Quantitative Analysis of ^{99m}Tc-DMSA During Acute Pyelonephritis for Prediction of Long-Term Renal Scarring

Anne Hitzel, MD[1,2]; Agnès Liard, MD[3]; Jean-Nicolas Dacher, MD, PhD[2,4]; Isabelle Gardin, PhD[1,2]; Jean-François Ménard, PhD[2,5]; Alain Manrique, MD[1,2]; and Pierre Véra, MD, PhD[1,2]

[1]Department of Nuclear Medicine, Centre Henri Becquerel, Rouen, France; [2]QUANT.I.F (Quantification en Imagerie Fonctionnelle) University Laboratory, Rouen, France; [3]Department of Pediatric Surgery, Rouen University Hospital Charles Nicolle, Rouen, France; [4]Department of Radiology, Rouen University Hospital Charles Nicolle, Rouen, France; and [5]Department of BioStatistics, Rouen University Hospital Charles Nicolle, Rouen, France

This study was performed to evaluate a quantitative method based on ^{99m}Tc-DMSA renal planar scintigraphy performed during acute pyelonephritis (APN) to detect kidneys at risk of scarring. **Methods:** A total of 43 children (5.8 ± 3.6 y old [mean ± SD]) were examined by ^{99m}Tc-DMSA scintigraphy during (DMSA 1) and 8 ± 2 mo after (DMSA 2) APN. Two levels of interpretation were performed independently: first, a semiquantitative analysis to classify the kidneys by considering the evolution between DMSA 1 and DMSA 2 (i.e., to determine which kidneys had developed scarring), and second, an automatic quantitative analysis of DMSA 1 to define and to evaluate a predictive index for kidney evolution from DMSA 1 to DMAS 2. The method consisted of determining an automatic threshold for the kidney and then calculating ratios of the count density in a given isocount *n*% (region of interest containing all the pixels with a value ≥ *n*% of the value of the pixel with the maximal activity value) to the count density in a 20% isocount ($C_{n\%}$) and the number of pixels in a given isocount to the number of pixels in a 20% isocount ($S_{n\%}$). **Results:** All kidneys normal at DMSA 1 remained normal at DMSA 2. For the automatic index, the $C_{70\%}$ ratio was considered the best index for the prediction of scarring. When this $C_{70\%}$ ratio was used, a cutoff value of 0.45 was able to predict scarring with a sensitivity of 0.83, a specificity of 0.78, a positive predictive value of 0.85, and a negative predictive value of 0.77. **Conclusion:** A cutoff value of 0.45 for the $C_{70\%}$ ratio calculated for ^{99m}Tc-DMSA scintigraphy performed during APN may be useful for detecting kidneys at risk of scarring.

Key Words: pyelonephritis; ^{99m}Tc-DMSA scintigraphy; quantification; scarring prediction

J Nucl Med 2004; 45:285–289

Acute pyelonephritis (APN) is a common infectious disease during childhood (*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 pediatric kidneys (*2*). Cortical renal scintigraphy with ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) was shown to be highly sensitive and specific for the detection and localization of acute inflammatory changes in APN (*3*). ^{99m}Tc-DMSA scintigraphy also is considered a reference technique for the diagnosis of renal scarring (*4–6*). However, to our knowledge, no clinical, biologic, or imaging findings during APN have been reported to be able to predict which infected kidney subsequently will develop scarring. The visual interpretation of ^{99m}Tc-DMSA scintigraphy performed during APN has been reported to provide excellent negative predictive value but only weak positive predictive value. The purpose of this study was to improve the acute-stage ^{99m}Tc-DMSA positive predictive value. We evaluated whether a quantitative method based on ^{99m}Tc-DMSA renal planar scintigraphy performed during APN could detect kidneys at risk of scarring.

MATERIALS AND METHODS

Patients

From July 1997 to April 2000, we prospectively evaluated 85 kidneys in 43 children (3 boys and 40 girls; age [mean ± SD], 5.8 ± 3.6 y; age range, 11 mo–15.5 y; 1 child had a single kidney). Our study was performed in accordance with the Helsinki criteria. Children were included after informed consent was obtained from both parents. Inclusion criteria were clinical findings consistent with APN, age of >6 mo, and ^{99m}Tc-DMSA scintigraphy performed at the acute stage of APN (DMSA 1). Each child had a routine clinical examination, including abdominal and lumbar palpation and arterial pressure measurement. Diagnosis of APN was based on clinical and laboratory findings: abdominal or lumbar fossa pain, fever of >38°C, and positive urine culture (i.e., >10 white blood cells/mm^3 and bacteriuria of ≥10^4 colony-forming units/mL). Exclusion criteria were urinary tract obstruction, grade III or higher vesicoureteric reflux determined in accordance with

Received May 27, 2003; revision accepted Oct. 9, 2003.

For correspondence or reprints contact: Pierre Véra, MD, PhD, Département de Médecine Nucléaire, Centre Henri Becquerel, 1 Rue d'Amiens, 76000 Rouen, France.

E-mail: pierre.vera@rouen.fnclcc.fr

an international grading study (*7*), and breakthrough infection between inclusion and follow-up. Standard intravenous antibiotic treatment was started immediately. All children had Doppler sonography to rule out pyonephrosis, obstruction, and abscess. Micturition cystourethrography was performed for all children to assess possible vesicoureteric reflux after the infection was treated.

At 8 ± 2 mo after acute infection, all children had follow-up clinical and biologic examinations on the same day (DMSA 2).

^{99m}Tc-DMSA Acquisitions

DMSA 1 and DMSA 2 were performed by a standard protocol. Injected activities of ^{99m}Tc-DMSA (Renocis; CisBioInternational) were calculated by following the recommendations of the European Association of Nuclear Medicine Paediatric Task Group (*8*). Data were obtained 4 h after intravenous injection of ^{99m}Tc-DMSA by use of a dual-head large-field-of-view γ-camera (DST-XL; SMVi; spatial resolution at 10 cm, 8.5 mm) equipped with low-energy high-resolution parallel collimators. Planar anterior, posterior, and left and right posterior oblique views in a 128 × 128 matrix were obtained 4 h after intravenous injection of ^{99m}Tc-DMSA. Young children unable to remain in the prone position were examined in the supine position. Acquisitions were continued to a total of 1,000 kilocounts. No sedation was used.

DMSA 1 and DMSA 2 Analyses

Two levels of interpretation were performed independently. First, a semiquantitative analysis was performed to classify the kidneys by considering the evolution between DMSA 1 and DMSA 2. This analysis was considered the reference for the remainder of the study. Second, an automatic quantitative analysis of DMSA 1 was performed to define and to evaluate a predictive index for kidney evolution from DMSA 1 to DMAS 2.

Semiquantitative Analysis of Kidney Evolution. To standardize the interpretation, a 9-point semiquantitative analysis of each kidney was performed. Each kidney was divided in thirds graded from 0 (no uptake) to 3 (normal uptake). The sum of the 3 scores for each kidney was calculated. A kidney was considered normal when the final score was ≥7. Renal scarring was defined as a final score of <7 on DMSA 2. A comparison between DMSA 1 and DMSA 2 scores was made, and 3 groups were obtained: normal unchanged (NU), when scores on DMSA 1 and DMSA 2 were ≥7; abnormal improved (AI), when the score was <7 on DMSA 1 and had improved by 2 points or more on DMSA 2; and abnormal unimproved (AU), when the score was <7 on DMSA 1 and had improved by less than 2 points on DMSA 2 (i.e., renal scarring).

The analyses were performed separately by 2 experienced observers who were unaware of the results of the clinical evaluation and the date of the ^{99m}Tc-DMSA scintigraphy (during APN or at follow-up). First, inter- and intraobserver reproducibilities were evaluated. Second, discrepancies were resolved by consensus. This consensus reading for each kidney was considered the reference for the remainder of the study.

Quantitative Analysis of DMSA 1. An automatic quantitative analysis of DMSA 1 was performed to establish a quantitative method that could help to detect kidneys at risk of scarring after APN. Successive thresholds (20%, 30%, 40%, 50%, 60%, 70%, and 80% the maximum pixel value) were automatically applied to the posterior view of each kidney. No background was subtracted. Two types of quantitative parameters were studied. The first one was related to the extent of the cortical uptake defect during APN (number of pixels: $S_{n\%}$), and the second one was related to intensity (count density: $C_{n\%}$), as both usually are considered for visual interpretation. For each threshold, they were expressed as a percentage of the counting rate for the 20% isocount *n*% (region of interest containing all the pixels with a value ≥ *n*% of the value of the pixel with the maximum activity value) for each kidney: $S_{n\%}$ = number of pixels in a given isocount/number of pixels in a 20% isocount, and $C_{n\%}$ = count density in a given isocount/count density in a 20% isocount.

Statistical Analysis

Descriptive statistics were expressed as mean ± SD. Inter- and intraobserver reproducibilities were evaluated by calculation of the mean ± SD of the absolute difference in DMSA 1 and DMSA 2 scores between the 2 observers.

A comparison of groups was based on an ANOVA. Calculations of sensitivity, specificity, positive and negative predictive values, and likelihood ratios were deduced from a receiver operating characteristic (ROC) curve analysis for $S_{n\%}$ and for $C_{n\%}$.

RESULTS

Semiquantitative Analysis

The inter- and intraobserver reproducibilities of the semiquantitative index are shown in Table 1. The reproducibilities of the semiquantitative score were very high. Discrepancies leading to different interpretations by the 2 observers were obtained for 5 of 85 kidneys during APN (5.8%) and for 6 of 85 (7%) at follow-up. The differences in kidney grading between the 2 observers were 1 point in 4 cases, 2 points in 6 cases, and 3 points in 1 case. The discrepancies were resolved by consensus.

During APN, 59 kidneys (69%) had a normal score (>7) on DMSA 1. All of these kidneys remained normal on DMSA 2 (NU group). The DMSA 1 score was abnormal in 26 kidneys (31%) during APN. Of these 26 kidneys, 14 (54%) showed an improvement in the score on DMSA 2 of more than 2 points and were classified in the AI group, and 12 (46%) showed an improvement in the score of less than 2 points and were classified in the AU group (Fig. 1).

Quantitative Analysis

Mean ± SD $C_{n\%}$ and $S_{n\%}$ values for the 3 groups of kidney evolution (NU, AI, and AU) are shown in Tables 2 and 3, respectively.

The separation of the 3 groups was better with $C_{n\%}$ ratios than with $S_{n\%}$ ratios (Table 4).

With a global ANOVA, it was possible to differentiate from the DMSA 1 results the NU, AI, and AU kidneys by use of $C_{n\%}$ ratios ($F = 14.6$, $P < 0.0001$). A 70% threshold ($C_{70\%}$) could differentiate the AU kidneys from the AI kidneys ($P = 0.004$) and the NU kidneys from the AI

TABLE 1
Reproducibility of Semiquantitative Grading System

Parameter	Mean ± SD reproducibility for: DMSA 1	DMSA 2
Interobserver	0.40 ± 0.60	0.33 ± 0.60
Intraobserver	0.40 ± 0.59	0.32 ± 0.59

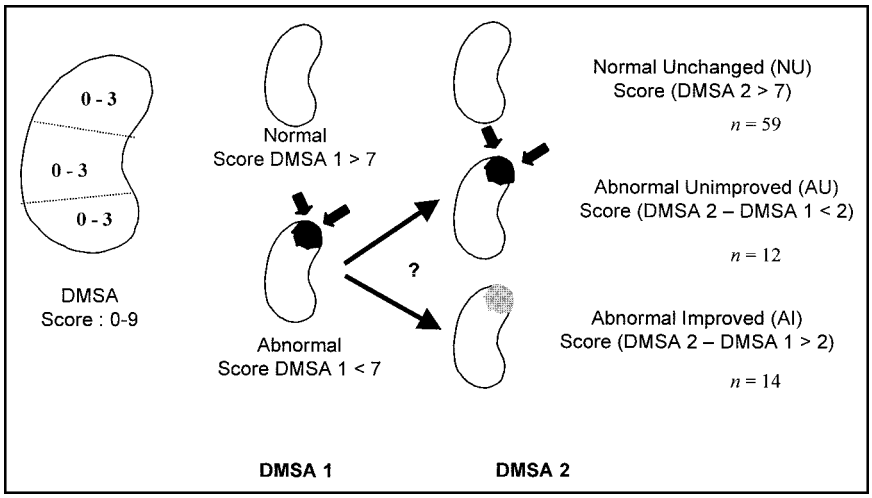

FIGURE 1. Classification of kidneys by the semiquantitative grading system.

kidneys ($P < 0.0001$). This 70% threshold provided the optimal area under the ROC curve for the prediction of renal scarring (Table 4). When a cutoff value of 0.45 was used for the $C_{70\%}$ ratio, the sensitivity and specificity of the 70% threshold were 0.83 and 0.78, respectively (Fig. 2) and the positive and negative predictive values were 0.85 and 0.77 for a prevalence of 0.53. The use of the cutoff value of 0.45 provided a likelihood ratio of 4.71.

Figure 3 shows an example of ^{99m}Tc-DMSA scintigraphy during APN and at follow-up.

DISCUSSION

This study demonstrates that an automatic analysis of ^{99m}Tc-DMSA scanning during APN may be helpful for indicating the risk of scarring (i.e., persistent abnormal uptake on a ^{99m}Tc-DMSA scan performed more than 6 mo after APN). The method consisted of determining a threshold for the kidney and then calculating $C_{n\%}$ and $S_{n\%}$ ratios. The $C_{70\%}$ ratio was considered the optimal predictor of scarring. With this ratio, a cutoff value of 0.45 was able to predict scarring with a sensitivity of 0.83, a specificity of 0.78, a positive predictive value of 0.85, and a negative predictive value of 0.77. The cutoff value of 0.45 for the $C_{70\%}$ ratio provided the highest likelihood ratio.

^{99m}Tc-DMSA renal scanning is widely used in clinical practice. It is considered the standard reference method for the diagnosis of APN and postinfection renal scarring. Interpretation is usually only qualitative, and differences in reproducibility have been reported (*9–13*). Because of its variable reproducibility, we preferred not to consider visual interpretation as the gold standard. In a previously reported series, Hitzel et al. reported a negative predictive value for scarring of 100% in a population of 57 children with APN (*14*). The corresponding positive predictive value was 62%, which was considered to be insufficient. The purpose of this study was to improve the acute-stage ^{99m}Tc-DMSA positive predictive value.

A semiquantitative uptake score was used as the gold standard for ^{99m}Tc-DMSA scan interpretation. This score was chosen because it is simple and can be determined rapidly. Moreover, we demonstrated the excellent reproducibility of this score. A minimal increase of 2 points in the semiquantitative analysis between DMSA 1 and DMSA 2 was considered sufficient to attest to an improvement in renal uptake and to classify a kidney in the AI group.

TABLE 2
$C_{n\%}$ Values for 3 Groups of Kidneys

$C_{n\%}$	Mean ± SD for the following group (*n*): AI (14)	AU (12)	NU (59)
$C_{30\%}$	0.93 ± 0.04	0.94 ± 0.03	0.95 ± 0.02
$C_{40\%}$	0.86 ± 0.05*	0.88 ± 0.04	0.90 ± 0.02
$C_{50\%}$	0.75 ± 0.07†	0.79 ± 0.07	0.83 ± 0.04
$C_{60\%}$	0.60 ± 0.11†	0.67 ± 0.08	0.71 ± 0.06
$C_{70\%}$	0.42 ± 0.14*‡	0.52 ± 0.09	0.54 ± 0.07
$C_{80\%}$	0.25 ± 0.10†	0.32 ± 0.06	0.34 ± 0.06

*$P < 0.001$ for comparison with NU.
†$P < 0.0001$ for comparison with NU.
‡$P < 0.005$ for comparison with AU.

TABLE 3
$S_{n\%}$ Values for 3 Groups of Kidneys

$S_{n\%}$	Mean ± SD for the following group (*n*): AI (14)	AU (12)	NU (59)
$S_{30\%}$	0.81 ± 0.08	0.82 ± 0.06	0.86 ± 0.03
$S_{40\%}$	0.68 ± 0.08*	0.71 ± 0.04*	0.75 ± 0.02
$S_{50\%}$	0.55 ± 0.08	0.79 ± 0.08	0.65 ± 0.05
$S_{60\%}$	0.41 ± 0.10*	0.56 ± 0.09	0.53 ± 0.06
$S_{70\%}$	0.26 ± 0.11	0.46 ± 0.08	0.37 ± 0.61
$S_{80\%}$	0.15 ± 0.07*	0.34 ± 0.08	0.22 ± 0.05

*$P < 0.0001$ for comparison with NU.

TABLE 4
Areas Under ROC Curves for $C_{n\%}/S_{n\%}$ Ratios

$C_{n\%}$	Area under ROC curve	SE	$S_{n\%}$	Area under ROC curve	SE
$C_{30\%}$	0.61	0.21	$S_{30\%}$	0.58	0.20
$C_{40\%}$	0.62	0.21	$S_{40\%}$	0.58	0.20
$C_{50\%}$	0.68	0.22	$S_{50\%}$	0.46	0.18
$C_{60\%}$	0.69	0.22	$S_{60\%}$	0.62	0.21
$C_{70\%}$	0.77	0.23	$S_{70\%}$	0.74	0.23
$C_{80\%}$	0.75	0.23	$S_{80\%}$	0.73	0.23

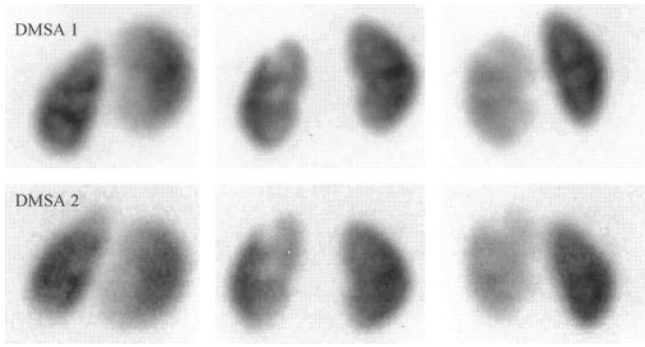

FIGURE 3. Left posterior oblique, posterior, and right posterior oblique views in a 6-y-old girl. During APN (DMSA 1), uptake defects were observed in each third of the left kidney and in the middle and inferior pole of the right kidney. $C_{70\%}$ was calculated to be 0.26 and 0.66 for the left and right kidneys, respectively. Seven months later (DMSA 2), the left kidney had developed multifocal scars, whereas the right kidney had normalized.

We used an automatic index to evaluate the positive predictive value of DMSA 1 (performed during acute infection) with regard to delayed persistent abnormalities (corresponding to renal scarring) on the ^{99m}Tc-DMSA scan performed at follow-up. We also tested both the intensity (i.e., severity) and the size (i.e., extent) of the uptake defect during APN because both parameters are considered for visual interpretation. Experimental studies have reported focal ischemia associated with APN. We postulated that the severity or extent of this ischemia during APN could lead to long-term renal scarring, as severe or extensive ischemia can lead to infarction in the myocardium. However, this "vascular" hypothesis does not consider the release of toxic enzymes, which also contributes to the production of abnormalities on ^{99m}Tc-DMSA scintigraphy during APN.

Successive thresholds were separately applied to each kidney. Before defining the 20% threshold as the reference for the calculation of $S_{n\%}$ and $C_{n\%}$, we tested several thresholds (5%, 10%, 15%, 20%, and 25%). The 20% threshold was considered the optimal detector for kidney contours and was used to calculate the indices for the rest of the study.

We tested 12 different indices. The ideal index would differentiate infected kidneys that would improve from those that would not. Although $C_{50\%}$ correctly separated the 3 groups of kidneys, we preferred $C_{70\%}$ because it was more accurate for discriminating among abnormal kidneys. The outcome of normal kidneys during APN was not the problem, because the excellent negative predictive value of ^{99m}Tc-DMSA scintigraphy was demonstrated previously (*14*). Furthermore, the area under the ROC curve was the highest when $C_{70\%}$ was used. The use of a cutoff value of 0.45 for this index provided a high positive predictive value of 0.85 for renal scarring. This type of index should be validated with a larger prospective series of patients.

Other parameters have been tested to evaluate whether they can predict renal scarring after APN, particularly in children with no or low-grade vesicoureteric reflux. Body temperature or biologic tests (white blood cell count and level of C-reactive protein) during APN have not been shown to be able to provide any pertinent information concerning the risk of scarring. Jakobsson et al. reported no difference among groups with regard to the duration of fever and the level of C-reactive protein or white blood cell

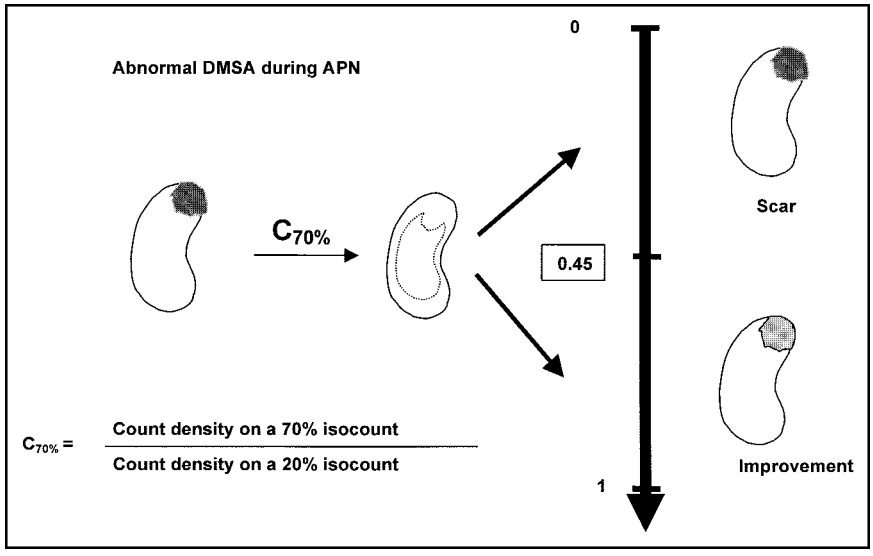

FIGURE 2. Evolution of a kidney after APN with regard to $C_{70\%}$.

count at the time of infection (*15*). Therapeutic delay has been associated with an increased prevalence of renal scarring in experimental and clinical reports (*16–18*). The age of the child also was found to influence the development of renal scarring. All of these results are still controversial, and conflicting data have been reported. No formal parameter has been isolated.

Stokland et al. (*12*) reported no relationship between age at infection and scarring. To our knowledge, no previously published report included an attempt to quantify the decreased uptake of ^{99m}Tc-DMSA (in terms of extent and severity) during APN to predict scarring.

The use of this type of index during APN should help to identify children at risk of renal scarring and also could influence treatment (type, administration, and duration) and follow-up management.

When both ultrasonography and ^{99m}Tc-DMSA scanning are normal during APN, the risk of renal scarring is low. It is then unlikely that voiding cystourethrography, which is an invasive and radiating procedure, will be beneficial.

CONCLUSION

A cutoff value of 0.45 for the $C_{70\%}$ ratio calculated for ^{99m}Tc-DMSA scintigraphy performed during APN might help to predict renal scarring. Patients with a value of >0.45 were at low risk of scarring after their pyelonephritis.

This study demonstrates that automatic determination of a threshold for kidneys in acute-phase ^{99m}Tc-DMSA scintigraphy performed during APN could help to detect infected kidneys at risk of scarring. Prospective follow-up of kidneys after APN with regard to $C_{70\%}$ is warranted to confirm the prognostic value of ^{99m}Tc-DMSA scanning.

ACKNOWLEDGMENTS

The authors thank Rouen University Hospital Charles Nicolle (Rouen, France) for financial support (grant 98.037HP) and Richard Medeiros, Rouen University Hospital medical editor, for his valuable advice in editing the article.

REFERENCES

1. Stamey T. *Pathogenesis and Treatment of Urinary Tract Infections*. Baltimore, MD: Williams & Wilkins; 1980:239–241.
2. Benador D, Benador N, Slosman DO, Nussle D, Mermillod B, Girardin E. Cortical scintigraphy in the evaluation of renal parenchymal changes in children with pyelonephritis. *J Pediatr*. 1994;124:17–20.
3. Rushton HG, Majd M, Chandra R, Yim D. Evaluation of ^{99m}Tc-dimercaptosuccinic acid renal scans in experimental acute pyelonephritis in piglets. *J Urol*. 1988;140:1169–1174.
4. Rushton HG, Majd M, Jantausch B, Wiedermann BL, Belman AB. Renal scarring following reflux and nonreflux pyelonephritis in children: evaluation with ^{99m}Tc-dimercaptosuccinic acid scintigraphy [published erratum appears in *J Urol*. 1992;148:898]. *J Urol*. 1992;147:1327–1332.
5. 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;148:1726–1732.
6. Smellie JM, Shaw PJ, Prescod NP, Bantock HM. ^{99m}Tc dimercaptosuccinic acid (DMSA) scan in patients with established radiological renal scarring. *Arch Dis Child*. 1988;63:1315–1319.
7. Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Mobius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. *Pediatr Radiol*. 1985;15:105–109.
8. Piepsz A, Hahn K, Roca I, et al. A radiopharmaceuticals schedule for imaging in paediatrics. Paediatric Task Group of the European Association of Nuclear Medicine. *Eur J Nucl Med*. 1990;17:127–129.
9. Shanon A, Feldman W, McDonald P, et al. Evaluation of renal scars by technetium-labeled dimercaptosuccinic acid scan, intravenous urography, and ultrasonography: a comparative study. *J Pediatr*. 1992;120:399–403.
10. Patel K, Charron M, Hoberman A, Brown ML, Rogers KD. Intra- and interobserver variability in interpretation of DMSA scans using a set of standardized criteria. *Pediatr Radiol*. 1993;23:506–509.
11. De Sadeleer C, Tondeur M, Melis K, et al. A multicenter trial on interobserver reproducibility in reporting on ^{99m}Tc-DMSA planar scintigraphy: a Belgian survey. *J Nucl Med*. 2000;41:23–26.
12. Stokland E, Hellstrom M, Jacobsson B, Jodal U, Sixt R. Renal damage one year after first urinary tract infection: role of dimercaptosuccinic acid scintigraphy. *J Pediatr*. 1996;129:815–820.
13. Everaert H, Flamen P, Franken PR, Peeters P, Bossuyt A, Piepsz A. ^{99m}Tc-DMSA renal scintigraphy for acute pyelonephritis in adults: planar and/or SPECT imaging? *Nucl Med Commun*. 1996;17:884–889.
14. Hitzel A, Liard A, Vera P, Manrique A, Menard JF, Dacher JN. Color and power Doppler sonography versus DMSA scintigraphy in acute pyelonephritis and in prediction of renal scarring. *J Nucl Med*. 2002;43:27–32.
15. Jakobsson B, Berg U, Svensson L. Renal scarring after acute pyelonephritis. *Arch Dis Child*. 1994;70:111–115.
16. Smellie JM, Ransley PG, Normand IC, Prescod N, Edwards D. Development of new renal scars: a collaborative study. *Br Med J*. 1985;290:1957–1960.
17. Miller T, Phillips S. Pyelonephritis: the relationship between infection, renal scarring, and antimicrobial therapy. *Kidney Int*. 1981;19:654–662.
18. Winberg J, Bollgren I, Kallenius G, Mollby R, Svenson SB. Clinical pyelonephritis and focal renal scarring: a selected review of pathogenesis, prevention, and prognosis. *Pediatr Clin North Am*. 1982;29:801–814.