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Risk of Renal Scarring in Children With a First Urinary Tract Infection: A Systematic Review

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KEY WORDS
urinary tract infection, vesicoureteral reflux, renal scarring

ABBREVIATIONS
UTI—urinary tract infection
DMSA—dimercaptosuccinic acid
APN—acute pyelonephritis
VUR—vesicoureteral reflux
CI—confidence interval

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WHAT'S KNOWN ON THIS SUBJECT: The risk of renal scarring in children with a urinary tract infection has not been systematically studied.

WHAT THIS STUDY ADDS: The pooled prevalence values from this study provide a basis for an evidence-based approach to the management of children with urinary tract infections.

abstract

BACKGROUND: To our knowledge, the risk of renal scarring in children with a urinary tract infection (UTI) has not been systematically studied.

OBJECTIVE: To review the prevalence of acute and chronic renal imaging abnormalities in children after an initial UTI.

METHODS: We searched Medline and Embase for English-, French-, and Spanish-language articles using the following terms: "Technetium ^{99m}Tc dimercaptosuccinic acid (DMSA)," "DMSA," "dimercaptosuccinic," "scintigra*," "pyelonephritis," and "urinary tract infection." We included articles if they reported data on the prevalence of abnormalities on acute-phase (≤15 days) or follow-up (>5 months) DMSA renal scans in children aged 0 to 18 years after an initial UTI. Two evaluators independently reviewed data from each article.

RESULTS: Of 1533 articles found by the search strategy, 325 full-text articles were reviewed; 33 studies met all inclusion criteria. Among children with an initial episode of UTI, 57% (95% confidence interval [CI]: 50–64) had changes consistent with acute pyelonephritis on the acute-phase DMSA renal scan and 15% (95% CI: 11–18) had evidence of renal scarring on the follow-up DMSA scan. Children with vesicoureteral reflux (VUR) were significantly more likely to develop pyelonephritis (relative risk [RR]: 1.5 [95% CI: 1.1–1.9]) and renal scarring (RR: 2.6 [95% CI: 1.7–3.9]) compared with children with no VUR. Children with VUR grades III or higher were more likely to develop scarring than children with lower grades of VUR (RR: 2.1 [95% CI: 1.4–3.2]).

CONCLUSIONS: The pooled prevalence values provided from this study provide a basis for an evidence-based approach to the management of children with this frequently occurring condition. *Pediatrics* 2010;126: 000

Parents of children with urinary tract infections (UTIs) often have many questions about their child's illness: Is this a simple bladder infection or does it involve the kidneys? What are the chances of recurrent UTIs? Will there be permanent sequelae from this infection? We explore answers to these questions by way of a systematic review. Review of individual studies, especially if the studies were conducted in referral centers (which tend to have a high proportion of children with recurrent UTIs and preexisting urologic abnormalities), may overestimate adverse outcome rates. On the other hand, studies in which the diagnosis of the index UTI was questionable may lead to underestimation of adverse outcome rates. A systematic review of studies that were conducted in unselected populations and that used using stringent diagnostic criteria, could be helpful in developing evidence-based management strategies for children with UTIs.

UTI in childhood is one of the principal causes of acquired renal scarring. Renal scarring has been associated with hypertension, preeclampsia, and end-stage renal disease decades later.[1–3] Knowledge of the prevalence of renal scarring among different subgroups of children can assist clinicians in selecting children who would benefit from additional imaging. For children with a low probability of scar formation, routine imaging may not be necessary. For such children, an indiscriminate approach to imaging might lead to more harm than benefit. We systematically reviewed the prognosis of children with UTIs to allow clinicians to make evidence-based decisions when caring for children with UTI.

METHODS

We searched Medline (from 1950 to January 2009) and Embase (from 1974 to January 2009) for articles on the prevalence of dimercaptosuccinic acid (DMSA) scan abnormalities in children 0 to 18 years of age after a first UTI. The following search terms were used: "Technetium Tc 99m dimercaptosuccinic acid (DMSA)," "DMSA," "dimercaptosuccinic," "scintigra*," "pyelonephritis," and "urinary tract infection." The search was limited to children 0 to 18 years of age. This electronic search was supplemented by a review of the bibliographies of the included articles.

We included all cohort studies of children presenting with a first UTI if data on the prevalence of abnormalities on the acute-phase ($\leq$15 days) or follow-up ($>$5 months) planar DMSA renal scans were presented in the article. DMSA is the current gold standard for the detection of renal parenchymal involvement. When radiolabeled DMSA is given to patients whose tubular cell function is impaired because of acute pyelonephritis (APN) or renal scarring, the scan shows a photon-deficient area(s). In addition to photopenia, renal scarring often is characterized by a contraction and loss of volume of the renal cortex. The cutoffs selected for the timing of the DMSA were chosen on the basis of the literature: photopenia from an APN is best seen within the first 2 weeks after diagnosis,[4] and more than 90% of abnormalities noted on scans conducted more than 5 months after the index UTI are persistent.[5]

We only considered studies describing clinical cohorts of children presenting with a UTI. Studies in which UTI was not the main criterion for inclusion were excluded. For example, in 1 retrospective study,[6] imaging results of 58 patients undergoing DMSA scanning after a first UTI were described. However, the 58 children included were chosen from a larger cohort of 159 children with UTIs. The criteria used to decide which children received a DMSA scan were not described. It is possible that only children at high risk were referred for a DMSA scan. Thus, to limit bias, we excluded studies describing a cohort of children referred for a DMSA scan, not a cohort of children presenting with UTIs. By limiting the analysis to children with their initial UTI, we hoped to minimize the number of children with preexisting acquired lesions that may have artificially inflated our renal scarring rates. A positive culture was defined by the recovery of any organisms from a suprapubic specimen, 10 000 or more colony-forming units (CFU)/mL from a catheterized specimen, or 100 000 or more CFU/mL from a clean-voided or bag specimen. We excluded studies that (1) did not specify the timing of the DMSA scan, (2) included insufficient data to calculate prevalence, (3) included only a highly selected subgroup of children (eg, postsurgical patients with urologic abnormalities), or (4) included fewer than 25 patients.

The following 3 outcomes were assessed:

- prevalence of abnormalities on a DMSA scan obtained within 15 days of diagnosis;
- incidence of UTIs during the follow-up period; and
- prevalence of abnormalities on a DMSA scan obtained 5 months to 2 years after diagnosis of UTI.

Statistical Methods

Two independent reviewers (Dr Shaikh and A.E.) determined study eligibility and abstracted relevant data by using a structured data-abstraction form. Differences were resolved by discussion. Data were imported into Stata 10.1 (Stata Corp, College Station, TX), and publication bias was assessed visually by examining funnel plots and by using the Egger test. Pooled estimates were calculated by using a random-effects model with inverse-variance weighting using the DerSimonian and

Laird method.[7] All reported confidence intervals (CIs) represent 95% CIs. We conducted meta-regression with regards to the following factors: year of study publication; country; definition of an abnormal DMSA scan result; clinical setting (outpatient, inpatient); overall illness severity (mild, moderate, severe); use of antimicrobial prophylaxis; proportion of children with vesicoureteral reflux (VUR); and the proportion of children with grades IV or V VUR. To assess study quality, we examined whether enrollment was consecutive and whether the study was prospective.[8] A total quality score was not calculated. Rather, we assessed each of the study-quality indicators separately.[9] We conducted sensitivity analysis by limiting the analysis to studies in which (1) bag specimens were not used and (2) all children were febrile.

Prevalence of acute-phase DMSA scan abnormalities was calculated by dividing the proportion of children with abnormal DMSA scan results by the number of children undergoing DMSA scanning.[10] We also examined whether results were influenced by the timing of the DMSA (conducted within 72 hours of diagnosis or afterward). Finally, when data were available, we conducted stratified meta-analyses according to the presence or absence of VUR.

The incidence of reinfection was calculated by dividing the number of children with 1 or more reinfections during the follow-up period by the number of children followed and by the duration of follow-up (number per person-year). Only studies with a loss to follow-up rate of 15% or less were included in this analysis.

Prevalence of renal scarring was calculated by dividing the number of abnormal follow-up DMSA scan results by the number of follow-up scans performed. In some studies, however, a follow-up DMSA scan was conducted only for children with an abnormal acute-phase scan result. For these studies, we assumed that a child with a negative acute-phase scan would have had a normal follow-up scan result if it had been performed. This approach is supported by the literature.[5,11] Only studies with a loss-to-follow-up rate of 15% or less were included in this analysis. When data were available, we conducted stratified meta-analyses according to the presence or absence of VUR and according to the grade of VUR (grades I and II versus III, IV, and V).

Statistical heterogeneity between and within groups was measured by using the χ^2 test for heterogeneity. We used clinical judgment and results of meta-regression analysis and sensitivity analysis to identify subgroups in which pooling would be acceptable. To evaluate the weight of particular articles on the pooled estimates, we performed influence analysis. This method recalculates the pooled prevalence estimate while omitting 1 study at a time. In addition, we used cumulative meta-analysis to examine the effect of year of publication on the results.

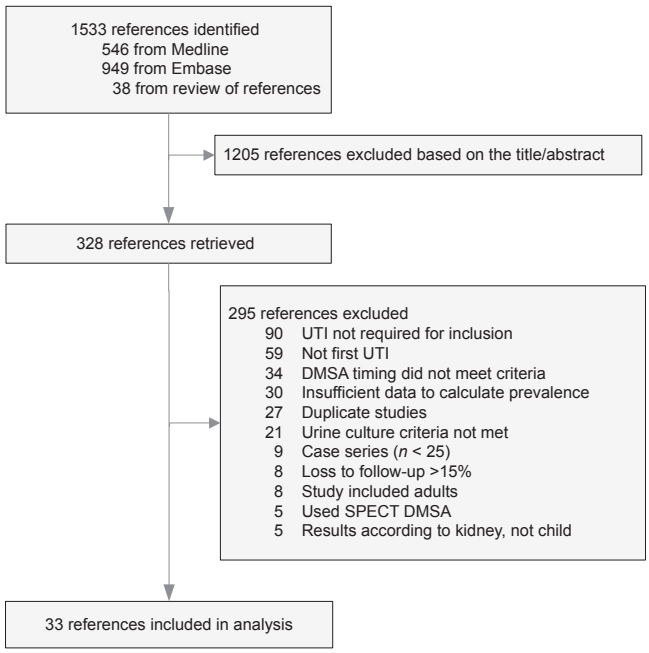

FIGURE 1
Flow diagram outlining the study-selection process. SPECT indicates single-photon emission tomography.

RESULTS

Description of Included Studies

Of 1533 articles found through our search strategy (Fig 1), we retrieved 328 for full-text review. A total of 33 articles, which included 4891 children, met all criteria for inclusion (Table 1). Most studies ($n = 26$) were conducted in an inpatient setting. In 25 studies, children with known uropathy or neurogenic bladder were excluded. Twenty studies were conducted in Europe, where most boys are uncircumcised, which may explain the relatively high proportion of boys in these studies (pooled prevalence: 41% [95% CI: 34–49]). Bag-collected urine specimens were used in 12 studies. Fever was required for inclusion in 17 studies, and an increased serum erythrocyte sedimentation rate and/or C-reactive protein level was required in 9 studies. The pooled prevalence of

TABLE 1 Characteristics of Included Studies

Study	*n*	Age Range, y	Male, %	All Febrile	Bags Used	VUR, %
Oh et al[22] (2008)	389	—	68	Yes	No	24
Sheu et al[23] (2008)	79	<10	42	Yes	No	40
Montini et al[24] (2007)	502	<7	36	No	Yes	20
Tseng et al[13] (2007)	142	<2	54	No	No	30
Lin et al[25] (2007)	114	<1	78	No	Yes	15
Agras et al[26] (2007)	105	<11	71	Yes	No	19
Karavanki et al[27] (2007)	60	<12	47	No	No	17
Chroustova et al[28] (2006)	382	0.5 to 19	30	Yes	Yes	7
Ataei et al[29] (2005)	52	5 to 12	15	Yes	No	21
Taskinen et al[30] (2005)	64	<16	55	Yes	Yes	22
Tuerlinckx et al[31] (2005)	63	<14	22	Yes	Yes	—
Zaki et al[14] (2005)	235	<10	12	Yes	No	32
Donoso et al[32] (2004)	143	<12	34	No	Yes	18
Ozcelik et al[33] (2004)	157	<11	21	Yes	—	—
Camacho et al[34] (2004)	152	<12	49	Yes	—	21
Pecile et al[35] (2004)	100	<13	31	Yes	No	18
Ditchfield et al[36] (2004)	193	<5	41	No	No	36
Imperiale et al[37] (2003)	58	<5	36	Yes	No	—
Prat et al[38] (2003)	77	<12	—	No	No	10
Fernandez-Menendez et al[39] (2003)	158	<14	41	No	Yes	22
Hoberman et al[19] (2003)	309	<2	11	Yes	No	37
Cascio et al[40] (2002)	57	<0.2	74	No	Yes	33
Levtchenko et al[41] (2001)	76	<15	—	Yes	No	—
Biggi et al[42] (2001)	101	<14	41	No	—	26
Martin Aguado et al[43] (2000)	103	<10	37	Yes	Yes	22
Fretzeyas et al[12] (2000)	83	<14	35	No	—	19
Morin et al[44] (1999)	70	<17	39	Yes	—	31
Panaretto et al[45] (1999)	290	<5	54	No	No	29
Jakobsson et al[5] (1997)	185	<10	30	No	Yes	37
Stokland et al[46] (1996)	175	<6	55	No	Yes	27
Tullus et al[47] (1994)	41	<9	—	Yes	—	31
Benador et al[48] (1994)	111	<16	55	No	Yes	—
Rosenberg et al[49] (1992)	65	—	32	No	No	—

— indicates missing data.

VUR was 24% (95% CI: 20–28). Only 2.5% (95% CI: 1.4–3.7) of the children had grades IV or V VUR.

Prevalence of Acute-Phase DMSA Scan Abnormalities Among Children With a First UTI

Overall, 57% (95% CI: 50–64) of children with an initial episode of UTI had evidence of DMSA scan abnormalities consistent with APN. As expected, the prevalence of DMSA scan abnormalities varied significantly across the 29 studies included in this analysis ($P <$ .001; in 4 studies, an acute-phase DMSA scan was not performed). Of the factors investigated through meta-regression, only the percentage of male subjects in the study was significantly associated with the prevalence of early DMSA scan abnormalities ($P =$ .045). Studies with a higher proportion of male subjects reported lower rates of early DMSA scan abnormalities. Limiting the analysis to studies in which DMSA scanning was conducted within the first 72 hours of the index UTI, to studies in which bag-collected urine specimens were not used, or to studies that included only febrile children did not alter the results significantly.

Children with VUR were 1.5 times (95% CI: 1.1–1.9) (Fig 2) more likely than children with no VUR to exhibit findings consistent with APN on the acute-phase DMSA scan (67 vs 49%; $P =$ .004). Limiting the analysis to studies in which the DMSA scan was conducted within the first 72 hours of the index UTI or to studies in which bag-collected urine specimens were not used did not change any of the inferences. Results of influence analysis showed that no single study dominated the results of this analysis. No evidence of publication bias was noted.

Prevalence of Reinfection

The overall incidence of UTI recurrence per year, from 6 studies, was 8% (95% CI: 5–11). The incidence of febrile recurrences per year, from 3 studies, was 6% (95% CI: 3–12). None of the clinical or demographic variables examined through meta-regression or sensitivity analysis (see "Methods") were associated with recurrence of UTIs.

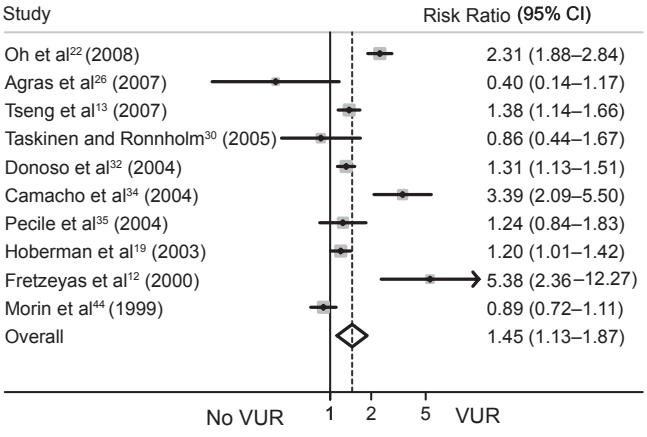

FIGURE 2
Risk of acute pyelonephritis according to the presence or absence of VUR.

Prevalence of Renal Scarring 5 Months to 2 Years After an Initial Episode of UTI

The overall prevalence of renal scarring, from 14 studies, was 18% (95% CI: 14–23). Limiting the analysis to studies in which bag-collected urine specimens were not used or to studies that included only febrile children did not alter results significantly.

Significant heterogeneity between studies ($P < .001$) was apparent. On meta-regression, year of publication was significantly associated with renal scarring ($P = .014$); and recent studies reported lower prevalence of renal scarring (Fig 3). Results of cumulative meta-analysis suggested that rates have been relatively stable at 15% (95% CI: 11–18) since 2002.

On stratified meta-analysis, both presence and grade of VUR were significantly associated with renal scarring. The prevalence of renal scarring was 2.6 times (95% CI: 1.7–3.9) (Fig 4) higher among children with VUR than among children with no VUR (41% vs 17%; $P < .001$). Renal scarring was 2.1 times (95% CI: 1.4–3.2) (Fig 5) more likely in children with grades III to V VUR than among children with grades I and II VUR (53% vs 25%; $P < .001$). Results of influence analysis showed that no single study significantly dominated these risk-ratio estimates. No evidence of publication bias was noted. Results were similar when the analysis was limited to studies that included only febrile children, to studies in which bag-collected urine specimens were not used, or to studies that were completed since 2002.

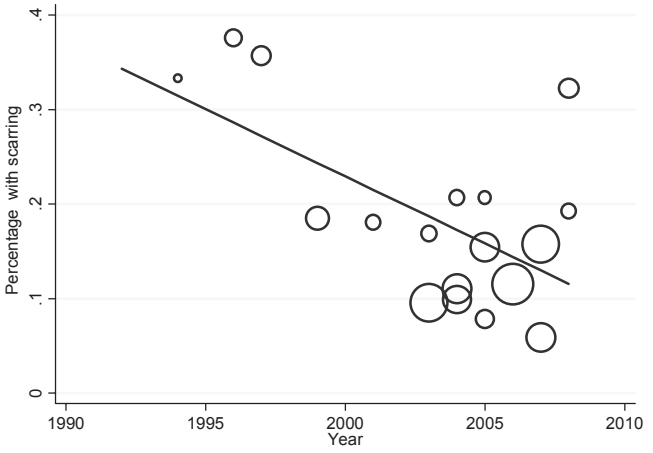

FIGURE 3
Influence of the year of publication on rates of renal scarring.

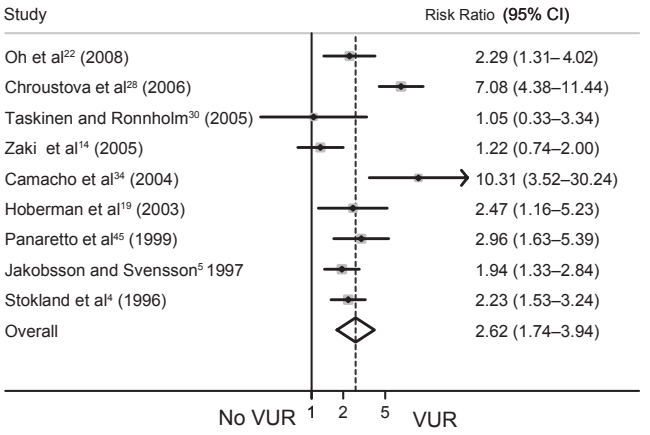

FIGURE 4
Risk of renal scarring according to the presence or absence of VUR.

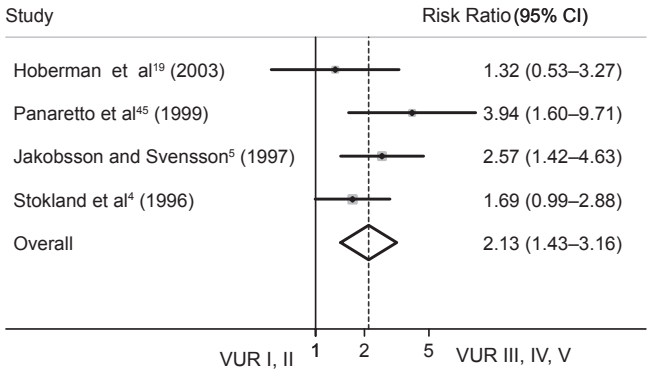

FIGURE 5
Risk of renal scarring according to the grade of VUR.

Prevalence of Preexisting Lesions and Appearance of New Lesions on DMSA Scans

The prevalence of abnormalities that were morphologically consistent with preexisting renal scarring or dysplasia on the acute-phase DMSA scan was reported from 4 studies.[11–14] Only 0.6% (95% CI: 0–1) of children had evidence of such lesions. Four other studies provided information on appearance of new renal lesions in areas that were unaffected on the acute-phase DMSA scan. Overall, 1.3% (95% CI: 0.2–2.2) of children developed new lesions. Given

the low rate of preexisting lesions and newly acquired lesions, most of the abnormalities on the follow-up DMSA scans were likely secondary to the index UTI.

DISCUSSION

This study provides a systematic overview of the prognosis of children with UTIs. Approximately 25% of children with a first UTI had VUR, 2.5% had high-grade (IV or V) VUR, and less than 1% had preexisting renal scarring and/or dysplasia. Approximately 57% of children with UTIs had DMSA scan findings consistent with APN. Nearly 8% of the children experienced at least 1 more UTI. Approximately 15% of children with a first UTI showed evidence of renal scarring 5 to 24 months later.

Although 2 previous systematic reviews examined the prognosis of children with UTIs, their focus was different.[15,16] The review by Gordon et al[16] focused on whether VUR accurately predicts DMSA abnormalities. The authors included studies irrespective of the duration between the index UTI and the DMSA scan, which may have introduced bias. The recent review by Faust et al[15] focused on answering a narrower question: What proportion of children with changes on the acute-phase DMSA scan end up with renal scarring? Because acute-phase DMSA scans are not routinely performed, this review does not address questions that most clinicians or parents are likely to pose. In addition, 10 of 16 studies used in the calculation of renal scarring rates did not meet inclusion criteria for our study.

Children with VUR had a higher risk of developing APN and renal scarring. VUR may potentiate APN by facilitating bacterial access to the kidney. Higher rates of APN may lead to higher rates of renal scarring. The observational nature of the data pooled in this study, however, does not allow us to reach any definitive conclusions regarding the causal pathways leading to APN or renal scarring. Accordingly, it is possible that the observed association between VUR and renal scarring is attributed to confounding. It has been argued, for example, that part of the association between VUR and renal scarring may be explained by the higher rates of renal dysplasia in children with VUR. With the improvements in routine prenatal ultrasonography, dysplastic kidneys are being identified with increasing frequency in some children (especially boys) with high-grade VUR. If these lesions are missed by the prenatal ultrasound, they could be confused with acquired renal scarring. However, we argue that in the studies included in this review, it is unlikely that renal dysplasia was a significant confounder. First, most of the studies explicitly excluded children with known genitourinary abnormalities. Second, the proportion of children with high-grade VUR was relatively small (2.5%). Third, the 4 studies that examined the prevalence of lesions consistent with renal dysplasia on the early DMSA scan all reported relatively low prevalence of dysplasia (0.6%). Fourth, even if some children with renal dysplasia were included in some of the studies, it is unlikely that the large differences in renal scarring rates observed between children with and without VUR (41% vs 17%) could be explained by inclusion of a few children with renal dysplasia. Finally, even if VUR and renal scarring are not causally related, these data suggest that identification of VUR can be a practical method of identifying children who are at risk for renal scarring.

Although we suggest that the identification of VUR may be important, VUR is neither necessary nor sufficient for the development of renal scarring. In fact, our analysis clearly shows that most APN and renal scarring occur in children with no VUR. Because VUR is not the only risk factor for renal scarring, a sole focus on VUR, as has been the dominant strategy for decades, is unlikely to result in large reductions in rates of renal scarring. This hypothesis is supported by recent reviews.[17]

The decision as to which tests, if any, should be conducted routinely in children with UTIs is necessarily informed by many factors. Data presented here can be used, to some extent, as a starting point. The low rate of preexisting abnormalities suggests that the yield of routine ultrasonography in children who present with an initial UTI and have no known genitourinary abnormalities on prenatal ultrasonography is likely to be low. This is in agreement with recent literature: ultrasonography modified management in less than 1% of the cases.[18–20] Although routine voiding cystourethrograms (VCUGs) are accurate at identifying children with VUR, they are expensive and invasive and miss a significant proportion of children who are at risk for renal scarring. Alternatively, an early DMSA scan may be used as a screening test (the "top-down" approach). In addition to identifying almost all children with significant VUR, it also can identify most children who are likely to scar.[13,21] Although children with a negative acute-phase DMSA scan result are unlikely to develop to a scar, like VCUGs, DMSA scans are expensive, invasive, and expose children to radiation. Furthermore, it is unclear how to best manage the large numbers of children with a positive acute-phase DMSA scan result (57% of all children with UTIs), most of whom (85%) will not scar. Additional research is warranted to help determine management strategies for children with UTIs.

The prevalence of renal scarring seems to be decreasing over time. Perhaps widespread availability of prena-

tal ultrasonography has led to early identification of children at high risk (eg, children with high-grade VUR and renal dysplasia). Inclusion of these children in earlier studies may have led to higher previously reported rates of renal scarring.

Our analysis has several limitations. First, differences in how data for subgroups were reported in the original studies limited our ability to pool data across studies. For example, we could not calculate the prevalence of renal scarring among children with grades IV and V VUR (high-grade VUR), because most of the studies only reported data for the subgroup of children with grades III to V VUR. Second, the heterogeneity among studies may be considered a limitation. Much of the heterogeneity, however, was likely because of the differences in the severity of illness of the patients included in the different studies. We explored reasons for these differences and presented stratified data for less heterogeneous subgroups of patients whenever possible. In addition, by limiting the review to well-defined cohorts of children presenting with an initial episode of UTI in whom DMSA scans were conducted systematically, by using rigorous definitions for the diagnosis of UTIs, and by careful attention to the timing of the DMSA scan, we believe that this systematic review provides a valuable overview of the prognosis of children with UTIs.

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