose a variety of anatomic abnormalities, it only indirectly detects VUR. Published studies report that the ability of US to detect grades I-V VUR is poor and varies among studies, with a sensitivity of 16-40% and NPV of 25-86% [10, 12, 14, 15]. However, improved detection rates have been reported in children with grades III-V VUR, with a sensitivity of 63-86% and NPV of 70-94% [18, 28, 29]. The present study reveals that US has modest sensitivity (68.4%) and NPV (87.6%) for disclosing grades III-V VUR. This is consistent with previously reported values for detecting high grade VUR [18, 28, 29].

Recent reports have also shown a significant correlation between reflux grade and RS frequency, suggesting that high grade VUR increases the risk of RS after UTI [6-8]. Although abnormal US is still not particularly predictive of a positive test, the post-test probability for a negative test is only 10%, indicating that a negative finding on US makes the diagnosis of grades III-V VUR unlikely. Antibiotic prophylaxis is not recommended in children with low grade (grades I-II) VUR and low grade VUR is a weak predictor of RS [30]. Thus, revealing low grade VUR is not so important clinically.

Previous studies have reported that many congenital abnormalities of the urinary tract are detected prenatally, however, the prevalence of post-UTI diagnosed obstructive uropathy and other anomalies have declined significantly, thereby reducing

Table 3. Risk Factors of Renal Scarring Using Bivariate Analysis (N = 310)

Parameter	RS+	RS-	Odds Ratio	95% CI	P
Age					
< 12	70	197	0.663	0.335	0.270
> 12	15	28			
Sex					
Boys	52	143	0.904	0.541	0.8
Girls	33	82			
VUR					
No	23	180	10.783	6.040	< 0.001
Yes	62	45			
VUR grade					
0-II	29	202	16.980	9.102	< 0.001
III-V	56	23			
US findings					
Normal	30	175	6.417	3.721	< 0.001
Abnormal	55	50			
Significant urological abnormalities					
No	66	211	4.339	2.062	< 0.001
Yes	19	14			
Nephromegaly					
No	71	223	22	4.83	< 0.001
Yes	14	2			

Table 4. Risk Factors of Renal Scarring Using Multivariant Analysis (N = 310)

Parameter	RS +	RS -	Odds Ratio	95% CI	P
Age					
< 12	70	197	1.793	0.735	0.3270
> 12	15	28			
Sex					
Boys	52	143	1.674	0.841	0.228
Girls	33	82			
VUR					
No	23	180	2.682	6.940	< 0.001
Yes	62	45			
VUR grade					
0-II	29	202	15.195	9.7102	< 0.001
III-V	56	23			
US findings					
Normal	30	175	1.957	3.8721	< 0.001
Abnormal	55	50			
Significant urological abnormalities					
No	66	211	2.367	2.962	< 0.001
Yes	19	14			
Nephromegaly					
No	71	223	25.107	4.683	< 0.001
Yes	14	2			

the value of US as the first line investigation in children after the first UTI [9, 13]. Recently, Jahnukainen et al [17] examined 155 children aged < 16 years with the first febrile UTI. There was abnormal US in 23 children (14.8%) and subsequent management of nine children was changed based on initial US findings. Prenatal US results were re-evaluated by the authors in all children with abnormal US during the first UTI, but in these cases, the association between antenatal US and US performed at the time of UTI was poor. As such, normal findings of antenatal US do not exclude the potential for significant urologic abnormalities detected later in life [16, 17].

In the current study, significant urologic abnormalities that led to further workup and management based on initial US examination were seen in 10.6% (33/310) of children. Seven of 33 children (21.2%) were eventually treated surgically even though hydronephrosis and other urologic abnormalities were not detected prenatally due to normal obstetric findings. The rate of surgical intervention for important structural abnormalities in this study is consistent with previously reported values of 22.2-44.4% [16-18]. Children with the significant urologic abnormalities were not detected prenatally, which can partially be explained by the fact that some parents may have irregular antenatal follow-up during pregnancy and provide incorrect obstetric information. Duplex kidney and ureterocele may also be missed on initial antenatal US. The current findings suggest that US performed in children with the first UTI can be used as the initial screening tool regardless of antenatal US results

[16, 17, 20].

In addition, parental counseling is also important in children with hypoplastic kidney, solitary kidney, and multicystic dysplastic kidney in order to prevent further renal damage, as congenital anomalies of the kidney and urinary tract are significant causes of chronic kidney disease in children [31]. Patient instructions of avoidance of potentially nephrotoxic factors in later life that may threaten unilateral hypoplastic, solitary, or multicystic dysplastic kidney should be emphasized to the parents of affected children.

Muller et al [32] examined 191 children aged < 1 year with the first UTI and identified those who had RS 1 year later. The US findings were abnormal in 46 infants (24%). While 46 infants (24%) had RS, only 19 had abnormal US (sensitivity 41%). Although US performed in children with acute UTI had a limited ability for detecting VUR and RS on follow-up DMSA examination, RS occurred in 88% of children with grades III-V VUR, in 27% of children with grades I-II VUR, and in only 16% of those without VUR. Their results indicated that grades III-V VUR were strong indicators of RS, which was similar to the findings here and in previous reports [6-8].

It was suggested that nephromegaly on initial US examination was an effective predictor for the diagnosis of acute lobar nephronia [26] and strongly associated with a high incidence of RS [32-34]. Fourteen of the 16 children (87.5%) with nephromegaly had late RS in this study, consistent with the previous reports [32-34]. Nephromegaly might reflect ex-

tensive, intense renal inflammation that increased the risk of developing RS. These findings emphasize the potential importance of careful assessment of initial kidney size using US in children after acute UTI.

This study has several strengths. Data were collected from a single center and involved prospectively and consecutively enrolled inpatient children. Thus, this study has a consistent strategy in managing children with febrile UTI. The children with an abnormal acute DMSA scan were followed up to identify those who developed RS.

This study also has some limitations. Firstly, it only enrolled hospitalized children aged ≤ 2 years with the first febrile UTI, which might pose a selection bias because most patients with UTI were managed as outpatients. Secondly, children with a febrile UTI or with a body temperature < 38 °C were all excluded. This study is also strict and only enrolled children with the first UTI and not general cases. Because it is also limited to hospitalized children, this may prevent further generalizations of the findings. Lastly, the reported cases may be too small to make a firm conclusion on the impact of US on the necessity of VCUG examination and subsequent management. Further prospective studies with larger cohorts are warranted.

In conclusion, abnormal US may carry a higher probability of grades III-V VUR and RS, and can affect the management in a significant number of children hospitalized with the first febrile UTI. Nephromegaly on initial US examination and grades III-V VUR are strongly associated with increased risk for late RS. The results of this study highlight that all children after the first febrile UTI should have US and that a negative finding on US makes the diagnosis of grades III-V VUR unlikely for children with the first febrile UTI. Children with normal US may not need VCUG, reducing further imaging in children and decreasing the risk of radiation exposure, family anxiety, and costs.

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