Importance of ultrasonographic findings in infants with the incidence of urinary tract infection for the first time

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Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections in children, along with bacterial respiratory infections. Vesicoureteral reflux (VUR) is an important risk factor for recurrent UTIs. Whether voiding cystography (VCG) should be performed on all patients at their first episode of a UTI is controversial because VCG is an invasive procedure that requires radiographic exposure and catheterization. Our results demonstrated that sex, clinical variables, laboratory variables, and ultrasonographic findings could predict the presence of VUR during the first episode of UTI in pediatric patients. In addition, we defined the indications for performing VCG in these patients. In this research, we stress on the importance of ultrasonographic findings in infants with the first occurrence of UTI.

Keywords: C-reactive protein; ultrasonography; urinary tract infection; vesicoureteral reflux; voiding cystography

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Whether all patients who present with their first episode of UTI should undergo voiding cystography (VCG) is controversial because VCG is an invasive procedure that requires radiographic exposure and catheterization [3]. Moreover, VUR is present in only 25–40% of children with febrile UTI and often occurs at a grade I or II level of severity [4, 5]. 99mTc-Dimercaptosuccinic acid (DMSA) scintigraphy is effective in predicting the presence of high-grade VUR [6, 7]. In Japan, however, only patients with high-grade VUR who are diagnosed by using VCG are likely to undergo DMSA scintigraphy because DMSA scintigraphy is not as accessible as VCG and is practiced at only a limited number of institutions. Therefore, the necessity of VCG in patients presenting with their first episode of UTI is difficult to determine.
Recently, we demonstrated that sex, clinical variables, laboratory variables, or/and ultrasonographic (US) findings could predict the presence of VUR in patients presenting with their first episode of UTI [8]. Among these variable factors, the grade of US findings was the most significant predictive factor of VUR. We retrospectively studied the medical records of 286 patients (median age: 5 months; range: 0.5–169 months) who presented with a first UTI without other evidence of urological disease. We defined a UTI as a fever with a body temperature of $\geq 38^\circ$C and urine sediments with white blood cell (WBC) counts of $\geq 10$ per high-power field of spun fresh urine. Furthermore, even if urinary findings were normal, the presence of renal abscesses or acute focal bacterial nephritis (AFBN) were regarded as manifestations of UTI. During the study period, 286 patients presented with a first UTI, of whom 200 (69.9%) underwent VCG. Sixty-nine patients (34.5%; median age, 4 months; range, 1–122 months) had VUR, whereas 131 patients (65.5%; median age, 5 months; range, 1–143 months) did not exhibit VUR. The patients who did not undergo VCG (median age, 7 months; range, 0.5–169 months) included those whose initial US findings did not show VUR (n = 65); those who exhibited transient abnormal US findings (n = 12); those who did not undergo US during the first UTI episode (n = 4); those who were transferred from another institution for comprehensive examination and treatment because they developed AFBN, renal abscess, or an inherited disease of the urinary system (n = 4); and those whose parents did not provide consent for participation in this study (n = 1).

We addressed the echo probe onto the lateral abdomen (Figure 1) and defined the abdominal US findings of the UTI patients. US findings were classified as grade I if these were normal; grade II if these indicated mild pyelectasis; grade III if these showed pyelectasis and dilation of the urinary tract; grade IV if these showed pyelectasis, dilation of the urinary tract, and abnormal movement of the ureter resembling urine reflux; and grade V if these indicated hydronephrosis of grade III or higher [9], hydroureter of $\geq 5$ mm in diameter, or pathological features such as renal scarring, renal abscess, and AFBN (Figure 2). Sixty-nine patients had VUR of various grades as follows: grade I (n = 3), grade II (n = 8), grade III (n = 17), grade IV (n = 26), and grade V (n = 15). Twenty of these patients exhibited VUR on both sides.

Abdominal US findings (P < 0.001), peak blood C-reactive protein (CRP) level (P < 0.001), fever duration (days) after the administration of antibiotics (P = 0.007), and sex (P = 0.001) significantly differed between the VUR and non-VUR groups. The VUR patients who had abnormal US findings included 1, 3, 7, 19, and 39 patients with grades I, II, III, IV, and V findings, respectively. Ninety-four percent (65/69) of the VUR patients and 50% (65/131) of the non-VUR patients presented with a US finding of grade III or
higher. For comparison between US grades IV and V, the $\chi^2$ test showed a sensitivity, a specificity, and an odds ratio (OR) of 84.1%, 68.7%, and 11.57 (95% confidence interval [CI], 5.5–24.3), respectively (P < 0.001).

Seventy-one percent (49/69) of the VUR patients and 28%
(37/131) of the non-VUR patients had peak blood CRP levels \( \geq 80 \text{ mg/L} \). For evaluation of CRP levels of \( \geq 80 \text{ mg/L} \) in VUR-positive patients, the \( \chi^2 \) test had a sensitivity, a specificity, and an OR of 71.0\%, 71.8\%, and 6.22\% (95\% CI, 3.27–11.86), respectively (\( P < 0.001 \)). The sensitivity, specificity, and OR for both US grades \( \geq IV \) and CRP levels \( \geq 80 \text{ mg/L} \) in VUR-positive patients were 47.8\%, 87.8\%, and 6.59 (95\% CI, 3.26–13.33), respectively (\( P < 0.001 \)). If the patients had either grade \( \geq IV \) US findings or a CRP level \( \geq 80 \text{ mg/L} \), the sensitivity, specificity, and OR were 92.8\%, 51.9\%, and 6.59 (95\% CI, 3.26–13.33), respectively (\( P < 0.001 \)).

The grades of the US findings and blood CRP levels were analyzed in multivariate logistic regression analyses (MLRA). The sensitivity, specificity, positive predictive value, and negative predictive value of \( x \geq 0.5 \) as an indicator of VUR positivity (\( \log_e (x/1 - x) = 1.1163 \times [US \text{ grade}] + 0.0761 \times [CRP \text{ level}] - 5.2319 \)) were 77.6\%, 87.0\%, 75.4\%, and 88.4\%, respectively.

Moreover, we performed MLRA of the grade of US findings, CRP level, fever duration, sex, and age as variables and calculated the probability of positivity for VUR. The sensitivity, specificity, positive predictive value, and negative predictive value of \( y \geq 0.5 \) as an indicator of VUR positivity (\( \log_e (y/1 - y) = 1.068 \times [US \text{ grade}] + 0.0875 \times [CRP] + 0.2138 \times [\text{Fever duration}] + 0.9553 \times [\text{Sex}] - 0.0092 \times [\text{Age}] - 5.9493 \)) were 77.6\%, 87.0\%, 75.4\%, and 88.4\%, respectively. Grade IV US findings and a blood CRP level of 80 mg/L produced a \( y \) value of \( \geq 0.5 \).

Grade of US findings, blood CRP level, fever duration, and sex were identified as significant predictive risk factors of VUR, with the grade of US findings being the most significant factor. In previous retrospective reports, abnormal US findings such as dilation of the ureter and pyelectasis were considered useful for predicting VUR \(^{10-12}\). On the contrary, other retrospective \(^{13}\) and prospective reports \(^{14-16}\) indicated that US findings are of little benefit for diagnosing VUR. Although the effectiveness of US findings in predicting VUR is controversial, in our study, US findings effectively predicted VUR. All of these reports validated the high specificity of US for predicting high-grade VUR. As the subjects with grade III US findings included many non-VUR patients and the use of grade V US findings as a diagnostic criterion was likely to exclude many VUR patients, we determined that grade IV US findings (ureteral dilation, pyelectasis, and abnormal movement of the ureter resembling urine reflux) could enhance the predictive value of US for diagnosing VUR. Although non-VUR patients were included in all grades of US findings, the number of VUR patients increased as the grade of US findings increased (Figure 1 in Kido et al\(^{[8]}\)).

Thirty percent (86/286) of our original study population were excluded because they did not undergo VCG (65 patients with normal US findings [grade I or II] and 12 patients with transient abnormal US findings [grade III or IV]). Some of the 86 patients may have developed VUR, and bias concerning whether the patients should undergo VCG is likely present. This study included only 11 low-grade VUR patients (grade I or II) but 58 high-grade VUR patients (grade \( \geq III \)). The differences in the distribution of VUR grades between our study and the study by Hoberman et al\(^{[14]}\) and the RIVUR trial\(^{[17]}\) reflects a bias. Because this study was a retrospective study, lack of diagnostic accuracy was a limitation. Moreover, retrospective or prospective studies of VUR children \(^{10-17}\) all differ in terms of the demographic characteristics of the population studied. These studies used different study designs, with differences in inclusion and exclusion criteria, as well as in the number of patients, patient age, health-care delivery systems, race and ethnic variables, and social and cultural characteristics that can influence the obtained results. These limit the feasibility of generalizing the findings to all populations. These venue and demographic differences may explain the disparate outcomes across the studies.

We could predict the presence or absence of VUR at a high specificity by classifying patients according to grade of US findings and CRP level. In fact, for grade \( \geq IV \) US findings and CRP levels \( \geq 80 \text{ mg/L} \), the specificity was 87.8\%. Even in the MLRA of the grades of US findings and CRP levels, not only the specificity but also the sensitivity were high. Therefore, using these 2 factors in combination may prove useful. Considering that 84\% (58/69) of the VUR patients in our study had high-grade VUR (grade \( \geq III \)), patients presenting with their first UTI may have high-grade VUR when they have both grade \( \geq IV \) US findings and CRP level \( \geq 80 \text{ mg/L} \). Therefore, we recommend performing VCG in patients presenting with their first UTI with grade \( \geq IV \) US findings and CRP levels \( \geq 80 \text{ mg/L} \). However, VCG may not be needed in patients presenting with their first UTI with grade \( \leq III \) US findings and CRP levels < 80 mg/L.

In conclusion, the grade of US findings, blood CRP levels, fever duration and sex were useful predictors of VUR according to our MLRA. Among these variables, the grade of US findings was the most significant predictive factor of VUR. We should perform abdominal US for all patients presenting with their first episode of UTI and carefully examine grade IV US findings.

VCG should be performed in pediatric patients with grade \( \geq IV \) US findings and CRP levels \( \geq 80 \text{ mg/L} \) but not in
patients with grade < III US findings and CRP levels < 80 mg/L. When either the US grade is ≥IV or CRP level is ≥80 mg/L, the formula derived from our MLRA will be informative for predicting VUR.

Among the patients presenting with their first episode of UTI who underwent US, some had transient abnormal US findings. If they had acquired normal US findings during antibiotic therapy, then VCG need not be performed. However, we should practice VCG for all patients with recurrent UTI.

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Conflict of Interest

None.

Abbreviations

AFBN: acute focal bacterial nephritis; CRP: C-reactive protein; MLRA: multivariate logistic regression analyses; US: ultrasonography; UTI: urinary tract infection; VCG: voiding cystography; VUR: vesicoureteral reflux.

Author’s contributions

JK was primarily responsible for protocol development, patient screening, enrollment, outcome assessment, preliminary data analysis, and writing of the manuscript. Y. Ueno participated in the development of the protocol and analytical framework of the study. Y. Ushijima and KS contributed in the same ways as Y. Ueno and were responsible for patient screening. MY supervised the design and execution of the study, performed the final data analyses, and contributed to the writing of the manuscript.

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