

## Prediction of Vesicoureteral Reflux in Children with First Urinary Tract Infection by Dimercaptosuccinic Acid and Ultrasonography

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### Abstract

**Objective:** Urinary tract infection (UTI) is one of the most common causes of febrile pediatric diseases. Also, vesicoureteral reflux (VUR) is a significant risk factor for UTI. Voiding cystourethrography (VCUG) is the method of choice for evaluation of VUR. This study was done to predict VUR by DMSA scan (technetium 99 m-labeled dimercaptosuccinic acid) and ultrasonography (US).

**Methods:** In a prospective study, all children with first time acute pyelonephritis were selected and evaluated by DMSA scan and US. Then VCUG was done with negative urine culture. All children with final diagnosis of obstructive congenital anomaly were excluded. The sensitivity, specificity, positive predictive values, negative predictive values, Confidence Interval of DMSA scan and US were calculated for prediction or exclusion of VUR.

**Findings:** Among 100 children with UTI diagnosis, VUR was detected in 39 children and 63 (31.5%) kidneys. DMSA scan was abnormal in 103 (51.5%) units, 45 units had VUR (PPV=44%), 79 units with normal DMSA scan had no VUR (NPV=81%). Of kidney units that were abnormal by DMSA or US, 51 units had VUR. PPV and NPV were 44% and 56%, respectively.

**Conclusion:** DMSA scan alone or with US cannot predict VUR (especially low grade VUR). But according to NPV, it seems that absence of VUR can be predicted. So, more studies are needed to determine the usefulness of DMSA scan and US instead of VCUG for detection of VUR.

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**Key Words:** Children; Urinary Tract Infections; DMSA Scan; Ultrasonography; Vesicoureteral Reflux

### Introduction

Urinary tract infection (UTI) is one of the most common causes of febrile infectious disease in children [1,2]. It is a risk factor for progressive

renal damage, hypertension and end stage renal failure [3-6].

Vesicoureteral reflux (VUR) is the most common predisposing factor for UTI and 25-40% of children with UTI have VUR [7-8]. Voiding cysto-

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urethrography (VCUG) is the method of choice for detection of VUR in children with UTI [9]. But this is an invasive procedure, the risk of irradiation is high and patients and their parents show poor compliance for medical care of the disease [10-12].

For detection of VUR, it is very important to choose procedures that are safe, noninvasive and accepted by the patients and their parents [13-14]. To evaluate urinary tract system, Ultrasonography (US) and technetium 99 m-labeled dimercapto-succinic acid scan (DMSA) are used for detection of urological abnormalities and renal parenchymal damage. Also there are some studies for prediction of VUR by these methods [10,15-17]. Although significant or high grade VUR were predicted by DMSA in some studies [15,18-19], it is ruled out by others [16,20].

According to these disagreements, this study was done to evaluate the prediction of VUR by DMSA scan and ultrasonography.

## Subjects and Methods

This prospective study was done during 2008-2010. All children who were referred to our center (Amirkola Children Hospital, Babol, Iran) with first time acute pyelonephritis were enrolled. Ultrasonography, DMSA renal scan and then VCUG were done in all patients.

Acute pyelonephritis was diagnosed in children with fever (higher than 38.5°C), having more than 5 white blood cells in urinalysis and more than 10<sup>5</sup> colony count of one micro organism in urine culture. Ultrasonography, DMSA renal scan and VCUG were done during 2-5 days after diagnosis when urine cultures were negative.

Children with congenital abnormality, ureteropelvic junction obstruction, ureterovesical junction obstruction and posterior urethral valve in final diagnosis were excluded.

Abnormal ultrasonography finding was defined if the patient had hydronephrosis, dilatation of ureter, increase of cortical echogenicity, decreased cortical thickness and increased kidney size. Also decrease of radioisotope uptake in DMSA renal scan was defined abnormal [21-22].

According to the Classification of International Reflux Study Committee, VUR was graded to I-V[23].

The positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, confidence interval (CI) and likelihood ratio of ultrasonography and DMSA for prediction of VUR were assessed.

The local ethics committee approved the study and informed consent was obtained from all patients or their parents.

The data were analyzed by SPSS and Fisher Exact test and  $P < 0.05$  was considered significant.

## Findings

Among 100 children with diagnosis of UTI, 88 (88%) patients were girls and others were boys. Mean age was 38 ( $\pm 37$ ) months (range 1-147 months). VUR was detected in 39 (39%) patients and was bilateral in 22 (22%) cases of these children. Sixty three (31.5 %) kidney unites (34 right and 29 left side) had VUR. Among 200 kidney units that were evaluated by VCUG, 137(68.8%) units had no VUR and 3 (1.5%), 29 (14.5%), 29 (14.5%) and 2 (1%) had VUR grade I-IV, respectively.

DMSA scan was abnormal in 86 (86%) patients and 17 (17%) children had bilateral involvement. Thirty (30%) patients had abnormal ultrasonography and bilateral involvement was detected in 11%. One hundred three (51.5%) units were abnormal in DMSA scan of which 45 (44%) units had VUR. Also, 79 (81%) units with normal DMSA renal scan had no VUR (Table 1).

One hundred fifty nine kidney units were normal in ultrasonography of which 44 (28%) units had VUR but in 41 units with abnormal ultrasonography, 19 (46 %) units had VUR (Table 1).

All children were divided into three age groups of less than 2 years, 2-5 years and more than 5 years old. In the first group, among 56 abnormal units in DMSA or ultrasonography, 23 (41%) units had VUR. In 48 normal units in both studies, VCUG was normal in 40 (83.3%) units. In 2-5 year-olds 27 units were abnormal in DMSA or ultrasonography, 59.3% of units had VUR and in

**Table 1:** Sensitivity, specificity, Positive Predictive Value, Negative Predictive Value, positive likelihood ratio and negative likelihood ratio values for prediction of VUR by DMSA scan and US in children with urinary tract infection

Parameters	DMSA (95%CI)	US (95%CI)	DMSA or US (95%CI)
Sensitivity (%)	71 (60-83)	30 (19-41)	81 (71-91)
Specificity (%)	58 (49-66)	84 (74-90)	53 (44-61)
PPV (%)	44 (34-53)	46 (31-62)	44 (35-53)
Negative Predictive Value (%)	81 (74-89)	72 (65-79)	86 (78-93)
Likelihood ratio (positive)	1.69 (1.31-2.17)	1.88 (1.1-1.3)	1.71(1.38-2.11)
Likelihood ratio (negative)	0.50 (0.33-0.75)	0.83 (0.7-0.99)	0.36(0.21-0.62)

DMSA: Dimercaptosuccinic acid; US: Ultrasonography; VUR: Vesicoureteral Reflux; CI: Confidence Interval

11 normal units, 81.1% of units had no VUR. In children more than 5 years old, 63.6% of units with abnormal DMSA scan or ultrasonography had VUR whereas 92% had no VUR when DMSA scan or ultrasonography was normal ( $P<0.05$ ).

Of 116 kidney units that were abnormal in ultrasonography or DMSA scan, 51 (44%) units had VUR (Table 1), whereas 72 (86%) units with normal ultrasonography or DMSA had no VUR. Twenty eight units were abnormal in both ultrasonography and DMSA scan of which 13 units had VUR (PPV= 46.7%).

To predict high grade VUR (i.e. grade III and higher) by DMSA scan, PPV and NPV were 84% and 94% respectively compared to units without VUR. These values were 29% and 54% for ultrasonography (Table 2).

DMSA scan was abnormal in 55% of units with grade II VUR; 72.5% of units in this group had abnormal ultrasonography or DMSA scan (Table 3). In grade III VUR, 83% of units had abnormal DMSA scan and 86.2% of units were abnormal in ultrasonography or DMSA scan (Table 3).

## Discussion

In the study, sensitivity, specificity, PPV and NPV of DMSA scan for prediction of VUR were 71%, 58%, 44% and 81%, respectively. Thirty nine percent of children with pyelonephritis had VUR and 51.5% of all renal units were abnormal in DMSA renal scan.

VCUG is the golden standard for detection of VUR. But this procedure is invasive and causes anxiety in the patients and their parents. So, recommendation of any procedure instead of VCUG is desirable for the patients and their parents. In Tseng study, sensitivity, specificity, PPV and NPV for prediction of VUR by DMSA were 71%, 58%, 44% and 88%, respectively [16]. Camacho reported 48% and 88% of PPV and NPV for prediction of VUR by DMSA scan [24].

It seems that abnormal DMSA instead of VCUG cannot be used for prediction of VUR because it is expected that about 40% of UTI children have VUR and the PPV of DMSA scan is not as high as this value (44%). But with normal DMSA, we can

**Table 2:** Prediction of high grade VUR by DMSA scan and ultrasonography (without low grade VUR) in children with urinary tract infection

Evaluation	DMSA		Ultrasonography	
	Normal	Abnormal	Normal	Abnormal
Abnormal VCUG (%)	26 (31%)	5 (6%)	9 (29%)	22 (16%)
Normal VCUG (%)	58 (69%)	79 (94%)	22 (71%)	9 (29%)
Total	84	84	31	137
Sensitivity (95%CI)	84% (71-97%)		29% (13-45%),	
Specificity (95%CI)	58% (49-66%)		84% (78-90%)	
Positive Predictive Value	31% (21-41%)		29% (13-45%)	
Negative Predictive Value	94% (89-99%),		84% (78-90%)	
Likelihood ratio (positive)	1.98 (1.54-2.54)		1.81 (0.92-3.53),	
Likelihood ratio (negative)	0.28 (0.12-0.63)		0.85 (0.67-1.07)	

DMSA: Dimercaptosuccinic acid;; VUR: Vesicoureteral Reflux; VCUG: Voiding cystourethrography

**Table 3:** Prediction of vesicoureteral reflux (VUR) by Dimercaptosuccinic acid (DMSA) scan and ultrasonography (US) in children with urinary tract infection according to grading of VUR

Grade VUR	US		DMSA		US or DMSA		DMSA + US		Total
	+	-	+	-	+	-	+	-	
No VUR	22	115	58	79	65	72	15	122	137
I	0	3	3	0	3	0	0	3	3
II	10	19	16	13	21	18	5	24	29
III	9	20	24	5	25	4	8	21	29
IV	0	2	2	0	2	0	0	2	2

$P > 0.05$

except that the probability of VUR is low (NPV=88%).

In this study, 19 (PPV=46%) units with abnormal ultrasonography had VUR and 15 (NPV=72.3%) units with normal ultrasonography had no VUR. Sensitivity, specificity, PPV and NPV of ultrasonography for prediction of VUR was 40%, 76%, 32% and 82% respectively in Mahant and Alshamsa studies [25,26].

So, using ultrasonography for prediction of VUR is not recommended and for detection of VUR, VCUG is preferred to ultrasonography.

Among 115 units with abnormal ultrasonography or DMSA scan, 51 units had VUR (PPV=44%) and NPV was 86%. Kass reported 77% NPV for prediction of VUR by abnormal ultrasonography or DMSA scan and does not recommend the ability of them for prediction of VUR [27]. Although according to our study, the probability of VUR is low, when both DMSA and ultrasonography are normal.

The sensitivity of ultrasonography and DMSA alone and ultrasonography plus DMSA for prediction of VUR were 67.2%, 65.5% and 83.3%, respectively in another study, although the VURs were of grade III and higher in this study [28]. In our study, sensitivity and specificity of ultrasonography for prediction of grade III and more of VUR were 29% and 84%. These values were 84% and 58% for DMSA scan. The sensitivity of DMSA for prediction of grade III-IV VUR was 60%, 79% and 95% respectively in Ajdinović's study [29]. NPV for ultrasonography and DMSA for prediction of absent high grade VUR in our study was 84% and 94% respectively.

Also NPV for high grade VUR by ultrasonography plus DMSA is reliable for prediction of absent VUR, PPV was not of high value for predicting the existence of VUR.

Urinary tract infection is more important in children less than 2 years old, therefore detection of VUR and prevention of UTI is of great importance. In our study PPV and NPV for prediction of VUR by DMSA scan in children less than 2 years old were 41.2 and 81.8%, respectively. These values were 37% and 88% in Tseny's study. Also, in other study of this age group, Lin reported 32.7% and 94.35% PPV and NPV of DMSA scan for prediction of VUR [17,30]. Also, in study by Lee et al, the prediction of VUR by ultrasonography were 41.7% and 86% in low and high grade VUR by ultrasonography, respectively, and 62.5% and 95% by DMSA. They assume ultrasonography and DMSA scan have limited diagnostic value in low grade VUR [31]. Also Preda et al reported 96% of infants less than 1 year old with dilatation of pelvicalyceal system (by ultrasonography) and VUR had abnormal DMSA scan. Also 72% of children with low grade VUR had abnormal DMSA scan [32].

In our study, there were no significant differences between PPV and NPV in this age group and older children, although, the NPV is more reliable for ruling out the VUR.

## Conclusion

Ultrasonography, DMSA scan and ultrasonography plus DMSA scan cannot predict the low grade VUR, whereas VCUG is more reliable and the standard method for detection of VUR. Although according to NPV, with DMSA scan plus ultrasonography, the absence of VUR can be predicted especially in high grade VUR.

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**Conflict of Interest:** None

## References

- Smellie JM, Hodson, CJ, Edwards D, et al. Clinical and radiological features of urinary infection in childhood. *Br Med J* 1964;2(5419): 1222-6.
- Rushton HG. Urinary tract infections in children. Epidemiology, evaluation, and management. *Pediatr Clin North Am.* 1997;44(5):1133-69.
- Jacobson SH, Eklöf O, Eriksson CG et al. Development of hypertension and uraemia after pyelonephritis in childhood: 27 year follow up. *Br Med J* 1989;299(6701):703-6.
- Smellie JM, Barratt TM, Chantler C, et al. Medical versus surgical treatment in children with severe bilateral vesicoureteric reflux and bilateral nephropathy: a randomised trial. *Lancet* 2001; 357(9265):1329-33.
- Merrick MV, Notghi A, Chalmers N, et al. Long-term follow up to determine the prognostic value of imaging after urinary tract infections. Part 1: Reflux. *Arch Dis Child* 1995;72(5):388-92.
- Downs SM. Technical report: urinary tract infections in febrile infants and young children. The Urinary Tract Subcommittee of the American Academy of Pediatrics Committee on Quality Improvement. *Pediatrics* 1999; 103(4):e54.
- Hansson S, Bollgren I, Esbjörner E, et al. Urinary tract infections in children below two years of age: a quality assurance project in Sweden. The Swedish Pediatric Nephrology Association. *Acta Paediatr* 1999;88(3):270-4.
- Stokland E, Hellström M, Jacobsson B, et al. Evaluation of DMSA scintigraphy and urography in assessing both acute and permanent renal damage in children. *Acta Radiol* 1998;39(4):447-52.
- Piepsz A, Ham HR. Pediatric applications of renal nuclear medicine. *Semin Nucl Med* 2006; 36(1):16-35.
- Hoberman A, Charron M, Hickey RW et al. Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med* 2003; 348(3):195-202.
- Cohen AL, Rivara FP, Davis R, et al. Compliance with guidelines for the medical care of first urinary tract infections in infants: a population-based study. *Pediatrics* 2005;115(6):1474-8.
- Otukesh H, Farjad R, Hoseini R, et al. The Evaluation of Cystosonography accuracy in diagnosis of Vesicoureteral Reflux in children. *Iran J Pediatr* 2006;16(1):7-12.
- Sorkhi H, Bakhshandeh Bali MK, Nooreddini HG. Randomized clinical trial of sedation with oral midazolam for voiding cystourethrography in Children. *MJIRI* 2010;24(2):67-71.
- Sorkhi H, Navaeifar MR, Nooreddini HG et al. Sonographic measurement of bladder wall thickness in healthy children. *Iran J Pediatr* 2009;19(4):341-6.
- Hansson S, Dhamey M, Sigström O, et al. Dimercapto-succinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. *J Urol* 2004; 172(3):1071-3.
- Moorthy I, Easty M, McHugh K, et al. The presence of vesicoureteric reflux does not identify a population at risk for renal scarring following a first urinary tract infection. *Arch Dis Child* 2005;90(7):733-6.
- Tseng MH, Lin WJ, Lo WT, et al. Does a normal DMSA obviate the performance of voiding cystourethrography in evaluation of young children after their first urinary tract infection? *J Pediatr* 2007;150(1):96-9.
- Polito C, Rambaldi PF, Signoriello G, et al. Permanent renal parenchymal defects after febrile UTI are closely associated with vesicoureteric reflux. *Pediatr Nephrol* 2006; 21(4):521-6.
- Rosenberg AR, Rossleigh MA, Brydon MP, et al. Evaluation of acute urinary tract infection in children by dimercaptosuccinic acid scintigraphy: a prospective study. *J Urol* 1992;148(5 Pt 2): 1746-9.
- Gordon I, Barkovics M, Pindoria S, et al. Primary vesicoureteric reflux as a predictor of renal damage in children hospitalized with urinary tract infection: a systematic review and meta-analysis. *J Am Soc Nephrol* 2003;14(3):739-44.
- Jakobsson B, Berg U, Svensson L. Renal scarring after acute pyelonephritis. *Arch Dis Child* 1994; 70(2):111-5.
- Rushton HG. The evaluation of acute pyelonephritis and renal scarring with technetium 99 m-dimercaptosuccinic acid renal scintigraphy: evolving concepts and future directions. *Pediatr Nephrol* 1997;11(1):108-20.
- Intrnational Reflux Study Committee. Medical vesus surgical treatment of primary vesicoureteral reflux: a prospective international

- reflex study in children. *J Urol* 1981;125(3):277-83.
24. Camacho V, Estorch M, Fraga G, et al. DMSA study performed during febrile urinary tract infection: a predictor of patient outcome? *Eur J Nucl Mol Imaging* 2004;31(6):862-6.
25. Alshamsam L, Al-Harbi A, Fakeeh K, et al. The value of renal ultrasound in children with a first episode of urinary tract infection. *Ann Saudi Med* 2009;29(1):46-9.
26. Mahant S, Friedman J, Mac Arthur C. Renal ultrasound findings and vesicoureteral reflux in children hospitalized with urinary tract infection *Arch Dis Child* 2002;86(6):419-20.
27. Kass Ej, Kernan KM, Carey JM. Pediatric urinary tract infection and the necessity of complete urological imaging. *BJU Int* 2000;86(1):94-6.
28. Lee MD, Lin CC, Huang FY, et al. Screening young children with a first febrile urinary tract infection for high-grade vesicoureteral reflux with renal ultrasound scanning and technetium-99m-labeled dimercapto succinic acid scanning. *J Pediatr* 2009;154(6):797-802.
29. Ajdinović B, Jauković L, Krstić Z, et al. Technetium-99m-dimercaptosuccinic acid renal scintigraphy in children with urinary tract infection. *Hell J Nucl Med*.2009;9(1):27-30
30. Lin CH, Yang LY, Wang HH, et al. Evaluation of imaging studies for vesicoureteral reflux in infants with first urinary tract infection. *Acta Paediatr Taiwan* 2007;48(2):68-72.
31. Lee HY, Soh BH, Hong CH, et al. The efficacy of ultrasound and dimercaptosuccinic acid scan in predicting vesicoureteral reflux in children below the age of 2 years with their first febrile urinary tract infection *Pediatr Nephrol* 2009; 24(10):2009-13.
32. Preda I, Jodal U, Sixt R, et al. Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection. *J Pediatr* 2007;151(6): 581-4.