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Voiding Cystourethrography Is Mandatory in Infants with Febrile Urinary Tract Infection

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Vesicoureteral reflux (VUR) is common condition in infants with febrile urinary tract infections (UTIs). Both VUR and febrile UTIs are risk factors for renal scars, characterized by glomerular hypertrophy with global or segmental sclerosis as cardinal features in pathology. Because renal scars may cause hypertension or chronic kidney diseases in later life, voiding cystourethrography (VCUG) has been mandatory for infants following their first febrile UTIs to identify VUR. However, increasing evidence suggests that the presence of VUR may not represent a direct risk factor for renal scars, which has led to an increase in the use of a stratified approach, in which VCUG is not performed for all patients. This study was conducted to verify whether the stratified approach is justified to identify infants at risk for renal scarring. The medical records of 306 infants with first febrile UTIs (median age, 4 months; 0-72 months) were reviewed. VUR was detected in 40.4% (67/166) of patients by the non-stratified approach, in which VCUG was performed in all patients. In contrast, VUR was identified in only 27.1% (38/140) of patients by the stratified approach, in which VCUG was performed only in the patients with high risk of developing renal scars. This difference in the discovery rate was significant (p = 0.02). Renal bladder ultrasonography had the sensitivities of as low as 45.7% and 52.9% in detecting VUR and in predicting renal scarring assessed by renal scintigraphy, respectively. In conclusion, VCUG should be performed in all infants after their first febrile UTIs.

Keywords: 99m-technetium dimercaptosuccinic acid scintigraphy; renal ultrasound; urinary tract infection; vesicoureteral reflux; voiding cystourethrography
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Introduction

Vesicoureteral reflux (VUR) is the retrograde passage of urine from the bladder into the upper urinary tract. It is the most common urologic abnormality in children, occurring in about 1% of newborns, and as high as 25 to 40% of young children with urinary tract infections (UTIs) (Merguerian et al. 1999). Conversely, UTIs are the most common factor associated with VUR, and are the risk factors for formation of renal scars, which are characterized by glomerular hypertrophy with global or segmental sclerosis as cardinal features in pathology. Renal scar may cause later problems, such as hypertension, chronic renal failure and, in some cases, end stage renal disease (Martinell et al. 2000; Duzova and Ozen 2003; Lin et al. 2003; Shiraishi et al. 2010). At the time of diagnosis, 30-50% of children with VUR were reported to have renal scarring by imaging studies (Weiss et al. 1992). Thus, UTIs, along with other etiologic factors including VUR, are important in the pathogenesis of renal scarring.

Taken together, it has been common to conduct imaging studies in children following UTIs due to concerns regarding the impact of VUR on renal scarring (Smellie et al. 1964). Accordingly, the American Academy of Pediatrics (AAP) published a practice parameter in 1999 that recommends the use of renal bladder ultrasonography (RBUS) and voiding cystourethrography (VCUG) to evaluate UTIs in all febrile infants in order to identify VUR (American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection 1999).

However, increasing evidence that the presence of VUR is not a direct risk factor for the development of renal scars has prompted both the AAP and the National Institute for Health and Clinical Excellence (NICE) in the UK to publish new guidelines recommending reduction in the use of imaging, including VCUG (Mori et al. 2007; Roberts 2011).

The study was conducted to verify the stratified approach recently recommended by the AAP and the NICE

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is effective in identifying children at risk for renal scarring.

Methods and Subjects

Patients admitted to Nakano Children's Hospital between January 2001 and December 2011 were enrolled and analyzed in the current study. The records of patients with their first UTIs who underwent investigations with RBUS and/or VCUG were reviewed. Patients with known urological abnormalities were excluded. UTIs were defined as a significant bacterial count of one type of bacterium in a urine specimen (Roberts 2011).

The subjects were classified into two groups, i.e., patients admitted before October 2007 (81 months between January 2001 and September 2007), and patients admitted after October 2007 (51 months between October 2007 and December 2011): during the former period, all patients underwent only RBUS and selected patients showing abnormalities on RBUS or atypical signs of UTIs were further evaluated with VCUG (stratified approach); during the latter period, all subjects underwent both RBUS and VCUG (non-stratified approach). The atypical features of UTIs included serious illness, raised serum creatinine levels, septicemia, high serum levels of C-reactive protein (≥ 8.0 mg/dL) and poor responses to suitable antibiotics (Mori et al. 2007). Clinicians' gut feeling that infections in children are more serious than suggested by clinical assessment was also justified to perform VCUG (Van den Bruel et al. 2012).

The abnormalities on RBUS included significant difference in the size of the kidneys (≥ 10 mm in diameter on the long axis), dilation of the renal pelvis with an anteroposterior diameter ≥ 5 mm, high echoic lesions and dilated ureters. VUR was diagnosed on VCUG and classified according to the international classification as shown in the Fig. 1 (Lebowitz et al. 1985). Late renal scans using 99m-technetium dimercaptosuccinic acid (99mTc-DMSA) were performed for patients with VUR three to six months after the occurrence of febrile UTIs to detect the development of renal scars. 99mTc-DMSA scintigraphy was performed according to a standard protocol (Subcommittee for Standardization of Radionuclide Imaging, Medical and Pharmaceutical Committee 1988). The injected dose of DMSA was calculated by the following formula dependent on the age of the patient: (standard adult dose) × (patient's age in years + 1)/(patient's age in years + 7); scintigraphic images were obtained 2 hours after intravenous injection of 99mTc-DMSA. The significant renal scarring was assessed by the findings of 99mTc-DMSA semi-quantitatively by one radiologist blinded to the results of RBUS and VCUG: the extent of cortical defects was evaluated by dividing the renal cortex into segments and counting the number of renal parenchymal segments affected; the severity was determined by the number of segments affected: mild (1-2), moderate (3-4), or severe (≥ 5) or as global atrophy characterized by a diffusely scarred and shrunken kidney (Carpenter et al. 2013).

The statistical analyses between the groups were completed using the Mann-Whitney *U*-test for continuous variables and the chi-square test with Yate's correction or Fisher's exact test for categorical data, respectively.

The ethics committee of Nakano Children's Hospital approved this study.

Results

Clinical characteristics of the subjects

As shown in Table 1, 306 infants, of whom 140 patients were treated by the stratified approach and 166 patients were treated by the non-stratified approach, were

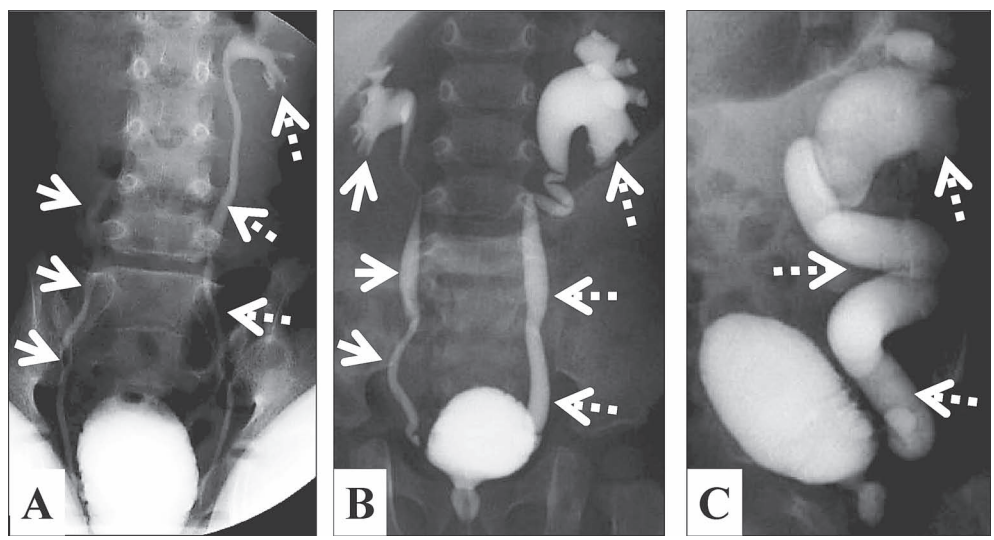

Fig. 1. International grading of vesicoureteral reflux grading by voiding cystourethrography.
Images were obtained from the patients enrolled in the current study. A. Antero-posterior view. Solid arrows denote the grade 1 reflux on right renal unit, in which contrast media only fill the ureter without dilation, while the dashed arrows denote the grade 2 reflux on left renal unit, in which contrast media fill the ureter and the collecting system without dilation. B. Antero-posterior view. Solid arrows denote the grade 3 reflux on right renal unit, in which contrast media fill and mildly dilate the ureter and the collecting system with mild blunting of the calyces while the dashed arrows denote the grade 4 reflux, in which contrast media fill and grossly dilate the ureter and the collecting system with blunting of the calyces. Some tortuosity of the ureter is also present. C. Lateral view. Dashed arrows denote the grade 5 reflux, in which contrast media fill grossly dilated collecting system. All the calyces are blunted with loss of papillary impression and intrarenal reflux may be present. There is significant ureteral dilation and tortuosity.

reviewed (male : female = 200 : 106). The median age was 4.0 months, and there were no significant differences between the approaches (5.0 months in the stratified approach [range 0-70 months] and 4.0 months in the non-stratified approach [range 0-72 months], $p = 0.31$).

Predicting VUR and late renal scarring with RBUS

As shown in Table 1, VCUG was performed in all patients (166/166 = 100%) in the non-stratified approach period and 72.9% of the patients in the stratified approach period (102/140). Among them, either unilateral or bilateral VUR was detected in 40.4% (67/166) of the subjects by the non-stratified approach and 27.1% (38/140) of the subjects by the stratified approach. This difference in the rate of identification in VUR was significant ($p = 0.02$) with male predominance. Regarding the number of children with high-grade VUR classified as grade 3, 4 or 5, there were 48 patients (48/166 = 29.0%) by the non-stratified approach and 23 patients (23/140 = 16.4%) by the selective approach. Again, this difference was significant ($p = 0.01$).

As shown in Table 2, a total of 268 patients with UTIs underwent both RBUS and VCUG during the whole study period. The power of detecting VUR with RBUS was calculated as follows: sensitivity: 45.7%, specificity: 84.7%, positive predictive value: 65.8%, negative predictive value: 70.8%.

As shown in Table 3, a total of 80 patients underwent full imaging studies, including RBUS, VCUG and 99mTc-

Table 1. Clinical characteristics of the subjects.

	Total	Stratified approach†	Non-stratified approach‡	*P* value
No. of patients	306	140	166	n.d.
Median age in month (range in month)	4.0 (0-72)	5.0 (0-70)	4.0 (0-72)	0.31
Gender (male : female)	200 : 106	85 : 55	115 : 51	0.12
No. of VCUG¶ (%)	268 / 306 (87.6%)	102 / 140 (72.9%)	166 / 166 (100%)	< 0.01
No. of identified VUR§ (%)	105 / 306 (34.3%)	38 / 140 (27.1%)	67 / 166 (40.4%)	0.02
Gender of the patients with VUR (male : female)	69 : 36	24 : 14	45 : 22	0.68
No. of high grade (grade 3-5) VUR§ (%)	71 (23.2%)	23 (16.4%)	48 (29.0%)	0.01

Stratified approach† were applied to the patients admitted during January 2001 and September 2007; Non-stratified approach‡ were applied to the patients admitted during October 2007 and December 2011.

VCUG¶, voiding cystourethrography; VUR§, vesicoureteral reflux.

Table 2. Power of detecting vesicoureteral reflux by renal bladder ultrasonography.

	VUR§	No VUR§	Total
Abnormal RBUS ƒ	48	25	73
Normal RBUS ƒ	57	138	195
Total	105	163	268

Sensitivity 45.7%, specificity 84.7%, positive predictive value 65.8%, negative predictive value 70.8%.

VUR§, vesicoureteral reflux; RBUS ƒ, renal bladder ultrasonography.

Table 3. Power to predict renal scarring in patients with vesicoureteral reflux by renal bladder ultrasonography.

	Abnormal DMSA#	Normal DMSA#	Total
Abnormal RBUS ƒ VUR grade (0 : 1 : 2 : 3 : 4 : 5) scarring grade (mild: moderate: severe)	27 (2 : 0 : 1 : 2 : 18 : 4) (14 : 9 : 4)	14 (0 : 0 : 0 : 6 : 6 : 2)	41
Normal RBUS ƒ VUR grade (0 : 1 : 2 : 3 : 4 : 5) scarring grade (mild: moderate: severe)	24 (1 : 1 : 2 : 7 : 12 : 1) (16 : 5 : 3)	15 (0 : 4 : 1 : 6 : 3 : 1)	39
Total	51	29	80

Sensitivity: 52.9%, specificity: 51.7%, positive predictive value: 65.9%, negative predictive value: 38.5%.

RBUS ƒ, renal bladder ultrasonography; DMSA#, 99m-technetium dimercaptosuccinic acid scan.

DMSA renal scans during the whole study period. These were the patients with VUR and their guardians gave us the informed consent to perform late 99mTc-DMSA renal scans. The power to predict renal scarring by RBUS was calculated: sensitivity: 52.9%, specificity: 51.7%, positive predictive value: 65.9%, negative predictive value: 38.5%.

Discussion

A strong association between childhood UTIs or VUR and renal scarring has been recognized for many years (Smellie et al. 1964). A recent systematic review revealed that children with VUR are more likely to develop pyelonephritis [relative risk (RR): 1.5] and renal scarring (RR: 2.6) compared with children without VUR (Shaikh et al. 2010). Furthermore, children with VUR of grade 3 or higher are more likely to develop scarring than children with lower grades of VUR (RR: 2.1) (Shaikh et al. 2010).

Therefore, the AAP previously recommended the use of routine imaging (RBUS and either VCUG or radionuclide cystography) following initial UTIs in febrile infants aged two months to two years (American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection 1999).

However, over the last decade, the management of children with febrile UTIs has become quite controversial regarding the need for such extensive investigations (Tullus 2012). The NICE issued new guidelines for the management of children with UTIs that utilize a stratified approach for imaging with the aim of applying imaging studies to at-risk groups of infants in a more focused manner (Mori et al. 2007). According to the guidelines, children with UTIs should undergo RBUS only if they are less than six months of age, have atypical UTIs or have had recurrent infections. The AAP also revised the guidelines to recommend the elimination of imaging in children with first febrile UTIs if there are no additional features indicated on RBUS, i.e., hydronephrosis, scarring or other signs of high-grade VUR or urinary tract obstruction.

Meanwhile, a recent retrospective study evaluating the applicability of the stratified approach for imaging in infants less than six months of age based on the NICE guidelines showed that a significant number of cases of VUR and renal scars would have been missed (Tse et al. 2009). In fact, we encountered several patients with febrile UTIs who did not have any abnormalities by initial RBUS screening and did not undergo further evaluations by the stratified manner developed recurrent UTIs. They were later found to have both high-grade VUR and renal scars by VCUG and DMSA. They changed our approach from stratified manner to non-stratified manner in October 2007.

In the present study, we compared the powers of identifying VUR and predicting renal scarring in young children with febrile UTIs by the stratified approach with those by the non-stratified approach. As a result, it was confirmed that the stratified approach, in which VCUG is not mandatory, left considerable number of patients with VUR undiagnosed among a larger number of patients at a single center: the power of detecting VUR with RBUS was as low as 45.7% and that it was estimated that 19 refluxes are missing in children evaluated with the stratified approach if considering the percentage (29%) of high-grade reflux identified in children by the non-stratified approach (Table 1). This means that 50% of the 38 typical UTIs, with no signs of abnormalities by RBUS, would have a high-grade reflux. This finding agreed well with the recent findings by Massanyi et al. (2013); according to their study, one hundred fifty-eight kidneys had evidence of VUR on VCUG, and initial RBUS demonstrated abnormality only in 25 (sensitivity 0.17); forty-five kidneys had high-grade VUR and RBUS revealed abnormality only in 16 (sensitivity 0.36). Based on these, they concluded that RBUS has poor sensitivity and negative predictive value for detecting high-grade VUR in patients less than 2 years who present with a febrile UTI, i.e., a significant number of patients who were diagnosed with high-grade VUR had a negative screening RBUS.

In addition to the poor sensitivity and negative predictive value for detecting VUR, the power of predicting renal scarring with RBUS was also as low as 52.9% in the current study.

Taken together, at present, the stratified approach cannot be justified and the use of VCUG should be recommended for all infants with first febrile UTIs. That is to say, non-stratified approach should be recommended. In agreement with our findings, the guidelines recently issued by the European Association of Urology recommend the use of VCUG in all young children with first febrile UTIs (Tekgül et al. 2012). Given the strong association between therapeutic time delay and renal scarring (Oh et al. 2012), it is essential to diagnose the children with high grade VUR, which increases the risk of developing febrile UTIs and renal scarring (Coulthard 2008).

There are limitations associated with our study due to the retrospective design; only admitted children were included and the authors reading the VCUG results were not blinded to the RBUS results. Any bias, however, would have been expected to be towards reporting more cases of VUR.

In summary, our findings suggest that a stratified approach in children with first febrile UTIs might miss a significant number of cases of VUR and renal scarring. Therefore, the use of VCUG should be recommended for such children until additional research helps us to determine the optimal management strategies.

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Conflict of Interest

The authors declare no conflict of interest.

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