

Color and Power Doppler Sonography Versus DMSA Scintigraphy in Acute Pyelonephritis and in Prediction of Renal Scarring

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Capabilities of color and power Doppler sonography (DS) were prospectively evaluated for diagnosis of acute pyelonephritis and for prediction of scarring by comparison with ^{99m}Tc-dimer-captosuccinic acid scintigraphy (DMSA). **Methods:** Fifty-seven children (mean age, 5 ± 3 y) with acute pyelonephritis were investigated by biologic testing, DS (DS 1), and DMSA (DMSA 1). Patients who were <6 mo old or had high-grade reflux or obstruction were excluded. Forty-five children had a clinical follow-up examination, biologic testing, DS (DS 2), and DMSA (DMSA 2) at a mean of 7 ± 2 mo after acute infection. Sonography (gray-scale and DS) was performed by 1 experienced radiologist who was unaware of patient data. DMSA studies were interpreted by 2 physicians who were unaware of patient data. **Results:** Temperature, neutrophil count, and C-reactive protein value were significantly higher in patients with abnormal DMSA 1 findings than in those with abnormal DS 1 findings (*P* < 0.05). When compared with DMSA 1, DS 1 had a sensitivity and specificity of 80% and 81%, respectively. At follow-up, all clinical and biologic data had normalized. Scarring after infection occurred in 51% of children. When compared with DMSA 2, DS 1 had positive and negative predictive values of 57% and 75%, respectively, and DMSA 1 had respective values of 62% and 100%. Reflux was not considered a good predictor of scarring. **Conclusion:** DS and DMSA results were concordant in 81% of kidneys with acute pyelonephritis. The predictive value of DS for renal scarring was not considered sufficiently high for DS to be used in routine practice.

Key Words: kidney; infection; sonography; radionuclide studies
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Acute pyelonephritis (APN) is a common childhood infectious disease (1). It may result in irreversible renal scarring, which itself can lead to long-term complications (hypertension, toxemia, reduced glomerular filtration, and

end-stage renal disease). Renal scarring as a complication of APN has been estimated to occur in up to 64% of affected pediatric kidneys (2). Early detection of renal parenchymal involvement in urinary tract infection is useful in treatment. Nevertheless, diagnosis of APN often remains difficult, especially in young children. No clinical or laboratory finding is specific. Cortical renal scintigraphy with ^{99m}Tc-dimer-captosuccinic acid (DMSA) has been shown to be highly sensitive and specific for detection and localization of acute inflammatory changes in APN (3). DMSA is otherwise considered a reference investigation for diagnosis of renal scarring (4–6). Enhanced CT has also been reported an efficient diagnostic tool but seems to be more widely used in adult radiology (7). Color and power Doppler sonography (DS) has been reported to be capable of showing gray-scale abnormalities and focal hypovascular areas in APN (Table 1) (8,9) and may be useful for predicting renal scarring (10). The aim of this study was to assess the value of DS performed during APN for diagnosing APN and for predicting the development of renal scars in comparison with DMSA as the reference.

MATERIALS AND METHODS

Clinical and Biologic Findings

From July 1997 to April 2000, we prospectively evaluated 57 children (7 boys, 50 girls; age range, 6 mo to 15.5 y; mean age ± SD, 5 ± 3 y; 1 child with a single kidney). This study was performed according to the Helsinki criteria and with the approval of the local Ethics Committee and the informed consent of both parents. To be included, a child had to have clinical findings consistent with APN, be older than 6 mo, have undergone DS at the acute stage of pyelonephritis (DS 1), and have undergone DMSA at the acute stage of pyelonephritis (DMSA 1). Each child received a standardized clinical examination including abdominal and lumbar fossa palpation, temperature and blood pressure measurement, and standardized blood studies including ionography, a differential blood count, a blood culture, and C-reactive protein (CRP) analysis. A urine sample (a clean catch in midstream) was taken for dipstick analysis and culturing. Usual intravenous antibiotic treatment was started immediately after clinical examina-

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TABLE 1
Interpretation Criteria for Renal DS and DMSA

DS	DMSA
Acute pyelitis: gray-scale sonography Thickening of pelvic or ureteral wall (also visible in cases of reflux) Renal sinus hyperechogenicity Mild dilatation (pelvis or ureter)	Normal findings Normal contour: smooth and continuous without indentations Homogeneous parenchymal uptake in all regions of both kidneys Normal size and shape of both kidneys
Acute nephritis: gray-scale sonography Increased renal size Triangular hyperechogenicity Focus of decreased vasculature (Doppler) Mass (pseudotumoral pyelonephritis)	Inflammation Slightly bulging or normal contour Single or multiple, local or diffuse areas of decreased activity in parenchyma, which are diffuse or, rarely, spheric, in at least 2 projections Mild to severe degree of photopenia or, rarely, complete absence of activity No volume loss
APN: DS Parenchymal triangular zone of decreased or absent flow	Scarring Diffuse or sharp indentation in contour with thinning of cortex Any shape defects with loss of renal volume Photopenia (usually severe) or absent activity

DMSA interpretation criteria are according to Patel et al. (13).

tion, and blood samples and cultures were obtained. APN was diagnosed if the patient had abdominal or lumbar fossa pain, fever $> 38^{\circ}\text{C}$, and positive results from the urine culture (i.e., > 10 white blood cells per cubic millimeter and bacteriuria to the extent of $\geq 10^4$ colony-forming units per milliliter). Children were excluded from the study if they had urinary tract obstruction, greater than grade III vesicoureteral reflux according to the International Grading Study (11), or breakthrough infection between inclusion and follow-up. Figure 1 summarizes the examination schedule.

DS

DS was performed by 1 experienced radiologist using a UM 9 HDI scanner (Advanced Technology Laboratories, Bothell, WA). In all patients, sonography included gray-scale and DS examination of both kidneys with a variable-frequency (5–7 MHz) curved transducer. Gray-scale sonography of the kidneys was performed in accord with our standardized local protocol. After severe dilatation was eliminated, corticomedullary differentiation was assessed with the patients prone. DS settings were adapted to patients to optimize visualization of the intrarenal vasculature. Both axial and longitudinal scans were obtained to provide a vascular map of the kidneys. Each kidney was judged to be normal or abnormal on the basis of the presence or absence of a triangular zone of decreased or absent flow in the parenchyma or any gray-scale

sonographic abnormality as described in Table 1. No spectral analysis was performed. DS findings were analyzed without knowledge of the DMSA findings.

DMSA

DMSA 1 was performed using a standard protocol. Injected activities were calculated following the recommendations of the European Association of Nuclear Medicine pediatric task group (12). Data were acquired on a dual-head, large-field-of-view gamma camera (DST-XL; SMVi, Buc, France) equipped with low-energy, high-resolution parallel collimators in a 128×128 matrix. Planar posterior, left posterior, and right posterior oblique views were obtained 4 h after intravenous injection of $^{99\text{m}}\text{Tc}$ -DMSA (Renocis; CIS Bio International, Gif-sur-Yvette, France). Young children unable to remain prone were positioned supine for examination. Acquisitions were continued to a total of 1,000 kilocounts or 900 s (15 min). No sedation was used. Two experienced physicians unaware of the sonographic results interpreted the findings according to the criteria of Patel et al. (13) (Table 1), and discrepancies were resolved by consensus. At the time of diagnosis, DMSA findings were judged to be abnormal when the criteria for inflammation were satisfied, and DMSA was considered to be the gold standard for diagnosing APN. At follow-up, DMSA findings were interpreted according to the criteria for

FIGURE 1. Examination schedule. VCUG = voiding cystourethrography.

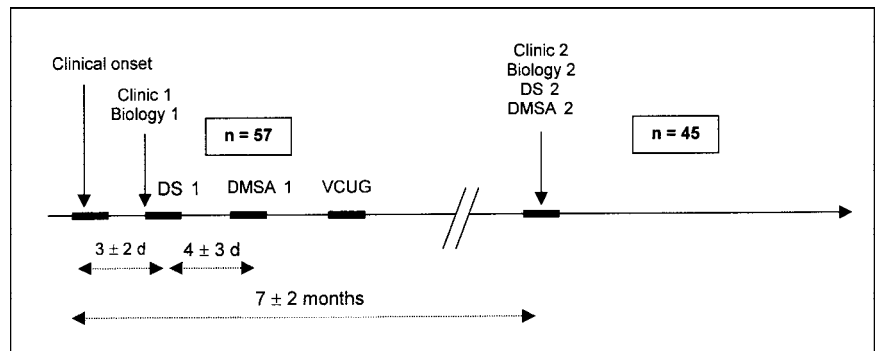


TABLE 2
Descriptive Clinical and Biologic Findings

Parameter	Acute phase (n = 57)	Follow-up (n = 45)
Temperature (°C)	39.2 ± 0.8	No fever
Sodium (mmol/L)	136.1 ± 2.7	140.1 ± 1.9
Potassium (mmol/L)	4.3 ± 0.7	4.4 ± 0.3
Urea (mmol/L)	4.2 ± 0.9	4.2 ± 1.0
Creatinine (μmol/L)	46.6 ± 10.1	41.7 ± 9.7
Protein (g/L)	68.6 ± 11.6	74.0 ± 4.4
White blood cells (×10 ⁹ /L)	16.0 ± 6.2	9.2 ± 7.2
Neutrophils (×10 ⁹ /L)	11.8 ± 5.3	3.8 ± 2.1
CRP (mg/L)	105.0 ± 76.5	46.7 ± 9.4

scarring, and DMSA was considered to be the gold standard for diagnosing renal scarring. Defects located centrally over the pelvicalyceal system were not considered abnormal. The relative renal function (split renal uptake) was evaluated, and a 45%–50% contribution to total renal function was considered normal.

VCUG

Voiding cystourethrography (VCUG) was performed after the intravenous treatment. Cyclic VCUG was performed on children who were not toilet trained (14). Reflux was graded in accord with the recommendations of the International Reflux Study (11).

Follow-Up

A mean of 7 ± 2 mo after acute infection, 45 children underwent a follow-up clinical examination. Twelve families refused follow-up. A blood sample was obtained for ionography, a differential blood count, and CRP analysis. DS 2 and DMSA 2 were performed on the same day. On sonography, the kidneys were measured to assess renal growth, and their contours were examined. DS 2 was performed in the same manner as DS 1, and DMSA 2 was performed and interpreted in the same manner as DMSA 1.

Statistics

The descriptive statistics were expressed as mean ± SD. Comparisons between clinical or biologic findings and DS or DMSA findings were performed using Mann-Whitney nonparametric tests. The diagnostic values (sensitivity, specificity, predictive values, and accuracy) of DS and DMSA were assessed with contingency tables. $P \leq 0.05$ was considered significant.

RESULTS

Clinical and Biologic Findings

Temperature and biologic findings during the acute phase and at follow-up are shown in Table 2. The mean temper-

ature, white blood cell count, neutrophil count, and CRP value were elevated during the acute phase. Forty-five children were reevaluated after the acute phase. All had normal clinical findings, including blood pressure, and all had normal renal function.

Imaging During Acute Phase

DS 1 was performed 3 ± 2 d after the onset of symptoms, and DMSA 1 was then performed 4 ± 3 d after DS 1. The mean split renal uptake was normal. Table 3 shows the percentage of renal abnormalities found by DS 1 and DMSA 1, considering each kidney and each patient. During the acute phase, DS showed abnormal findings in 86% of children and DMSA, in 82%.

Table 4 shows the clinical and biologic findings with regard to imaging results.

Table 5 compares DS 1 and DMSA 1. In 14 kidneys of 13 children, pyelitis was identified (isolated in 7; associated with a focus of nephritis in 7). In these 14 kidneys, DMSA 1 showed abnormal findings in 10 and normal findings in 4 (3 kidneys with isolated pyelitis on DS 1; 1 kidney with associated pyelitis and nephritis).

Follow-Up Imaging

Scarring-related abnormalities found on DS 2 and DMSA 2 are summarized in Table 3. The prevalence of scarring was 51% on DMSA 2. Table 6 shows the predictive values of DS 1 and DMSA 1 for scarring. Eight children with normal DMSA 1 findings were followed up. Of these children, DS 1 showed normal findings in 3, pyelitis in 2, and a focus of decreased flow in 3. In none of these children did scarring subsequently develop.

Reflux

Reflux was found in 9 right kidneys (3 grade I, 4 grade II, and 2 grade III) and in 9 left kidneys (2 grade I, 4 grade II, and 3 grade III). The predictive values for scarring are shown in Table 7.

DISCUSSION

An early and reliable diagnostic tool for APN would be useful for selecting those children with urinary tract infection who require intravenous antibiotics. Such an examination and treatment could decrease the prevalence of renal scarring and its long-term complications. DMSA scintigra-

TABLE 3
Abnormal Imaging Findings During Acute Pyelonephritis and During Follow-Up

DS 1			DMSA 1			DS 2			DMSA 2		
RK	LK	Patients	RK	LK	Patients	RK	LK	Patients	RK	LK	Patients
24/57	30/56	49/57	28/57	26/56	47/57	4/45	8/44	11/45	14/45	14/44	23/45
42%	54%	86%	49%	46%	82%	9%	18%	24%	31%	32%	51%

RK = right kidney; LK = left kidney.

Data are number and percentage of renal abnormalities as defined in Tables 1 and 2 compared with total number of examined kidneys or patients.

TABLE 4
Clinical and Biologic Findings with Regard to Acute-Phase Imaging Results

Parameter	DMSA 1			DS 1		
	Abnormal (n = 47)	Normal (n = 10)	P	Abnormal (n = 49)	Normal (n = 8)	P
Temperature (°C)	39.4 ± 0.7	38.6 ± 0.8	0.02*	39.3 ± 0.8	38.7 ± 0.8	0.7
Sodium (mmol/L)	135.9 ± 2.3	136.7 ± 4.0	0.2	136.1 ± 2.7	136.0 ± 2.1	0.8
Potassium (mmol/L)	4.2 ± 0.6	4.7 ± 0.7	0.8	4.3 ± 0.7	5.1 ± 0.4	0.06
Urea (mmol/L)	4.2 ± 0.8	4.3 ± 1.3	0.9	4.1 ± 0.8	5.6 ± 0.9	0.03*
Creatinine (μmol/L)	47.3 ± 11.4	44.2 ± 9.2	0.6	46.9 ± 9.7	44.0 ± 16.5	0.6
Protein (g/L)	68.6 ± 12.8	68.8 ± 4.4	0.6	68.8 ± 12.1	66.3 ± 4.9	0.2
White blood cells (×10 ⁹ /L)	16.9 ± 6.4	12.4 ± 3.6	0.02*	16.4 ± 6.3	12.8 ± 4.2	0.2
Neutrophils (×10 ⁹ /L)	12.8 ± 5.3	8.2 ± 3.5	0.01*	12.1 ± 5.5	9.6 ± 3.9	0.4
CRP (mg/L)	123.0 ± 76.0	43.0 ± 38.0	0.001*	113.0 ± 76.0	57.0 ± 65.0	0.04*

*Statistically significant.

phy and CT have long been known to be highly sensitive and specific (2,3,7,15). Sonography is usually performed on an emergency basis to rule out pyohydronephrosis. Recently, gray-scale and DS findings associated with pyelonephritis have been described (8,16,17). However, the sensitivity of sonography was shown to remain inferior to that of DMSA, and sonography was therefore not considered a reference method (18). Roberts (19) described the “vascular phase” (slow vascular flow) of pyelonephritis, which corresponded to the DMSA findings described by Majd and Rushton (20). In our prospective work, we compared the diagnostic values of DS and DMSA and particularly tested the following hypothesis: In children with APN and positive sonographic findings during the acute phase, subsequent scarring could be prone to develop in the same location.

Our population data confirmed the established predominance of girls (88%) among children (excluding neonates) with APN. Children who were <6 mo old were excluded because the pathophysiology is thought to be different in infants (21). Patients with known obstruction and high-grade reflux were not included because we wished to select children with pyelonephritis developing in a nondilated urinary tract. Biologic findings were consistent with pyelonephritis in the acute phase in all. The predictive values of body temperature and biologic tests were calculated. In no

patient did any of these parameters provide pertinent information on the risk of scarring. Children with abnormal DMSA 1 findings had a significantly higher body temperature and a more severe biologic infection (Table 4) than did those with normal DMSA 1 findings. Only the CRP value correlated significantly with the DS 1 result. Such a difference may indicate that DMSA is more accurate for diagnosing APN. In spite of a 51% rate of scarring (abnormal DMSA 2 findings) among the children who were followed up, in none of these had any clinical symptom, such as hypertension or biologic deterioration of renal function, yet developed. Perhaps the rate of scarring was slightly overestimated because of the relatively short follow-up (7 mo), which might have been too limited to confirm that the demonstrated abnormalities were related to true scarring (22). However, combining imaging studies with routine clinical follow-up has been convenient. Finally, we chose a free period close to 6 mo before reinvestigation because some transient defects persist for up to 4 mo after APN before showing resolution on DMSA scans (5).

To avoid heterogeneity in sonographic findings, the same operator, using the same equipment, performed all studies in both the acute and the delayed phases of the study. In a recent study in which several operators performed sonogra-

TABLE 5
Diagnostic Value of DS 1: Comparison with DMSA 1

Category	Se	Sp	Accuracy
RK + LK Patients	80%	81%	81%
	94%	50%	86%

Se = sensitivity; Sp = specificity; RK = right kidney; LK = left kidney.
n = 57.

TABLE 6
Predictive Value of DS 1 and DMSA 1 for Scarring: Comparison with DMSA 2

Category	DS 1		DMSA 1	
	PPV	NPV	PPV	NPV
RK + LK Patients	49%	83%	61%	98%
	57%	75%	62%	100%

PPV = positive predictive value; NPV = negative predictive value; RK = right kidney; LK = left kidney.
n = 45.

TABLE 7

Predictive Value of VCUG-Shown Reflux for Scarring: Comparison with DMSA 2

Category	PPV	NPV
RK	11%	64%
LK	50%	73.5%
RK + LK	32%	69%

PPV = positive predictive value; NPV = negative predictive value; RK = right kidney; LK = left kidney.
n = 45.

phy, interindividual variation occurred and the results of the study were less favorable to sonography (23). However, we emphasize that the same sonography equipment was used throughout our whole study to keep the DS results homogeneous.

In our study, DMSA 1 and DMSA 2 were performed using the same acquisition protocol, and reproducibility was ensured by double-blind analysis. SPECT was not performed. In a recent metaanalysis, SPECT DMSA resulted in a higher number of false-positive findings than did the established planar method (24). Moreover, SPECT is more expensive and, to yield clear images, requires that children be restrained at least twice as long (25 min vs. 12 min). As much as possible, we minimized the delay between sonography and DMSA to allow comparisons. However, DMSA 1 was performed 4 ± 3 d after DS 1. This difference in the timing of studies occurred because DMSA was not as available as was sonography, especially on weekends. However, we do not know whether some of the DMSA 1 studies with negative findings could, if performed sooner, have shown positive findings.

During the acute phase, the sensitivity of DS was 80% and the specificity was 81% in comparison with DMSA (Table 5). These findings confirm those of previous studies (8,16,17) and show the relative accuracy of sonography in detection of APN. The performance of sonography was slightly better for the right kidney (86% agreement on the right side vs. 75% on the left side), which is easier to image because of the hepatic window. For 10 patients satisfying the clinical and biologic criteria of APN, the results of DMSA 1 remained negative. DS 1 showed positive findings in 5 of these 10 patients (2 patients with isolated pyelitis of the left kidney, 1 with a focus of nephritis involving the left lower pole, and 2 with a focus of nephritis involving the left upper pole) and negative findings in 5 others. Such patients illustrate the statistical problem of lack of sensitivity in scintigraphy, which was thought to be the gold standard. Some of these patients might have had urinary tract infection without involvement of the renal parenchyma. In other cases, sonography might have revealed some lesions that remained invisible on DMSA. Rushton et al. (3) reported negative DMSA findings for piglets with APN. None had

severe infection. The kidneys were grossly normal, and histopathologic findings consisted only of minimal microscopic foci of inflammatory cells.

Some kidneys with isolated pyelitis on sonography were shown to have a polar focus of decreased uptake on DMSA (4/7 kidneys), but pyelitis could not, of course, be visualized. We believe that sonography and DMSA do not strictly show the same disorder and that they can sometimes be complementary. Because DMSA scan sensitivity is not 100%, normal DMSA findings do not fully exclude upper urinary tract disease. No scarring developed in kidneys affected with isolated pyelitis.

Seven months later, 45 children were reexamined. Scarring had developed in 51%, and this rate can be compared with the 41% rate reported by Rushton and Majd (5). The results of imaging did not confirm our hypothesis: In fact, positive DS 1 results do not accurately predict the development of scarring. Moreover, in the acute phase, no other clinical, biologic, or imaging indicator could predict the patients in whom scarring would develop after infection. However, a definite conclusion can be drawn about children with normal DMSA findings during the acute phase, because in none of them did scarring subsequently develop. The difference between the 100% negative predictive value of DMSA 1 and the 75% negative predictive value of DS 1 stemmed from only 2 patients with false-negative DS 1 results (Table 6).

The development of scarring was not related to the presence of vesicoureteral reflux. This point agrees with previous reports. Rushton et al. (4) postulated that after APN had occurred, the development of scarring was independent of the presence or absence of reflux.

Children who have reflux after urinary tract infection usually receive antibiotic prophylaxis. The effect of such treatment in children with high-grade reflux (greater than grade III) is under evaluation. The treatment has been thought to decrease the prevalence of end-stage renal disease (25). However, given the results of this study, we postulate that management of children with no reflux or with reflux less than grade III could perhaps be changed. Because the presence of reflux does not correlate with the development of scarring, reflux should no longer remain the only reason to start antibiotic prophylaxis. In children with normal DMSA findings during APN, antibiotic prophylaxis does not seem useful, regardless of whether low-grade reflux is present. A further postulate is that patients with negative DMSA and DS findings would not need to undergo VCUG.

In contrast, children with abnormal DMSA findings during APN could be considered at risk of scarring. Adequate follow-up, including sonography, to assess renal growth and DMSA to detect scarring should be considered. Also, in these children, antibiotic prophylaxis may be useful even if reflux is absent.

CONCLUSION

A high rate of scarring after infection (51%) was found at an average follow-up interval of 7 mo. DS and DMSA were concordant in 81% of kidneys and 86% of patients for the diagnosis of APN. Therefore, DS can be considered relatively reliable in the acute phase, and the sensitivity should increase still further with new equipment. However, the predictive values of DS were relatively low, and it cannot yet be recommended as an accurate predictor of scarring. The positive predictive value of DMSA appeared insufficient as well. However, in no child with normal DMSA findings during APN did scarring develop. This study raises the question of whether the decision to use antibiotic prophylaxis in children with urinary tract infection should be based on the presence of scintigraphic abnormality rather than only on the presence of low-grade vesicoureteral reflux.

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