

Tchnetium Tc 99m Dimercaptosuccinic Acid Renal Scintigraphy in Children With Acute Pyelonephritis

Correlation With Other Imaging Tests

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Introduction. Urinary tract infection is the most common serious bacterial infection in children. The aim of this study was to compare the value of different laboratory and imaging techniques in detecting renal involvement in acute pyelonephritis.

Materials and Methods. In a cross-sectional study of patients 1 month to 14 years of age diagnosed with urinary tract infection were examined with systemic inflammatory markers, renal ultrasonography, voiding cystourethrography (VCUG), and technetium Tc 99m dimercaptosuccinic acid (^{99m}Tc-DMSA) renal scintigraphy. A total of 1467 pediatric patients were eligible for treatment of pyelonephritis. Evaluations included a complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), urinalysis, urine culture, and measurement of serum blood urea nitrogen and creatinine levels.

Results. The results of ^{99m}Tc-DMSA scans were normal in 20.2%, mild decreased cortical uptake in 45.0%, moderate decreased cortical uptake in 12.3%, severe decreased cortical uptake in 12.0%, and decreased cortical function plus irregularity or scar formation in 10.5%. Voiding cystourethrography showed vesicoureteral reflux in 25.9%. The sensitivity of ^{99m}Tc-DMSA for prediction of vesicoureteral reflux was 84.1% with a negative predictive value of 80.6%. Significant differences were found in the level of blood leukocyte count ($P = .03$), urine leukocyte count ($P = .003$), ESR ($P = .008$), and age ($P = .04$) between patients with normal and abnormal ^{99m}Tc-DMSA scan results.

Conclusions. We found that in patient with clinical signs of pyelonephritis, ^{99m}Tc-DMSA renal scintigraphy can detect pyelonephritis more accurately than the other inflammatory and imaging tests.

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INTRODUCTION

Urinary tract infection (UTI) is by far the most common serious bacterial infection in febrile young infants.¹ The incidence of childhood UTI

is unknown. Jakobsson and colleagues found an average incidence of 1% for both sexes.² It is believed that 8% of girls and 2% of boys are estimated to have at least one episode of UTI during childhood.³

Recurrence of UTI after the first infection occurs in 50% of girls in the 1st year of follow-up and in 75% of the cases in a 2-year period.⁴ The presence of renal scarring has been documented in 5% to 15% of the children assessed after the first febrile UTI. According to this fact, special attention has been given to early diagnosis and treatment of acute infectious episodes in children with UTI, in addition to the reduction of chronic kidney damage and its clinical consequences.⁵⁻⁸

The presentation of UTI may be vague with nonspecific symptoms.⁹ Accurate diagnosis of pyelonephritis using clinical and laboratory parameters is often difficult, especially in children. The main aims of this prospective study were to compare the value of different laboratory and imaging techniques including renal ultrasonography, and cortical scintigraphy with technetium Tc 99m dimercaptosuccinic acid (^{99m}Tc-DMSA) in detecting renal involvement in acute pyelonephritis.

MATERIALS AND METHODS

Between June 2003 and February 2009, a cross-sectional study of patients 1 month to 14 years of age was done. The ethics committees of Shahid Beheshti University of Medical Sciences and the Pediatric Infectious Research Center approved this study. Pediatric patients with documented UTI and imaging evidence of upper tract involvement based on ^{99m}Tc-DMSA renal scintigraphy were examined with systemic inflammatory markers, renal ultrasonography, and voiding cystoureterography (VCUG). The excluding criteria were any evidence of renal insufficiency, previous known urological problems or intervention, hypertension, recent history of antibiotic taking, concurrent extrarenal infection.

Empirical treatment was the same in all of the children (intravenous ceftriaxone, 75 mg/kg/d, with or without intravenous amikacin, 15 mg/kg/d). Children were considered febrile if their parents reported fever at home or if they had a body temperature higher than 38.5°C rectally or 38°C orally, at admission. The evaluation to be performed in our department included a complete blood count; C-reactive protein (CRP); erythrocyte sedimentation rate (ESR); measurement of serum blood urea nitrogen, creatinine, and electrolyte levels; urinalysis; and urine culture. Depending

on the child's age, the latter was to be performed through suprapubic aspiration, clean catch bag, or clean voiding.

The diagnosis of UTI was deemed certain in the following instances: any amount of gram-negative bacteria grown in urine cultures obtained through suprapubic aspiration, more than 5×10^4 colonies per milliliter of a single pathogen grown in urine cultures obtained through bladder catheterization (excluding *Lactobacilli*, *Corynebacteria*, and coagulase-negative *Staphylococci*), more than 10^5 colonies per milliliter of a single pathogen in urine cultures obtained through clean voiding or in patients with negative urine cultures, significant leukocyturia in febrile children with clinical signs and symptoms (fever, abdominal pain, anorexia, dysuria, and vomiting) and laboratory results in favor of UTI (leukocyte count, $> 10\,000$ per high-power field; ESR, > 20 mm/h; and CRP, $\geq 1+$). The diagnosis of pyelonephritis was documented by ^{99m}Tc-DMSA scintigraphy (evidence of decreased cortical uptake in each part of the kidneys). Glomerular filtration rate was calculated according to the Schwartz formula, which was in normal range in all of the participants.

Data were expressed as mean \pm standard deviation or frequency (percent), where appropriate. The SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA) was used for statistical analyses. Findings were compared using the Mann-Whitney U test, Fisher exact test, and Pearson chi-square test, and the receiver operative characteristic (ROC) curve was used for analysis of diagnostic test values. Statistic tests were 2-tailed and considered significant when P value was less than .05.

RESULTS

A total of 1467 patients were enrolled in this study. The children's age ranged from 1 to 168 months (mean, 36.2 ± 35.0 months). Of the patients, 1157 (78.9%) were girls and the rest of them were boys. Baseline data of the patients are shown in Table 1. The chief complaints were fever in 57.2%, dysuria in 15.4%, diarrhea in 4.6%, gross hematuria in 5.3%, febrile convulsion in 4.5%, malodor urine in 2.1%, flank pain in 1.3%, and a combination of 2 or 3 symptoms in 9.6%.

A positive CRP (> 20 mg/dL) and an abnormal ESR (> 20 mm/h) were seen in 45.2% and 70.0%,

Table 1. Baseline Data of Children With Pyelonephritis

Parameter	Mean (Min to Max)
Age, mo	36.2 ± 35.0 (1 to 168)
Body weight, kg	12.70 ± 7.80 (1.7 to 59.0)
Systolic blood pressure, mm Hg	97.3 ± 12.3 (70 to 120)
Diastolic blood pressure, mm Hg	60.4 ± 10.0 (40 to 80)
Blood leukocyte count, × 10 ⁹ /L	11.20 ± 4.64 (7.5 to 23.4)
Polymorphonuclear, %	50.9 ± 23.2 (4 to 96)
Hemoglobin, g/dL	10.89 ± 3.70 (7.5 to 12.1)
Erythrocyte sedimentation rate, mm/h	40.2 ± 29.3 (12 to 129)
Blood urea nitrogen, mg/dL	13.0 ± 11.3 (3 to 26)
Serum creatinine, mg/dL	0.65 ± 0.50 (0.2 to 1.0)
Serum sodium, mEq/L	137.0 ± 11.7 (129 to 148)
Serum potassium, mEq/L	4.80 ± 1.20 (3.2 to 6.5)
Urine erythrocyte count, /HPF	5.0 ± 1.0 (0 to 50)
Urine leukocyte count, /HPF	19.0 ± 18.0 (19 to 80)
Urine specific gravity	1029.0 ± 20.0 (1002 to 1038)
Urine pH	5.5 ± 0.7 (5 to 8)

respectively. Leukocyturia was detected in all of the patients, microscopic hematuria in 20.0%, and proteinuria in 23.5%. The results of ^{99m}Tc-DMSA scans were normal in 20.2%, mild decreased cortical uptake in 45.0%, moderate decreased cortical uptake in 12.3%, severe decreased cortical uptake in 12.0%, and decreased cortical function plus irregularity or scar formation in 10.5%. Therefore, 79% of the patient with pyelonephritis had evidence of pyelonephritis on ^{99m}Tc-DMSA renal scintigraphy. The results of renal ultrasonography were abnormal in 31.5% (nephrolithiasis in 3.1%, decreased cortical thickening in 1.5%, and mild to severe hydronephrosis in 26.9%). Voiding cystourethrography showed vesicoureteral reflux in 25.9% (grade 1 in 10.7%, grade 2 in 7.3%, grade 3 in 4.7%, and grade 4 in 3.2%; Table 2). There was no significant correlation between these imaging studies (VCUG and ultrasonography, $r = 0.14$, $P < .001$; and VCUG and ^{99m}Tc-DMSA, $r = 0.07$, $P = .02$; and ultrasonography and ^{99m}Tc-DMSA, $r = 0.07$, $P = .01$). Ultrasonography and VCUG could not be very good predictive tests for ^{99m}Tc-DMSA changes in pyelonephritic patients (actual

Table 2. Results of Technetium Tc 99m Dimercaptosuccinic Acid (^{99m}Tc-DMSA) Scintigraphy, Ultrasonography, and Voiding Cystourethrography (VCUG) in Children With Pyelonephritis

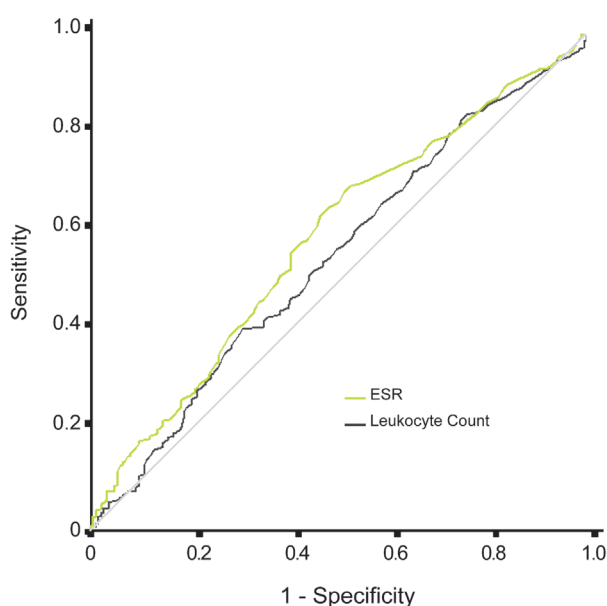
Imaging Results	Percent
^{99m} Tc-DMSA (n = 1184)	
Normal	20.2
Abnormal	79.8
Mild decreased cortical uptake	45.0
Moderate decreased cortical uptake	12.3
Severe decreased cortical uptake	12.0
Irregularity or scar	10.5
Ultrasonography (n = 1402)	
Normal	68.5
Abnormal	31.5
Fullness	9.2
Hydronephrosis	17.7
Stone	3.1
Decreased cortical thickness	1.5
VCUG (n = 1243)	
Normal	74.1
Abnormal	25.9
Vesicoureteral reflux grade 1	10.7
Vesicoureteral reflux grade 2	7.3
Vesicoureteral reflux grade 3	4.7
Vesicoureteral reflux grade 4	3.2

agreement 38.0% and 64.9%, kappa = 0.04 and kappa = 0.14, respectively). On the contrary, the sensitivity of ^{99m}Tc-DMSA for prediction of vesicoureteral reflux was 84.1% with a negative predictive value of 80.6% (likelihood ratio, 0.71; 95% confidence interval, 0.53 to 0.96).

Significant differences were found in the level of blood leukocyte count ($P = .03$), urine leukocyte count ($P = .003$), ESR ($P = .008$), and age ($P = .04$) between patients with normal and abnormal ^{99m}Tc-DMSA scan results. The sensitivity and specificity of other inflammatory markers for prediction of pyelonephritis in our patients, with ^{99m}Tc-DMSA scintigraphy deemed as the golden standard diagnostic method, and are outlined in Table 3. Erythrocyte sedimentation rate has the highest sensitivity and urine erythrocyte count showed the highest specificity for prediction of pyelonephritis (Figure).

Table 3. Sensitivity and Specificity of Inflammatory Markers for Prediction of Pyelonephritis

Marker	Sensitivity (95% CI), %	Specificity (95% CI), %
Erythrocyte count	55.2 (51.9 to 58.4)	51.5 (44.9 to 58.0)
Urine leukocyte count	71.8 (68.7 to 74.8)	40.2 (33.8 to 46.8)
Urine erythrocyte count	21.2 (18.6 to 24.0)	82.8 (77.4 to 87.3)
C-reactive protein	46.4 (42.9 to 49.9)	54.2 (46.8 to 61.4)
Erythrocyte sedimentation rate	89.8 (87.4 to 91.8)	16.0 (11.0 to 22.0)



Receiver operating characteristics curve of blood leukocyte count and erythrocyte sedimentation rate (ESR) for prediction of pyelonephritis (area under the curve, 0.545 and 0.583, respectively).

DISCUSSION

Accurate diagnosis of pyelonephritis in children using clinical and laboratory parameters is often difficult, and location of urinary tract infection has a serious implication in diagnosis, treatment, and prognosis of these patients. The authors evaluated a total of 1467 pyelonephritic children in this query and showed that ^{99m}Tc -DMSA scintigraphy has the highest sensitivity and specificity for detection of pyelonephritis compared to the other imaging and inflammatory studies. However kidney ultrasonography and VCUG are helpful imaging studies in this regard, they are able to predict renal involvement in acute pyelonephritis (actual agreement, 38% and 64.9%; kappa = 0.04 and kappa = 0.14, respectively). According to this study, other inflammatory markers such as blood leukocyte count, urine leukocyte count, and ESR can predict ^{99m}Tc -DMSA changes in pyelonephritis, but their sensitivity and specificity are not very significant (area under the curve in ROC analysis, 0.545 and 0.583, respectively).

Rushton and Majd reported that ^{99m}Tc -DMSA scan has high sensitivity (87%) and specificity (100%) as a diagnostic test for pyelonephritis.¹⁰ In our study, 79% of pyelonephritis patients showed evidence of pyelonephritis on ^{99m}Tc -DMSA renal scan, which is comparable with Tseng and colleagues' study

which showed evidence of pyelonephritis on ^{99m}Tc -DMSA scan in 70% of pediatric patients with pyelonephritis.¹¹ In our study group, about 10% exhibited scar formation or irregularity by ^{99m}Tc -DMSA renal scan. Hoberman and associates reported scar formation in 9.5% of pediatric pyelonephritic patients.¹² However, Tseng and colleagues reported a much lower rate of 1.4% for scar,¹¹ and Lin and colleagues¹³ published their study with a very high rate of scar formation (57%). The reason for different rates of scar formation in these studies might be the difficulty for scar detection in acute phase; ^{99m}Tc -DMSA scintigraphy may overdiagnose or underdiagnose scar formation.^{10,14} In none of these studies a second ^{99m}Tc -DMSA scan was performed to confirm the scar in pyelonephritic patients. Thus, it seems all of these queries were carried out in the same situation, but the rates for scar are distinct. It shows that the rate of scar is related to several predisposing factors which should be taken into account whenever we want to report the prevalence of scar. Therefore, we decided to continue this study to perform a second ^{99m}Tc -DMSA scintigraphy and bring forward our virtual scar rate in the future.

In this study, 25.9% of pyelonephritic patients showed vesicoureteral reflux on VCUG, similar to studies of Hansson and colleagues¹⁴ and Jakobsson and coworkers,¹⁵ which showed vesicoureteral reflux in 25% to 26%, and close to Tseng and colleagues' report of 29.6% vesicoureteral reflux in their patients¹¹ and Lin and colleagues' reported rate of 31% in pediatric pyelonephritic group.¹³ We also found that the sensitivity of ^{99m}Tc -DMSA for prediction of vesicoureteral reflux on VCUG is 84.1% with a negative predictive value of 80.6%, corroborating the previous studies. Tseng and colleagues determined that the sensitivity, specificity, and negative predictive value for abnormalities on ^{99m}Tc -DMSA scans for detecting vesicoureteral reflux on VCUG were 88%, 36%, and 88% respectively.¹¹ This means that a negative ^{99m}Tc -DMSA renal scan result decreases the probability for finding of vesicoureteral reflux, especially high-grade reflux, on VCUG. If we acknowledge missing a small number of low-grade reflux in our pyelonephritic patients, we can decide not to perform VCUG in acute setting of UTI if ^{99m}Tc -DMSA is normal. Through this way, we can reduce VCUG testing by 30%.¹¹

CONCLUSIONS

In each acute UTI episode with clinical signs of pyelonephritis, ^{99m}Tc -DMSA scintigraphy can detect pyelonephritis more than the other inflammatory and imaging tests. We suggest that a negative result on a ^{99m}Tc -DMSA scan can be used to skip VCUG, which is important to decrease this procedure and its complications, including unpleasantness to the child, possible risk of trauma, secondary infection, radiation exposure, and common refusal by parents.

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CONFLICT OF INTEREST

None declared.

REFERENCES

- Bonsu BK, Harper MB. Leukocyte counts in urine reflect the risk of concomitant sepsis in bacteriuric infants: a retrospective cohort study. *BMC Pediatr*. 2007;7:24.
- Jakobsson B, Esbjorner E, Hansson S. Minimum incidence and diagnostic rate of first urinary tract infection. *Pediatrics*. 1999;104:222-6.
- Stark H. Urinary tract infections in girls: the cost-effectiveness of currently recommended investigative routines. *Pediatr Nephrol*. 1997;11:174-7; discussion 80-1.
- Larcombe J. Urinary tract infection in children. *Bmj*. 1999;319:1173-5.
- Rosenberg AR, Rossleigh MA, Brydon MP, Bass SJ, Leighton DM, Farnsworth RH. Evaluation of acute urinary tract infection in children by dimercaptosuccinic acid scintigraphy: a prospective study. *J Urol*. 1992;148:1746-9.
- Tappin DM, Murphy AV, Mocan H, et al. A prospective study of children with first acute symptomatic *E. coli* urinary tract infection. Early ^{99m}Tc dimercaptosuccinic acid scan appearances. *Acta Paediatr Scand*. 1989;78:923-9.
- Pylkkanen J, Viiska J, Koskimies O. The value of level diagnosis of childhood urinary tract infection in predicting renal injury. *Acta Paediatr Scand*. 1981;70:879-83.
- Hellstrom M, Jacobsson B, Marild S, Jodal U. Voiding cystourethrography as a predictor of reflux nephropathy in children with urinary-tract infection. *AJR Am J Roentgenol*. 1989;152:801-4.
- Santen SA, Altieri MF. Pediatric urinary tract infection. *Emerg Med Clin North Am*. 2001;19:675-90.
- Rushton HG, Majd M. Dimercaptosuccinic acid renal scintigraphy for the evaluation of pyelonephritis and scarring: a review of experimental and clinical studies. *J Urol*. 1992;148:1726-32.
- Tseng MH, Lin WJ, Lo WT, Wang SR, Chu ML, Wang CC. Does a normal DMSA obviate the performance of voiding cystourethrography in evaluation of young children after their first urinary tract infection? *J Pediatr*. 2007;150:96-9.
- Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med*. 2003;348:195-202.
- Lin KY, Chiu NT, Chen MJ, et al. Acute pyelonephritis and sequelae of renal scar in pediatric first febrile urinary tract infection. *Pediatr Nephrol*. 2003;18:362-5.
- Hansson S, Dhamey M, Sigstrom O, et al. Dimercaptosuccinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. *J Urol*. 2004;172:1071-3; discussion 3-4.
- Jakobsson B, Berg U, Svensson L. Renal scarring after acute pyelonephritis. *Arch Dis Child*. 1994;70:111-5.

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