

## Vesicoureteral Reflux in Hospitalized Children with Urinary Tract Infection: The Clinical Value of Pelvic Ectasia on Renal Ultrasound, Inflammatory Responses and Demographic Data

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**Background:** The aims of this study were to determine whether renal pelvis dilation on ultrasound was reliable in predicting vesicoureteral reflux (VUR) and to assess the relationship of other clinical information of VUR in children with urinary tract infection (UTI).

**Methods:** We retrospectively reviewed clinical data, renal echo, and voiding cystourethrogram (VCUG) results in hospitalized children with their first episode of UTI, aged from 1 month to 5 years, during a 1-year period.

**Results:** There were 114 children with 228 kidneys eligible for the study. Unilateral pelvis size greater than 8 mm had 2.4 ( $p=0.049$ , 95% CI: 1.0-5.9) and 3.7 ( $p=0.025$ , 95% CI: 1.2-11.3) times greater risk for VUR and severe reflux, respectively. The sensitivity in detecting severe reflux was 27.8%, and the specificity was 90.5%. The positive and negative predictive values in suggesting severe VUR were 20.0% and 93.6%, respectively. The sum of bilateral pelvis sizes greater than 16 mm had higher risk for VUR and severe reflux (4.1 and 4.6 times) and similar specificity and negative predictive value for severe reflux. Age, gender, C-reactive protein, leukocytosis, pyuria and acute pyelonephritis did not show significant relationships to the reflux.

**Conclusions:** Unilateral pelvis size greater than 8 mm or the sum of the bilateral pelvis sizes greater than 16 mm was associated with VUR, especially severe VUR. The possibility of severe reflux was lower than 10% when the reverse criteria were applied. However, the dilation of the renal pelvis did not predict all VUR precisely. We concluded that VCUG should still be performed in hospitalized children with UTI.

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**Key words:** vesicoureteral reflux, renal ultrasound, voiding cystourethrogram.

It has been estimated that 8% of girls and 2% of boys have urinary tract infections (UTI) during childhood.<sup>(1)</sup> Primary vesicoureteral reflux (VUR) is

detected in 18% to 40% of children investigated for their first occurrence of UTI.<sup>(2,3)</sup> VUR is a well-known risk factor for UTI and renal damage.<sup>(4)</sup> The

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current practice guidelines of the American Academy of Pediatrics recommend that ultrasound and either voiding cystourethrogram (VCUG) or radionuclide cystography should be performed after the initial UTI in febrile infants and young children.<sup>(5)</sup> VCUG is also suggested for children younger than 5 years with UTI, school-aged girls who have had two or more occurrences of UTI, and any male with UTI.<sup>(6)</sup>

VCUG is currently the most sensitive and universally accepted modality for the diagnosis of VUR. However, VCUG requires urethral catheterization, exposure to radiation, and exposing risk of contrast medium allergy.<sup>(7)</sup> Therefore, some parents are reluctant to allow a VCUG to be performed on their children after the diagnosis of UTI. On the other hand, renal ultrasound provides a non-invasive and radiation-free method, and has been highly accepted by patients, parents, and physicians.<sup>(8)</sup>

Trials to detect VUR by ultrasonography were undertaken to eliminate the radiation exposure intrinsic in nuclear or fluoroscopic cystography.<sup>(9)</sup> The purpose of this study was to determine whether the degree of renal pelvis dilation on ultrasound was a reliable sign for predicting primary VUR. If this expectation is proven correct, non-invasive renal ultrasound might play an important role in detecting VUR. Furthermore, we also assessed whether age, gender, inflammatory response of UTI, and acute pyelonephritis (APN) based on ultrasound findings were associated with VUR in children with UTI.

## METHODS

We retrospectively collected and reviewed the demographic data, laboratory data, ultrasound results and VCUG results of all children, aged 1 month to 5 years old, who were admitted to Chang Gung Children's Hospital with their first episode of urinary tract infection, dated from January 2001 through January 2002. To be included in this study, the children must have fulfilled the following criteria: (1) bacterial colony count of urine culture obtained from a sterile bag greater than or equal to  $10^5$  colony-forming units per milliliter or any number of bacterial growth from sterile suprapubic urine aspiration; and (2) children received both renal ultrasound and VCUG due to the first occurrence of UTI. Children were excluded if they had any one of the following

situations: (a) a previous diagnosis of UTI; (b) previous genitourinary tract surgery; (c) anatomic anomalies such as urogenital and neurological problems, like multicystic kidneys, dysplastic kidneys, obstructive hydronephrosis, and neurogenic bladder; or (d) simultaneous enterocolitis.

VCUG was performed under fluoroscopic guidance with the child awake as described previously.<sup>(10)</sup> VUR at VCUG was graded using the International Reflux Study Committee System.<sup>(11)</sup> A grade of 4 or 5 VUR was considered as severe reflux.

The interpersonal differences of renal ultrasound findings in our study were minimized as much as possible. All renal ultrasonography was performed and interpreted by only two experienced, well-trained physicians. According to the report by Tsai et al, the size of the renal pelvis was not significantly different in children aged from 1 day to 15 years in healthy Taiwanese children.<sup>(12)</sup> Therefore, it is reasonable that measurements of the baseline and dilated renal pelvises are comparable in our study age groups. Patients were examined in the supine, prone, and lateral decubitus positions. The maximal AP diameter of the renal pelvis at renal ultrasound was measured. After multiple trials of statistical groupings to judge the cut-off point in each group, and after reviewing reports in the literature, the maximal AP diameters of the renal pelvis sizes on ultrasound were classified into five groups. These included the following groups: group 1, 0-2 mm; group 2, 2.1- 5 mm; group 3, 5.1-8 mm; group 4, 8.1-13 mm; and group 5, >13 mm. We used the Fisher's exact test and logistic regression model to evaluate the correlation between the renal pelvis dilation with VUR or severe VUR in the corresponding kidneys. We also assessed the association of VUR or severe VUR with the following clinical information: age, gender, blood and urine leukocyte counts, C-reactive protein (CRP) and APN diagnosed by renal ultrasound by Fisher's exact test or Chi-square test.

## RESULTS

There were 114 children (79 male and 35 female) with 228 kidneys eligible for examination in this study. The median age of the children was 6 months with a range from 1 to 60 months. VUR occurred in 28.9% (33/114) of the patients in 20.6% (47/228) of the kidneys. Severe VUR was observed

in 12.3% (14/114) of the patients in 7.9% (18/228) of the kidneys.

Table 1 shows the distribution of VUR grading according to the five groups of renal pelvis sizes on ultrasonography in the corresponding kidneys. The percentage of VUR was higher in groups 4 and 5. Group 1 was higher than groups 2 and 3.

Table 2 shows the relationship of unilateral pelvis size and the sum of bilateral renal pelvis size on ultrasonography to VUR in the corresponding kidneys. Compared with children with unilateral renal pelvis sizes less than 8 mm (groups 1, 2 and 3), children with pelvis sizes more than 8 mm (groups 4 and 5) had a greater prevalence for VUR (36% to 18.7%,  $p=0.063$ ) and severe VUR (20% to 6.4%,  $p=0.033$ ). Using a logistic regression model, unilateral pelvis sizes more than 8 mm were significantly

associated with VUR as well as severe VUR. The odds ratio for VUR and severe VUR was 2.4 ( $p=0.049$ , 95% CI: 1.0-5.9) and 3.7 ( $p=0.025$ , 95% CI: 1.2-11.3), respectively. The specificities of pelvis size greater than 8 mm in suggesting VUR and severe VUR were also found to be greater than 90% (91.2% and 90.5%, respectively). However, the sensitivity was only 19.1% and 27.8% for VUR and severe VUR, respectively. The positive predictive value of pelvis size greater than 8 mm in suggesting severe VUR was 20.0%, and the negative predictive value was 93.6%.

Using the sum of bilateral pelvis sizes greater than 16 mm as an index, a stronger association with VUR (58.3% to 25.5%,  $p=0.037$ ) and severe VUR (33.3% to 9.8%,  $p=0.040$ ) was shown than when using an index of unilateral size greater than 8 mm. The index also revealed the risk in having VUR (OR: 4.1,  $p=0.025$ , 95% CI: 1.2-14) and severe VUR (OR: 4.6,  $p=0.029$ , 95% CI: 1.2-18). The sensitivity and specificity were similar to those predicted by unilateral pelvis sizes greater than 8 mm. The positive predictive value of the sum of bilateral pelvis sizes greater than 16 mm in suggesting severe VUR was 33.3%, and the negative predictive value was 90.2%.

The influence of age and gender on VUR was analyzed. A higher incidence for VUR (32%) and severe VUR (15%) was found in male patients than in female patients (23% in VUR and 6% in severe

**Table 1.** The Distribution of VUR Grading According to the Five Groups of Renal Pelvis Sizes on Ultrasonography in Corresponding Kidneys.

Renal pelvis size by ultrasound	VUR					Reflux/total (%)		
	I	II	III	IV	V			
Group 1 (0-2.0mm)	0	1	2	4	0	7/	25	( 28.0)
Group 2 (2.1-5.0mm)	2	2	7	4	0	15/	90	( 16.7)
Group 3 (5.1-8.0mm)	3	6	2	4	1	16/	88	( 18.2)
Group 4 (8.1-13mm)	1	0	3	3	1	8/	24	( 33.3)
Group 5 (>13mm)	0	0	0	1	0	1/	1	(100.0)
Total	6	9	14	16	2	47/	228	( 20.6)

**Table 2.** The Relationship of Unilateral and the Sum of Bilateral Renal Pelvis Sizes on Ultrasonography to VUR and Severe VUR in Corresponding Kidneys.

Size of echo pelvis	VUR				Severe VUR			
	Percentage (reflux/total)	OR (95% CI)	Sensitivity/ Specificity	PPV/ NPV	Percentage (reflux/total)	OR (95% CI)	Sensitivity/ Specificity	PPV/ NPV
Unilateral								
≤8mm	18.7% (38/203)	1			6.4% (13/203)	1		
>8mm	36.0% (9/25)*	2.4* (1.0-5.9)	19.1% 91.2%	36.0% 81.3%	20.0% (5/25)†	3.7** (1.2-11.3)	27.8% 90.5%	20.0% 93.6%
Sum of Bilateral								
≤16mm	25.5% (26/102)	1			9.8% (10/102)	1		
>16mm	58.3% (7/12)‡	4.1 †† (1.2-14)	21.2% 93.8%	58.3% 74.5%	33.3% (4/12) <sup>§</sup>	4.6 <sup>^</sup> (1.2-18)	28.6% 92.0%	33.3% 90.2%

**Abbreviations:** OR: odds ratio; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; Fisher's exact test: \* $p=0.063$ ; † $p=0.033$ ; ‡ $p=0.037$ ; § $p=0.040$ ; Logistic regression model: \* $p=0.049$ ; \*\* $p=0.025$ ; †† $p=0.025$ ; ^ $p=0.029$

VUR); however, this difference did not reach statistical significance ( $p=0.38$ ). We classified all children into four age groups (< 3, 3-6, 6-12, >12 months). A lower incidence for VUR and severe VUR were found in children older than 1 year of age than in those younger than 1 year. Again, this difference did not demonstrate a significant association ( $p=0.80$ ).

We also analyzed the association of inflammatory responses of UTI and APN based on the results of ultrasound with VUR and severe VUR. Leukocyte counts per high power field (HPF) in urine were classified into four levels, including < 10, 10-45, 45-75, and > 75. The level of pyuria did not show any significant association with VUR or severe reflux ( $p=0.90$  and  $0.63$ , respectively). Leukocyte counts ( $\times 10^3$ ) in the blood were classified into four levels, including < 10, 10-15, 15-18, and >18. The level of leukocytosis did not reveal any association with reflux or severe reflux ( $p=0.25$  and  $0.67$ , respectively). Different levels of serum CRP (mg/L), including < 15, 15-50, 50-75, 75-130, and > 130, also did not correlate with reflux or severe reflux ( $p=0.61$  and  $0.48$ , respectively). APN, when diagnosed using ultrasound, did not show a significant correlation with reflux or severe VUR.

## DISCUSSION

Our study provides evidence that unilateral pelvis size greater than 8 mm or the sum of bilateral size greater than 16 mm increased the risk for VUR in hospitalized children with UTI, especially in severe VUR. However, due to the low sensitivity and low positive predictive value, the dilation of the pelvis on ultrasound did not precisely predict all grades of VUR. On the other hand, the indexes had high specificity and a negative predictive value. Therefore, in patients with the unilateral pelvis size less than 8 mm or the sum of bilateral size less than 16 mm, the possibility of severe reflux was much lower. In order to reliably predict all grades of VUR and to prevent occult renal damage, we suggest VCUG should be performed in hospitalized children with UTI.

There have been similar studies that investigated the dilation of the collecting system on renal ultrasound in predicting VUR in children with UTI or other urinary tract problems.<sup>(10,13-15)</sup> Most studies have shown that findings from renal ultrasound did not

produce good correlations with VUR. Mahant et al. retrospectively reviewed the renal ultrasound and VCUG results of 162 children under 5 years of age with their first occurrence of UTI. They claimed that the sensitivity and specificity of ultrasound in predicting VUR were only 40% and 76%, respectively.<sup>(10)</sup> In another study, Davey et al. found the frequency of VUR in children with mild renal pelvic distension did not differ significantly from that in children without distension on renal ultrasound (39% vs. 33.3%,  $p=0.365$ ).<sup>(13)</sup> DiPietro et al. also observed that only two of 21 children with VUR aged 5 years or older had abnormal renal ultrasound scans.<sup>(15)</sup>

Previous studies only used simple parameters for renal echo findings, such as "mild", "moderate", or "severe" renal dilatation,<sup>(13)</sup> "dilation of the pelvicalyces" or "dilatation of the collecting system".<sup>(10)</sup> We further classified the range of renal pelvis sizes into groups in order to re-evaluate the correlation between renal pelvis size and VUR in Chinese children. In this study, although unilateral renal pelvis sizes greater than 8 mm or the sum of bilateral sizes greater than 16 mm did not precisely predict VUR in children with UTI, these two indexes were shown to be significant risk factors for VUR, especially for severe reflux.

The sum of bilateral pelvis sizes greater than 16 mm might have combined two measurement parameters in renal ultrasound and predicted VUR more precise than the unilateral size greater than 8 mm. Polito et al. reported that unilateral refluxing kidneys had low prevalence of contra-lateral renal damage in children with UTI and VUR.<sup>(16)</sup> Their study suggested that if VUR caused such changes in the pelvis sizes, the influence was supposed to be independent for each side of the renal pelvis. Therefore, the sum of bilateral pelvis sizes greater than 16 mm indicated a higher risk for VUR than unilateral sizes greater than 8 mm in children with UTI.

The explanation why renal ultrasound findings are not sensitive to detect VUR in children with their first episode of UTI remains unclear. In this study, although dilatation of renal pelvis showed low sensitivity in detecting VUR, both high specificity and a significant odds ratio of indexes for severe reflux indicated that VUR had still contributed to the dilatation of the pelvis to some degree. Some reports claimed that VUR was a dynamic and intermittent process, leading to the insensitivity of routine renal

ultrasound in the detection of reflux.<sup>(14,17)</sup> Ultrasound investigations might also have missed low grade VUR in some children.<sup>(18)</sup> The real mechanism should be studied in the future.

Urinary tract infection is often an ascending process caused by virulent bacteria. VUR, especially severe reflux, predisposes patients to parenchymal and pelvis infection of the kidneys by facilitating the transport of bacteria from the bladder to the upper urinary tract.<sup>(6)</sup> Therefore, a high grade of VUR is a risk factor for APN.<sup>(19)</sup> Our data revealed that there was no significant relationship between APN and VUR. Previously, researchers reported that renal ultrasound only diagnosed 30% of patients with APN, and suggested pyelonephritis was best diagnosed using DMSA renal scans.<sup>(6)</sup> Ultrasonography did not seem to identify all cases of APN and did not provide sufficient information to evaluate the relationship with reflux.

Bacteria cause most urinary tract infections in children, and elevated CRP levels or leukocytosis is a useful predictor of serious bacterial infection in febrile children.<sup>(20)</sup> We assumed that VUR or severe reflux might enhance the inflammatory responses to UTI. Our results revealed that the inflammatory responses, including urine and blood leukocyte counts and serum CRP levels, were not significantly related to VUR or severe reflux. Therefore, the inflammatory reaction of UTI might also be influenced by multiple factors such as the virulence of the bacteria, the immunity of the host, and the stage of the disease, not only VUR.

In summary, a pelvis greater than 8 mm and the sum of bilateral pelvis sizes greater than 16 mm significantly increased risk for VUR, especially severe reflux. The possibility of severe reflux was lower than 10% if the reverse criteria were applied. However, these indexes did not precisely predict all grades of VUR. We concluded that VCUG is still strongly recommended in hospitalized children with their first episode of UTI.

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# 對泌尿道感染的住院孩童以腎臟超音波之腎盂擴張及其他臨床指標預測膀胱輸尿管逆流

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**背景：**本研究之目的在於評估因泌尿道感染而住院之病童，探討其腎臟超音波是否能有效地預測膀胱輸尿管逆流，並探討相關性的臨床指標，和膀胱輸尿管逆流之間的關係。

**方法：**本研究以回溯性的方法收集在一年期間，年齡在1個月至5歲之間，因第一次泌尿道感染而住院之病童，探討其臨床相關資料、腎臟超音波下腎盂的大小，和膀胱輸尿管逆流之間的關係。

**結果：**總共114個病人，228個腎臟符合研究條件。腎臟超音波下腎盂的大小大於8毫米者，分別有2.4倍 ( $p=0.049$ , 95% CI: 1.0-5.9) 和3.7倍 ( $p=0.025$ , 95% CI: 1.2-11.3) 的危險性會有膀胱輸尿管逆流和嚴重性膀胱輸尿管逆流的發生，其中針對嚴重性膀胱輸尿管逆流的敏感度為27.8%，特異性為90.5%，陽性預測值為20.0%，陰性預測值為93.6%。兩側腎盂大小相加的和於16毫米者，同樣有較高的危險性會有膀胱輸尿管逆流和嚴重性膀胱輸尿管逆流的發生。年齡、性別、急性腎盂腎炎、臨床檢驗值中的發炎指數、尿液及血液中白血球的數目，和膀胱輸尿管逆流的發生率並無明確的相關性。

**結論：**在腎臟超音波檢查顯示腎盂大於8毫米或兩側腎盂大小相加的和於16毫米者，其發生膀胱輸尿管逆流的危險性較大，尤其是嚴重性膀胱輸尿管逆流。相反如果腎盂小於8毫米或兩側腎盂相加的和於16毫米者，其發生嚴重性膀胱輸尿管逆流的可能性則低於百分之十。然而，腎臟超音波仍無法精確地診斷所有程度的膀胱輸尿管逆流。因此針對泌尿道感染而住院之病童，仍需接受排尿膀胱尿道攝影來早期診斷膀胱輸尿管逆流。

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**關鍵字：**膀胱輸尿管逆流、腎臟超音波、排尿膀胱尿道攝影。

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