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# ALTERNATIVE APPROACHES TO THE PROGNOSTIC STRATIFICATION OF MILD TO MODERATE PRIMARY VESICoureTERAL REFLUX IN CHILDREN

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## ABSTRACT

**Purpose:** We compared the prognostic stratification of primary vesicoureteral reflux by performing staging voiding cystourethrography in all children with a urinary tract infection or only in those with renal scarring on  $^{99m}$ technetium-dimercapto-succinic acid (DMSA) scintigraphy.

**Materials and Methods:** Staging voiding cystourethrography and DMSA scintigraphy were performed in 105 children with a urinary tract infection and reflux persistence was assessed by radionuclide cystography after a 2-year followup.

**Results:** Staging voiding cystourethrography revealed no reflux in 51 children (DMSA positive in 3), grades I to II reflux in 21 (DMSA positive in 6) and grade III reflux in 33 (DMSA positive in 19). On followup radionuclide cystography no new reflux was detected, and it was no longer demonstrated in 23 children (8 with grade III and 15 with grades I to II reflux). The finding of grade III reflux on staging voiding cystourethrography had a 76% positive and a 92% negative value for predicting persistent reflux with an 87% predictive accuracy. Limiting the evaluation of voiding cystourethrography data to the 28 children with a positive DMSA scan the combination of renal scarring and grade III reflux had an 84% positive and an 83% negative predictive value with 83% accuracy. This approach would have prevented 77 children from having to undergo voiding cystourethrography.

**Conclusions:** Performance of staging voiding cystourethrography exclusively in children with renal scarring on a DMSA scan resulted in predictive accuracy that was close to what was achieved by performing voiding cystourethrography in all children with a urinary tract infection. To be able to limit cystourethrography to a select population could prove to be cost-effective.

**KEY WORDS:** vesico-ureteral reflux, urinary tract infection, dimercaptosuccinic acid, radionuclide imaging

Except for the severely dilated forms primary vesicoureteral reflux is expected to resolve spontaneously and medical treatment to prevent urinary tract infection is the current therapeutic choice.<sup>1-3</sup> Since the most feared consequence of reflux in children is reflux nephropathy,<sup>4</sup> and because there is a relationship between renal scarring and significant reflux,<sup>5-10</sup> renal cortical scintigraphy with  $^{99m}$ technetium (Tc)-dimercapto-succinic acid (DMSA) has become the first line imaging technique for children with a urinary tract infection.<sup>1,5,7-13</sup> Others have proposed that the evaluation of reflux by voiding cystourethrography or radionuclide cystography could be limited to patients with renal damage on a DMSA scan.<sup>5,7,10</sup> However, the consequences of missing vesicoureteral reflux in children without renal involvement at the time of the staging evaluation are unclear. Furthermore, several reports indicate that reflux severity influences the rate of spontaneous resolution.<sup>2,3,14</sup> Thus, the lack of information about reflux severity in children with a negative DMSA scan may prevent a correct prognostic stratification of reflux response to medical treatment. We compared the prognostic stratification of vesicoureteral reflux based on the performance of staging voiding cystourethrography in all patients with a urinary tract infection versus

doing voiding cystourethrography in those with renal scarring on DMSA scintigraphy.

## METHODS

**Patient population.** The study population was selected from the children referred to our laboratory after a documented urinary tract infection. According to the official policy of the Italian Society of Pediatric Nephrology, a staging evaluation, including imaging techniques, is indicated in certain patients with a urinary tract infection, including those younger than 1 year, with symptoms or signs suggesting acute pyelonephritis and with recurrent urinary tract infections. Exclusion criteria were patient age older than 10 years, no informed parental consent, urinary tract dilatation on routine ultrasonography and urinary tract obstruction causing secondary reflux. Of the potentially eligible patients 12 had dilatation of the urinary tract on routine ultrasonography and, therefore, they were excluded from study. Subsequent voiding cystourethrography showed grade IV reflux in 10 cases and grade V reflux in 2, including 1 with posterior urethral valves. Thus, the study cohort included 62 female and 43 male patients 3 to 120 months old (mean age  $33 \pm 29.5$ ).

**Study protocol.** The study protocol had been previously approved by the Ethics Committee of our institution. Patients were seen at least 3 months after an acute urinary tract infection<sup>7,13</sup> and after urine cultures repeated for 1 month were negative.<sup>7,8</sup> The study protocol included DMSA

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scanning for the detection of renal scarring, and voiding cystourethrography for vesicoureteral reflux detection and grading. For prognostic stratification the status of the most severely involved kidney and urinary tract was considered in each case. Independently of DMSA scan and voiding cystourethrography results, all patients entered a followup protocol with periodic clinical examinations and urine cultures, and appropriate antibiotic treatment for each acute urinary tract infection. In select cases (age less than 2 years and/or a febrile urinary tract infection as the initial clinical presentation) long-term low dose antibacterial prophylaxis was also given during the symptom-free phases. At least 2 years after study entry and when a recent urinary tract infection was excluded by multiple urine cultures, reflux status was assessed by radionuclide cystography while renal status was determined by a second DMSA scan. Evaluation of the followup data was done without access to the results of the staging imaging procedures.

**Imaging studies.** Voiding cystourethrography was performed without previous preparation or sedation. The bladder was catheterized using an appropriate Foley catheter and slowly filled with radiographic contrast material until the sensation of a full bladder and the need to void were noticed or until voiding began around the catheter. Voiding was then allowed during fluoroscopy. The voiding phase was recorded on videotape and static images were obtained using a spot camera. Degree of vesicoureteral reflux was classified according to the International Reflux Study Committee.<sup>15</sup>

Radionuclide cystography was performed using the direct technique. The bladder was catheterized with an appropriate Foley catheter. No sedation was used. The tracer-containing solution (14.8 MBq, <sup>99m</sup>Tc-pentetic acid in 500 ml. isotonic saline) was slowly instilled to fill the bladder until the sensation of the need to void was noticed. The filling and voiding phases were recorded with a dynamic acquisition mode, 1 frame per 5 seconds on 64 × 64 matrices, using a large field of view gamma camera equipped with a high resolution collimator. Vesicoureteral reflux was evaluated by an experienced observer blinded to all other patient data. For study purposes only the presence or absence of reflux was considered.

DMSA scintigraphy was performed according to our usual clinical protocol. The administered dose was 0.74 MBq/kg. body weight, and 3 hours later analogue images (500,000 counts) were recorded in the posterior and both posterior oblique projections with the patient supine and the gamma camera head directly beneath the examination bed. A large field of view gamma camera equipped with an ultra-high resolution collimator was used. The studies were also stored on a computer to allow digital image enhancement when necessary for a better evaluation. The images were evaluated by an experienced observer blinded to other patient data. Renal scars were classified according to the criteria of Goldraich et al.<sup>13</sup>

**Statistical analysis.** When appropriate, data are expressed as mean plus or minus standard deviation. The comparison of continuous variables among groups was done using 1-way analysis of variance. Proportions were compared using Fisher's exact test and  $p < 0.05$  was considered significant.

## RESULTS

**Staging evaluation.** Clinical presentations were a febrile urinary tract infection in 55 children (mean age  $30.8 \pm 29.6$  months), cystitis in 40 (mean age  $36.1 \pm 31.5$  months, not significant versus the first group) and covert bacteriuria in 10 (mean age  $68.8 \pm 36$  months,  $p < 0.005$  versus the other groups). According to the staging voiding cystourethrography 54 children had grades I to III primary reflux in at least 1 of the 2 kidneys and 51 had normal bilateral systems. The DMSA scan showed renal scarring in 37 kidneys of 28 pa-

tients. Overall 33 children had grade III (dilated) reflux, 21 had grades I to II (nondilated) reflux and 51 did not have reflux. DMSA scan was positive in 28 children and negative in 77. Febrile urinary tract infection was the clinical presentation of 26 of 28 children with a positive scan and of 49 of 54 with any grade of reflux. The DMSA scan was positive in 25 of 54 patients (46%) with and 3 of 51 (6%) without reflux ( $p < 0.0001$ ). DMSA scarring was seen in 19 of 33 patients (58%) with grade III reflux and in 6 of 21 (29%) with grades I to II reflux ( $p < 0.05$ ). Conversely reflux was present in 25 of the 28 patients (89%) with a positive DMSA scan versus 29 of the 77 (38%) without renal scarring ( $p < 0.0001$ ). Grade III reflux was present in 19 of 28 patients (68%) with a positive DMSA scan versus 14 of 77 (18%) without renal scarring ( $p < 0.0001$ ). When both tests were considered, 19 of the 25 children with reflux and a positive DMSA scan had dilatation. Of the 77 children with a negative scan 48 had no signs of reflux, 15 had reflux without dilatation and 14 had reflux with dilatation (fig. 1).

**Followup data.** Followup was completed in all patients 24 to 77 months (mean  $31 \pm 14$ ) after initial staging. During followup the overall mean number of acute urinary tract infections per patient was  $0.7 \pm 1.6$ . At least 1 acute urinary tract infection developed during followup in 26% of patients. Followup radionuclide cystography remained normal in the 51 patients without vesicoureteral reflux, whereas of the remaining 54 reflux persisted in 31 and completely resolved in 23.

Followup DMSA scintigraphy showed persistent unchanged renal scarring in 28 kidneys, disappearance of a mild (grade 1) scar in 5 and scar grading improvement in 4. Two kidneys with persistent reflux (1 grade II and 1 grade III) were positive on the followup scan. The table shows the followup data of the different subsets of patients with vesicoureteral reflux, as defined by dilated versus nondilated reflux, positive versus negative DMSA scan and reflux resolution versus persistence on radionuclide cystography. These subsets were not significantly different from each other in terms of demographic data, therapeutic regimen or urinary tract infection incidence during followup. In regard to clinical presentation, a significantly higher incidence of febrile urinary tract infections was noted in children with a positive than a negative DMSA scan.

**Staging data and vesicoureteral reflux status** (fig. 2). Of the 51 patients without reflux on staging voiding cystourethrography none had reflux at followup, whereas of the 54 with reflux 23 (43%) had no signs of reflux on followup radionuclide cystography. Thus, vesicoureteral reflux detection without grading was poorly predictive of reflux persistence (pos-

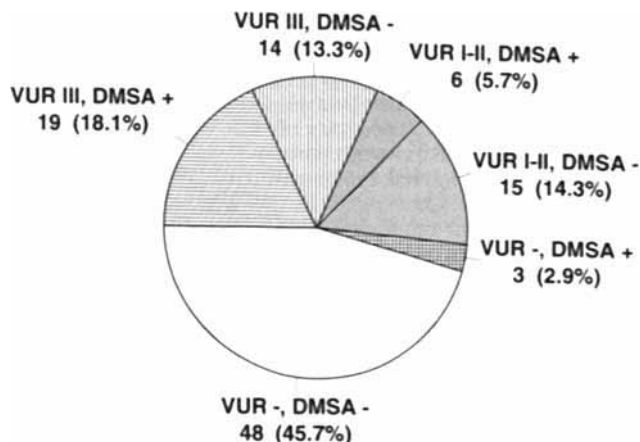


FIG. 1. Division of patient population according to staging examinations. VUR, vesicoureteral reflux.

## Comparison of subsets of children according to reflux grade, DMSA scan and reflux status

	Staging			Followup		
	Mean Pt. Age $\pm$ SD (mos.)	Sex (M:F)	% Pts. With Febrile Urinary Tract Infection	% Pts. on Prophylaxis	% Pts. With Urinary Tract Infection	Mean No. Urinary Tract Infections/Pt. $\pm$ SD
Reflux grade:						
I to II	34 $\pm$ 29	7:14	90	90	38	1.4 $\pm$ 2.3
III	33 $\pm$ 30	14:19	91	97	54	1.3 $\pm$ 1.9
DMSA scan:						
Pos.	37 $\pm$ 32	10:15	100*	100	52	1.6 $\pm$ 2.4
Neg.	29 $\pm$ 37	11:18	83*	90	45	1.1 $\pm$ 1.7
Reflux status:						
Resolved	29 $\pm$ 28	11:12	83	91	39	1.1 $\pm$ 1.8
Unchanged	36 $\pm$ 30	10:21	97	97	55	1.5 $\pm$ 2.2

\* p &lt; 0.05.

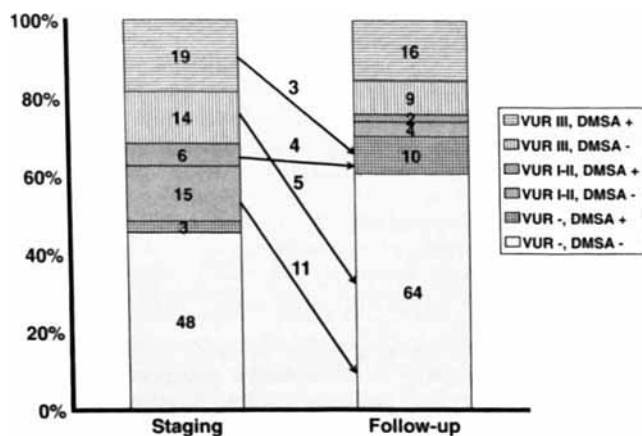


FIG. 2. Vesicoureteral reflux (VUR) status among various groups and numbers of children identified by staging examinations.

itive predictive value 57%). Reflux persisted in 25 patients (76%) with grade III and 6 (29%) with grades I to II reflux ( $p < 0.001$ ). Thus, grade III reflux on staging voiding cystourethrography was an adverse prognostic indicator compared to grade I or II, or absent reflux (76% positive and 92% negative predictive values, and 87% predictive accuracy).

Vesicoureteral reflux persisted in 18 of the 28 patients (64%) with a positive DMSA scan and in 13 of the 77 (17%) without renal scarring ( $p < 0.0001$ ). Thus, a prognostic stratification of vesicoureteral reflux based only on the adverse significance of renal scarring on a staging DMSA scan had 64% positive and 83% negative predictive values with 78% predictive accuracy. If the reflux evaluation had been performed only in patients with a positive DMSA scan, 25 with reflux would have been identified and 29 would have been missed. However, the rate of reflux resolution was 7 of 25 (28%) and 16 of 29 patients (55%), respectively ( $p < 0.0001$ ). Therefore, the combined findings of renal scarring and any grade of reflux had a positive predictive value of 72% for reflux persistence, a negative predictive value of 84% and a predictive accuracy of 80%. When reflux grade is also considered, children with positive DMSA scans and grade III reflux were a high risk group with 16 of 19 (84%) still having reflux at followup. Conversely the risk was significantly lower ( $p < 0.0001$ ) for the remaining 86 patients since only 15 (17%) had reflux on followup radionuclide cystography. Consequently the positive predictive value of the combination of DMSA scanning and grade III vesicoureteral reflux was 84%, negative predictive value was 83% and predictive accuracy was 83%.

## DISCUSSION

The possible complications of undetected or ineffectively treated vesicoureteral reflux are extremely severe,<sup>4</sup> making the diagnosis of possible reflux in children with urinary tract infections pertinent. However, reflux is important mainly

because it is a contributor to the development of upper urinary tract infections and subsequent renal damage.<sup>12</sup> Recognizing renal involvement in children with a urinary tract infection is mandatory and it is currently achieved using DMSA scintigraphy.<sup>1,5,7-13</sup> More controversial are the choice and value of a staging examination to detect reflux and to classify its severity.<sup>1</sup> The role of ultrasonography is limited in the detection of structural and morphological abnormalities of the most severe grades of vesicoureteral reflux. Radionuclide cystography and voiding cystourethrography are more sensitive and the latter test also allows accurate grading of reflux severity, but dosimetric and economic problems are important limitations to their use in all children with a urinary tract infection. Thus, since DMSA scintigraphy should be performed in most children with a urinary tract infection, it has been proposed to restrict the evaluation of vesicoureteral reflux to those with signs of renal damage.<sup>5,7,10</sup> However, the prognostic disadvantage of missing the diagnosis of reflux in children with a negative DMSA scan must be assessed. Furthermore, there is a demonstrated relationship between the rate of spontaneous resolution of mild to moderate reflux and its severity.<sup>2,3,14</sup> Therefore, another potentially important prognostic factor would be missed in patients with a negative DMSA scan. In this study we tried to compare the prognostic stratification obtained by investigating and grading reflux in an entire pediatric population affected by urinary tract infections with more selective approaches that limit the search for reflux and its grading to those with a positive staging DMSA scan.

Our data confirm that negative staging voiding cystourethrography is highly predictive of the absence of reflux at followup as well. However, the converse is not true because at followup reflux had resolved in almost half of the affected patients. Regarding the prognostic implications of reflux grading, in the entire study population the identification of dilated (grade III) reflux was effective in defining a high risk population. However, persistence of reflux was noted in approximately a third of those with nondilated grades I and II reflux.

On the other hand, previously reported data about the higher rate of vesicoureteral reflux in patients with signs of renal scarring were confirmed.<sup>5-10</sup> The rate of scarring in kidneys without reflux was significantly lower than that in kidneys with reflux (6% versus 52%,  $p < 0.0001$ ). Accordingly, the simplistic approach of classifying patients with a positive DMSA scan as a group at high risk for persistent reflux achieves good negative predictive value and predictive accuracy but only moderate positive predictive value. The positive predictive value increases when limiting the evaluation of voiding cystourethrography data to children with a positive DMSA scan. In addition, the combination of renal scarring and dilated reflux represents a highly effective discriminating criterion to differentiate those at higher risk for persistent vesicoureteral reflux. The predictive values and accuracy of this approach appear close to those obtained with staging voiding cystourethrography in all patients with a urinary tract infection but this prediction is

achieved without performing voiding cystourethrography in many patients, which results in a remarkable gain in terms of cost and dosimetry. The most important drawback of this approach is that in our study the presence of reflux in 29 patients would have been missed. However, 2 points must be considered. 1) The 55% resolution rate in these cases of reflux was significantly higher than that in cases of reflux and an abnormal DMSA scan (28%,  $p < 0.0001$ ). 2) The underestimation of reflux diagnosis could be greatly reduced if the clinical presentation before staging were also considered. Considering that 24 of the 29 children had a febrile urinary tract infection, we hypothesize that, independent of clinical presentation, children with a positive DMSA scan should undergo staging voiding cystourethrography to detect reflux and accurately grade its severity to identify those with grade III reflux. These patients are at highest risk for persistent reflux. Conversely children with a negative DMSA scan and a febrile urinary tract infection should undergo staging radionuclide cystography to detect reflux. The higher cost and radiation exposure of voiding cystourethrography are probably not justified because of the better prognosis in this group.

Some limitations of our study must be considered. The choice of voiding cystourethrography as the staging examination to detect reflux could be criticized because radionuclide cystography is known to be less expensive and to have better dosimetry<sup>16</sup> without loss in accuracy.<sup>1</sup> However, our choice was justified by the clinical need to evaluate possible urinary tract malformations and by the desire to grade reflux severity accurately. Indeed, the importance of the latter factor in children with a positive DMSA scan is a major result of our study. Another limitation is that we did not perform any kind of quantification of relative renal function on the basis of the DMSA scan, which may have allowed the recognition of initial renal damage in kidneys without overt renal scarring,<sup>17</sup> and increased the number of patients undergoing voiding cystourethrography. We also ignored other techniques, such as renal sequential scintigraphy with <sup>123</sup>Iodine hippurate or <sup>99m</sup>Tc-mercaptoacetyl triglycine, which are reported to identify effectively renal damage<sup>18,19</sup> and make indirect radionuclide cystography possible. However, this technique is known to be less accurate than direct radionuclide cystography for reflux detection and does not allow reliable reflux grading.<sup>20</sup>

In conclusion, our study confirms the central role of DMSA scintigraphy in the evaluation of patients with a urinary tract infection, and provides some evidence to support the concept of performing voiding cystourethrography only in children with an abnormal DMSA scan. This approach appears to be a cost-effective method to predict the response to medical treatment of mild to moderate primary vesicoureteral reflux.

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## EDITORIAL COMMENT

The data in this report are important. The authors have created a strong argument for always performing cystography (particularly in younger children), principally to identify vesicoureteral reflux. Whether voiding cystourethrography or radionuclide cystography is performed to detect reflux is of minimal importance. Only in adopting this algorithm is it possible to delineate the reflux negative, DMSA negative group (45.7%) from the reflux positive, DMSA negative group (27.6%). The former group can be managed expectantly or by periodic surveillance urine cultures, whereas the latter group is at risk for acute pyelonephritis and reflux nephropathy, and should receive antimicrobial prophylaxis with surveillance urine cultures until the cessation of reflux.

The relatively low incidence (3%) of nonreflux pyelonephritis (reflux negative, DMSA positive) in this series differs greatly from that in most other large series of children with febrile urinary tract infections. Indeed, 60 to 80% of infants and younger children with febrile urinary tract infections and positive DMSA scans have no evidence of vesicoureteral reflux. Of these lesions 60% resolve but 40% remain and cause irreversible renal cortical scarring. Therefore, this group of children remains at extremely high risk for episodes of acute pyelonephritis, primarily on the basis of dysfunctional voiding patterns as well as bacterial virulence (*P-fimbriated Escherichia coli*).

This report emphasizes the role of the DMSA renal scan in triaging

children at risk for infection related renal injury. Application of this philosophy helps the clinician provide consistent upper tract surveillance and protection, which in the long run aids in the preservation of renal function in the children under our care.

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#### REPLY BY AUTHORS

Performing voiding cystourethrography or radionuclide cystography is the sole method to exclude definitely vesicoureteral reflux in children with urinary tract infections. However, this study also dem-

onstrates that by limiting the evaluation of reflux to children with renal scarring or a febrile urinary tract infection, only 5 of 54 (9%) with reflux in our population would have been missed (and 4 had resolution during followup). However, approximately half of the children would not have undergone voiding cystourethrography or radionuclide cystography. Thus, the use of more selective approaches to vesicoureteral reflux evaluation, which could become necessary in a cost containment era, produces a limited and probably acceptable hazard that could be further reduced by considering other risk factors, such as young patient age or recurrent urinary tract infections. Regarding the best technique to assess vesicoureteral reflux, we believe that in high risk children with renal scarring the higher dosimetry and costs of voiding cystourethrography are warranted to obtain an accurate grading of reflux.