Original Investigation

Identification of Children and Adolescents at Risk for Renal Scarring After a First Urinary Tract Infection
A Meta-analysis With Individual Patient Data

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IMPORTANCE No studies have systematically examined the accuracy of clinical, laboratory, and imaging variables in detecting renal scarring in children and adolescents with a first urinary tract infection.

OBJECTIVES To identify independent prognostic factors for the development of renal scarring and to combine these factors in prediction models that could be useful in clinical practice.

DATA SOURCES MEDLINE and EMBASE.

STUDY SELECTION We included patients aged 0 to 18 years with a first urinary tract infection who underwent follow-up renal scanning with technetium Tc 99m succimer at least 5 months later.

DATA EXTRACTION AND SYNTHESIS We pooled individual patient data from 9 cohort studies.

MAIN OUTCOMES AND MEASURES We examined the association between predictor variables assessed at the time of the first urinary tract infection and the development of renal scarring. Renal scarring was defined by the presence of photopenia on the renal scan. We assessed the following 3 models: clinical (demographic information, fever, and etiologic organism) and ultrasonographic findings (model 1); model 1 plus serum levels of inflammatory markers (model 2); and model 2 plus voiding cystourethrogram findings (model 3).

RESULTS Of the 1280 included participants, 199 (15.5%) had renal scarring. A temperature of at least 39°C, an etiologic organism other than *Escherichia coli*, an abnormal ultrasonographic finding, polymorphonuclear cell count of greater than 60%, C-reactive protein level of greater than 40 mg/L, and presence of vesicoureteral reflux were all associated with the development of renal scars ($P \leq .01$ for all). Although the presence of grade IV or V vesicoureteral reflux was the strongest predictor of renal scarring, this degree of reflux was present in only 4.1% of patients. The overall predictive ability of model 1 with 3 variables (temperature, ultrasonographic findings, and etiologic organism) was only 3% to 5% less than the predictive ability of models requiring a blood draw and/or a voiding cystourethrogram. Patients with a model 1 score of 2 or more (21.7% of the sample) represent a particularly high-risk group in whom the risk for renal scarring was 30.7%. At this cutoff, model 1 identified 44.9% of patients with eventual renal scarring.

CONCLUSIONS AND RELEVANCE Children and adolescents with an abnormal renal ultrasonographic finding or with a combination of high fever (≥39°C) and an etiologic organism other than *E coli* are at high risk for the development of renal scarring.

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Urinary tract infection (UTI) is the most common serious bacterial infection in young children. In approximately 10% to 15% of cases, UTI leads to permanent renal scarring.[1] Substantial scarring leading to a reduction in kidney function has been associated with hypertension, preeclampsia, and end-stage renal disease decades later.[2-6] The exact incidence of end-stage renal disease attributable to renal scarring secondary to UTIs during childhood remains uncertain but appears to be rare.[7]

Our first objective was to identify independent prognostic factors linked to the development of renal scarring and to determine the importance of these factors relative to each other. Conflicting data, mostly from small studies, exist regarding prognostic factors for renal scarring. For example, age, delay in treatment, male sex, and presence of fever have all been suggested as important prognostic factors for renal scarring in some studies[8-10] but not in others.[11-18] Furthermore, little data exist regarding the relative importance of these factors. For example, although the association between vesicoureteral reflux (VUR) and renal scarring has been a consistent finding in the literature,[1] the magnitude of the association between specific grades of VUR and renal scarring is less clear.

Our second objective was to develop an easily implementable clinical prediction model that could be used to identify children at risk for renal scarring. Such identification is important because children with scarring may benefit from closer follow-up and/or more aggressive management. In children with a very low probability of scar formation, routine imaging may result in more harm than benefit. Without a method of stratifying risk, all children with UTI are necessarily treated in the same manner. Uniform treatment may lead to overtreatment of low-risk children and undertreatment of high-risk children.

Because renal scarring is uncommon, most individual studies are too small to allow meaningful multivariate modeling.[19] Accordingly, we conducted a meta-analysis using individual patient data to address the questions posed in this study.

Methods

Design

Our meta-analysis used individual patient data extracted from cohort studies of children and adolescents (aged 0-18 years; hereinafter referred to as children for purposes of this study) with a first UTI who underwent renal scanning with technetium Tc 99m (^{99m}Tc) succimer (dimercaptosuccinic acid) at least 5 months after the index episode. Approval by an ethics committee was not sought because this systematic review consists of previously published studies.

Search Methods for Identification of Studies

We searched MEDLINE (1950 through September 27, 2011) and EMBASE (1974 through September 27, 2011) using Medical Subject Headings terms (*technetium, Tc 99m dimercaptosuccinic acid,* and *urinary tract infection*) and text words (*DMSA, dimercaptosuccinic, scintigra*, pyelonephritis, renal, kidney, pyelonephritis, urinary tract infection*, vesicoureteral, nephropath*, scar*, damage*, defect*, uptake, photopenia,* and *contour* lesion photopeni**). The search was limited to studies of children aged 0 to 18 years. Two authors (N.S. and T.S.) independently screened the titles and abstracts. This electronic search was supplemented by review of the bibliographies of the articles included.

Inclusion Criteria

We included studies with positive findings of a urine culture, defined by the recovery of any organisms from a suprapubic specimen, more than 10 000 colony-forming units/mL from a catheter-collected specimen, or more than 100 000 colony-forming units/mL from a clean-voided or a bag specimen. Studies that included only neonates (<2 months) were excluded because the causes of scarring are likely different in this population.

Exclusion Criteria

We excluded studies in which UTI was not the main criterion for inclusion (ie, studies that included only a small, highly selected subgroup of children with UTI). Inclusion of such studies may have biased our results. For example, we excluded studies describing cohorts of children referred for ^{99m}Tc succimer scanning because the reasons for referral could be related to the predictors being evaluated. We also excluded studies describing a highly selected subgroup of patients such as postoperative patients with urologic abnormalities, children with VUR, and studies with more than 30% loss to or unavailability for follow-up or with fewer than 25 participants. We limited the analysis to children and adolescents with a first-diagnosed UTI in the hopes of minimizing the number of patients with preexisting acquired lesions.

Methods of Contacting Authors of Included Studies

We used electronic mail as the main method of contacting study authors. If the corresponding author did not respond, we contacted the coauthors. If this attempt was unsuccessful, we used the telephone and regular mail to contact the authors.

Predictors

The following factors were considered for inclusion in the prediction model: age, sex, measured temperature at the time of diagnosis, duration of fever before presentation, grade of VUR (defined by the guidelines of the International Reflux Study in Children),[10] the organism isolated from culture (*Escherichia coli* vs other), results of renal ultrasonography (normal vs any abnormality), and levels of inflammatory markers (C-reactive protein, erythrocyte sedimentation rate, procalcitonin, and polymorphonuclear cells). In addition to data on the primary predictors, the year of enrollment and method of urine collection (bag vs other) were also gathered. The use of antimicrobial prophylaxis for VUR, recurrence of UTI, and evidence of pyelonephritis on an early ^{99m}Tc succimer scan were not included in the models because these variables are not known at the time of diagnosis of a first UTI.

Outcome

The presence or absence of renal scarring, defined as any photopenia with or without a change in the renal contour, on a planar ^{99m}Tc succimer scan obtained at least 5 months after the ini-

tial UTI was the primary outcome measure. Scarring is most commonly manifested by the presence of wedge-shaped photon-deficient areas on the scan. In some studies, an abnormal finding on the renal scan was defined by the presence of photopenia, whereas in others it was defined by the presence of photopenia plus a change in contour. Because most children with photopenia on a late ^{99m}Tc succimer scan are also likely to have changes in renal contour, we felt justified in combining studies using either definition. In some of the included studies, a late renal scan was not performed if results of an early scan were shown to be normal. Because children who have normal findings on an early ^{99m}Tc succimer scan will invariably have normal findings on a late scan,[20] for the purpose of this study, these children were presumed to have a normal outcome on the renal scan. We chose 5 months as the cutoff because more than 90% of abnormalities noted on scans conducted at least 5 months after the index UTI are persistent.[21] Because of the lower specificity of the ^{99m}Tc succimer scan when using single-photon emission computed tomography,[22] studies using this method were excluded.

Statistical Analysis

Our goals were to identify variables predictive of renal scarring in univariate analysis and combine them into multivariate models. We developed and compared the predictive ability of 3 increasingly invasive strategies for evaluating a first-diagnosed UTI in children. We first examined how well a model that included only information gathered routinely in clinical practice (history, examination results, and renal ultrasonographic findings) could predict scarring (model 1). Next, we determined whether the addition of serum inflammatory markers would improve the predictive ability of model 1 (model 2). Finally, we determined whether the addition of information about the presence and degree of VUR would improve model 2 (model 3).

We combined all individual participant data into a single meta-analytic logistic regression model (ie, a 1-stage approach).[23] To account for heterogeneity between studies, all models included a categorical variable termed *study* (with 9 categories, 1 for each of the 9 studies included). Predictors associated with the outcome ($P < .25$)[24] were included in multivariate analysis. Backward selection[25] was used in developing the initial models. We tested the impact of dropping variables using the likelihood ratio test statistic. We also compared the β coefficients in the nested models; a change of 10% was considered significant.[26] Finally, we dichotomized continuous variables that remained in the model based on clinically established cutoffs (temperature, ≥39°C[27,28]; C-reactive protein level, >40 mg/L[29] [to convert to nanomoles per liter, multiply by 9.524]). For each model, we developed a risk score[30] by assigning a point score for the variables in the model. We assigned a score of 1 to the variable with the lowest regression coefficient. The score for the remaining variables was obtained by dividing their regression coefficient by the coefficient of the variable with the lowest regression coefficient and then rounding to the nearest integer. The total score for a given model was calculated by adding the scores for each of the predictors included in that model. For each model, we then calculated the test characteristics (sensitivity, specificity, positive and negative predictive values, and likelihood ratios) for all possible scores. The overall predictive ability of the model was estimated by the area under the receiver operating characteristic curve. Goodness of fit was assessed using the Hosmer-Lemeshow test. Internal validity of each model was assessed by performing the bootstrap procedure (1000 iterations).

Subgroup Analysis

We performed subgroup analyses with respect to dysplasia, the method of urine collection, and age. Congenital renal dysplasia may account for some of the observed lesions. If many children with dysplasia were included, then variables associated with dysplasia instead of acquired scarring might have been selected for the models. However, all but 1 study explicitly excluded children with known genitourinary anomalies. Furthermore, because high-quality prenatal ultrasonography has been routine in most centers during the last 15 years, many patients with significant congenital dysplasia would have been identified and thus excluded from these studies. In the subgroup analysis, we excluded children with potential dysplasia (ie, children enrolled before 1997 or children in the 1 study that may have included patients with preexisting genitourinary anomalies).

Because urine specimens collected using perineal bags are often contaminated, we examined data in the subgroup of children in whom bags were not used. Finally, because the pathophysiological features of UTI and/or scarring may be different in neonates, we conducted an analysis excluding all children younger than 2 months.

Results

Literature Search and Included Studies

Our search strategy yielded 1833 articles, of which 23 met our inclusion criteria (eFigure in the Supplement).[20,31-52] A list of all excluded studies is available from the authors on request. The authors of 9 of these articles provided data for analysis.[20,33,35,38-40,42,48,49] The authors of the other 14 articles* did not respond to requests for data or could not provide data (eTable in the Supplement). Of the 14 excluded articles, 3 did not provide data regarding the number of children with renal scarring. The proportion of children with renal scarring in the remaining 11 excluded articles was similar to that of the included articles ($P = .19$). The characteristics of the 9 included studies are summarized in **Table 1**. Six studies[33,35,38,42,48,49] were observational and 3 studies[20,39,40] were randomized trials. The mean number of children in each study was 171. Of the 1479 children eligible for evaluation, 1280 had data on our primary outcome, late ^{99m}Tc succimer scanning.

Participant Characteristics

Demographic, laboratory, and imaging characteristics of these 1280 children are presented in **Table 2**; 64.6% were girls; 82.7% were younger than 24 months; 48.1% had a temperature of at least 39°C; and 8.4% were infected with an organism other than *E coli*. The renal ultrasonographic finding was abnormal in 19.9% of children. Any VUR and VUR of grades IV to V was present in 29.1% and 4.1% of children,

*References 31, 32, 34, 36, 37, 41, 43-47, 50-52

Table 1. Characteristics of the 9 Included Studies

Source	No. of Children	Location	Age Range, mo	Setting	Fever Requirement	Prospective Study	Bag Collection	Excluded Known Renal Abnormalities
Bressan et al,[33] 2009	72	Europe	0.2-36	Outpatient	Yes	Yes	Yes	Yes
Craig et al,[35] 1998	304	Australia	0-60	Inpatient/outpatient	No	Yes	Yes	Yes
Hoberman et al,[20] 1999	309	United States	1-24	Inpatient/outpatient	Yes	Yes	No	Yes
Kotoula et al,[38] 2009	57	Europe	2-108	Inpatient	No	Yes	Yes	Not stated
Levtchenko et al,[39] 2001	80[a]	Europe	1.5-180	Inpatient	Yes	Yes	Yes	Yes
Montini et al,[40] 2007	450[b]	Europe	1-84	Inpatient	No	Yes	Yes	Yes
Prat et al,[42] 2003	77	Europe	1-144	Outpatient	Yes	Yes	No	Yes
Taskinen and Rönnholm,[48] 2005	62[c]	Europe	0.2-186	Inpatient	Yes	Yes	Yes	Yes
Tuerlinckx et al,[49] 2005	68[d]	Europe	1-168	Inpatient	Yes	Yes	Yes	Yes

[a] Includes only children with a first-diagnosed urinary tract infection (UTI); 9 children with missing late technetium Tc 99m succimer scans were excluded in the original study but included here.

[b] Includes only eligible children with a UTI.

[c] Three children with genitourinary anomalies were excluded; 1 child with a low C-reactive protein level was excluded in the original study but included here.

[d] Includes only children with a first-diagnosed UTI; 17 children with missing procalcitonin levels were excluded in the original study but included here.

Table 2. Predictors of Renal Scarring in 1280 Children With a First-Diagnosed UTI

Characteristic[a]	No. of Patients[b]	No (%) With Scarring	OR for Scarring (95% CI)[c]	*P* Value
Age, mo				
<24	1057	142 (13.4)	0.53 (0.36-0.78)	<.01
≥24	221	57 (25.8)	1 [Reference]	
Sex				
Female	827	135 (16.3)	1.33 (0.95-1.88)	.10
Male	452	64 (14.2)	1 [Reference]	
Fever ≥39°C[33,39,48]				
Yes	509	97 (19.1)	2.29 (1.57-3.34)	<.01
No	549	59 (10.7)	1 [Reference]	
Fever duration >24 h[35,38,39,42]				
Yes	376	57 (15.2)	1.11 (0.72-1.71)	.64
No	682	70 (10.3)	1 [Reference]	
PMN count >60%[33,42,48]				
Yes	363	83 (22.9)	1.91 (1.30-2.82)	<.01
No	494	58 (11.7)	1 [Reference]	
CRP level >40 mg/L[35]				
Yes	512	116 (22.7)	3.01 (1.97-4.57)	<.01
No	451	47 (10.4)	1 [Reference]	
Organism other than *Escherichia coli*[48]				
Yes	101	27 (26.7)	2.20 (1.34-3.62)	<.01
No	1105	159 (14.4)	1 [Reference]	
Abnormal ultrasonographic finding[39,48]				
Yes	224	71 (31.7)	3.79 (2.61-5.49)	<.01
No	902	100 (11.1)	1 [Reference]	
VUR grade				
None	884	98 (11.1)	1 [Reference]	NA
I and II	200	35 (17.5)	1.82 (1.18-2.81)	.01
III	112	30 (26.8)	3.56 (2.18-5.82)	<.01
IV and V	51	35 (68.6)	22.48 (11.29-44.77)	<.01

Abbreviations: CRP, C-reactive protein; NA, not applicable; OR, odds ratio; PMN, polymorphonuclear cell; UTI, urinary tract infection; VUR, vesicoureteral reflux.

SI conversion factor: To convert CRP to nanomoles per liter, multiply by 9.524.

[a] Studies in which the given characteristic was not evaluated are cited by source.

[b] Numbers of children eligible for evaluation vary for each characteristic owing to missing data (number missing = 1280 − number evaluable).

[c] Odds ratios are calculated from a meta-analytic logistic regression model that included a categorical variable termed *study*.

respectively. Renal scarring was present in 199 patients (15.5%), and 100 of these (50.3%) had VUR. The proportion of children with renal scarring increased with the increasing grade of VUR (from 98 of 884 [11.1%] in children with no VUR to 35 of 51 [68.6%] in children with grade IV or V VUR).

Risk Factors for Renal Scarring

The following factors were associated with renal scarring (listed in descending order of importance): grade IV or V VUR, abnormal ultrasonographic finding, grade III VUR, C-reactive protein level of more than 40 mg/L, temperature

Table 3. Comparison of 3 Multivariate Models in Predicting Renal Scarring[a]

	Model 1[b]			Model 2[c]			Model 3[d]		
Predictor Variable	OR (95% CI)	*P* Value	Points[e]	OR (95% CI)	*P* Value	Points[e]	OR (95% CI)	*P* Value	Points[e]
Temperature ≥39°C	2.30 (1.56-3.40)	<.001	1	1.81 (1.08-3.03)	.03	1	1.78 (1.05-3.03)	.03	1
Organism other than *Escherichia coli*	2.31 (1.36-3.94)	.002	1	2.33 (1.14-4.76)	.02	1	NA	NA	NA
Abnormal ultrasonographic finding	3.61 (2.42-5.37)	<.001	2	2.13 (1.22-3.72)	.01	1	NA	NA	NA
Female sex	NA	NA	NA				1.89 (1.03-3.48)	.04	1
PMN count >60%	NA	NA	NA	2.17 (1.33-3.56)	<.01	1	2.34 (1.40-3.93)	<.01	1
CRP level >40 mg/L	NA	NA	NA	2.66 (1.57-4.52)	<.01	2	2.65 (1.53-4.59)	<.01	2
VUR grade[f]									
I and II	NA	NA	NA	NA	NA	NA	NA	NA	NA
III	NA	NA	NA	NA	NA	NA	2.90 (1.48-5.71)	<.01	2
IV and V	NA	NA	NA	NA	NA	NA	23.70 (6.56-85.63)	<.01	6

Abbreviations: CRP, C-reactive protein; NA, not applicable; OR, odds ratio; PMN, polymorphonuclear cell count; VUR, vesicoureteral reflux.

SI conversion factor: To convert CRP to nanomoles per liter, multiply by 9.524.

[a] Models are described in the Statistical Analysis subsection of the Methods section.

[b] For model 1, the Hosmer-Lemeshow goodness of fit χ^2 is 0.83; the area under the receiver operating characteristic (ROC) curve is 0.69 (95% CI, 0.65-0.73).

[c] For model 2, the Hosmer-Lemeshow goodness of fit χ^2 is 0.46; the area under the ROC curve is 0.72 (95% CI, 0.67-0.77).

[d] For model 3, the Hosmer-Lemeshow goodness of fit χ^2 is 0.17; the area under the ROC curve is 0.74 (95% CI, 0.69-0.79).

[e] Ranges of points are 0 to 4, 0 to 6, and 0 to 13 for models 1, 2, and 3, respectively.

[f] Categories are mutually exclusive for scoring purposes.

of at least 39°C, organism other than *E coli*, polymorphonuclear cell count of more than 60%, and grade I or II VUR (Table 2). The odds of renal scarring in children with grade IV or V VUR were 22 times higher than in children with no VUR. In contrast, the odds of renal scarring in children with grade I or II VUR were only marginally higher than in children with no VUR. Age, sex, and duration of fever before presentation were not significantly associated with renal scarring. The prevalence of renal scarring in boys younger than 6 months (14.6%) was not significantly different from the prevalence in the sample as a whole ($P = .48$). Because of the large amount of missing data, procalcitonin levels and erythrocyte sedimentation rate were not included in the models. In addition, because some variables were not measured in some of the studies, imputation was not possible.

Models for Renal Scarring

Table 3 summarizes the predictive abilities of the 3 multivariate models. Model 1 included abnormal ultrasonographic findings, an etiologic organism other than *E coli*, and fever of at least 39°C as predictor variables. In addition to the 3 variables in model 1, model 2 also included C-reactive protein level of more than 40 mg/L and polymorphonuclear cell count of more than 60%. In model 3, the presence of grade IV or V VUR was by far the variable most strongly associated with renal scarring. Having an organism other than *E coli* or an abnormal ultrasonographic finding was no longer significant in model 3. The areas under the receiver operating characteristic curve for models 1, 2, and 3 were 0.69, 0.72, and 0.74, respectively. Thus, information about serum biomarker levels and voiding cystourethrogram (VCUG) only increased the predictive ability over model 1 by 3 and 5 percentage points, respectively. The use of dichotomous variables in the models (eg, using temperature ≥39°C instead of temperature as a continuous variable) was accompanied by negligible (<1%) reductions in the predictive ability of the models. Owing to missing data in 1 or more of the variables, models 1, 2, and 3 included 1053, 632, and 626 participants, respectively.

The accuracy of each model at predicting renal scarring at selected cut points is presented in **Table 4**. A model 1 score of 2 or more had a sensitivity and specificity of 44.9% and 82.4%, respectively. A model 1 score of 2 or more also would have detected 68.2% of those patients with grade IV or V VUR. Model 1 was very robust; the variables chosen for the model and their respective point scores were identical in the subgroups examined. Subgroup analysis for the 2 other models was limited because of small sample size, but in general these models appeared to be less robust than model 1. Specifically, for model 2, limiting by age or by year of enrollment affected the model little, but limiting by method of collection resulted in a parsimonious model (abnormal ultrasonographic results and not *E coli* dropped out). For model 3, limiting by age or by year of enrollment resulted in the sex variable dropping out, and limiting by method of collection resulted in changes in the point scores (β coefficients) for some of the variables. For all 3 models, the mean area under the receiver operating characteristic curve obtained via bootstrapping was very similar to the values reported above (difference of <1.5%).

Discussion

In this study of an individual patient data meta-analysis of 1280 children with a first UTI from 9 studies, we developed a prediction model that provides clinicians with a method of identifying the subgroup of children with a first UTI who are at risk for renal scarring. Our data show that children with a model 1 (clinical information and ultrasonographic finding) score of 0 or 1 (78.3% of the sample) are at low or intermediate risk for scarring from their first-diagnosed UTI. These children have nor-

Table 4. Comparison of the Accuracy of the 3 Models in Predicting Renal Scarring

Model, Score[a]	Patients With Score, %	Sensitivity, %	Specificity, %	PPV, %[b]	NPV, %[b]	Positive LR	Negative LR
1							
≥1	63.0	84.6	40.8	19.9	93.8	1.43	0.38
≥2	21.7	44.9	82.4	30.7	89.6	2.55	0.67
2							
≥2	62.2	87.0	42.5	22.1	94.6	1.51	0.31
≥4	19.9	43.0	84.4	34.1	88.7	2.76	0.68
3							
≥3	55.8	82.0	49.2	23.5	93.5	1.62	0.37
≥5	18.1	49.0	87.8	43.4	90.1	4.03	0.58

Abbreviations: LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

[a] Models are described in the Statistical Analysis subsection of the Methods section.

[b] Calculated using observed prevalence for renal scarring (15.6%).

Table 5. Risk for Renal Scarring by Model 1 Score[a]

Score	No. of Patients	Patients With Scarring, No. (%)	Patients With VUR Grade IV or V, No./Total No. (%)	Risk
0	390	24 (6.2)	5/384 (1.3)	Very low
1	435	62 (14.3)	9/423 (2.1)	Intermediate
≥2	228	70 (30.7)	30/228 (13.2)	High
Total	**1053**[a]	**156** (14.8)	**44/1035** (4.3)	Baseline

Abbreviation: VUR, vesicoureteral reflux.

[a] Includes only the 1053 children in model 1.

mal renal ultrasonographic findings and no more than 1 of the following: temperature of at least 39°C or an organism other than *E coli*. Their risk for scarring (6.2% in children with a score of 0 and 14.3% in children with a score of 1) is no higher than the baseline risk (15.6%). Children with a model 1 score of 2 or more (21.7% of the sample) represent a high-risk group in whom the risk for renal scarring is twice the baseline risk (**Table 5**). These children (1) have an abnormal renal ultrasonographic finding or (2) have a temperature of at least 39°C and an etiologic organism other than *E coli*. Because approximately one-third of children with a model 1 score of 2 or more have renal scarring, this group merits close clinical follow-up and consideration for a late ^{99m}Tc succimer scan. However, the potential merits of obtaining a late scan clearly need to be explored in future prospective studies before the scan can be recommended.

We were also able to determine the relative importance of various independent predictors of renal scarring in patients with first-diagnosed UTI. Current UTI guidelines recommend performing renal ultrasonography for some children with a first-diagnosed UTI but limit the recommendation to young children[53,54] or to children with an atypical UTI.[55,56] Our findings suggest that renal ultrasonography is an important predictor of renal scarring regardless of age, sex, and clinical appearance. Furthermore, whereas the guidelines from the National Institute for Health and Care Excellence in the United Kingdom[55] identify infection with an organism other than *E coli* as an important risk factor, the guidelines from the American Academy of Pediatrics in the United States[54] do not. Our data, which are consistent with those of previous studies,[57,58] suggest that infection with organisms other than *E coli* increases the risk for renal scarring.

As expected, the presence of grade IV or V VUR was by far the most important risk factor for the development of scarring. This degree of VUR, however, was only present in 4.1% of children. Thus, although our data confirm the importance of high-grade VUR as a risk factor for renal scarring, they do not resolve the difficult question of how to identify this important but small subgroup of children without subjecting all children to a VCUG.

We also identified several factors that were not associated with scarring. In contrast to some previous studies,[8-10,59,60] most of which were completed in the 1980s, younger age and male sex were not associated with an increased risk for renal scarring. In fact, we found that older age and female sex were weak predictors of renal scarring. This discrepancy may be related to higher likelihood of inclusion of children with unrecognized dysplasia in some of these previous studies. Similar to recent reports, we did not find an association between fever duration of more than 24 hours before presentation and renal scarring.[61,62] However, this finding does not mean that timely diagnosis and treatment of UTI are unimportant. Early diagnosis of UTI may prevent pain and discomfort, unnecessary diagnostic workup for other conditions, and progression from cystitis to pyelonephritis.[61]

Our meta-analysis has several limitations. First, not all eligible studies were included. However, we found no difference between studies that were included and those that were excluded with regard to the proportion with renal scarring. Second, 13.5% of children had no data on the primary outcome. Third, we were limited by the complete absence of some of our predictor variables from some of the studies. This limitation was particularly true for the serum inflammatory markers and VCUG tests. Because children who underwent blood collection or VCUG may have been different from children who did not undergo these procedures, the calculated sensitivity and specificity values for models 2 and 3 may be inaccurate. Fourth, we did not have detailed information regarding the imaging tests; for example, most studies reported the ultrasonographic findings as normal or abnormal. Fifth, the models presented herein need to be validated in

an independent data set. Finally, although our sample likely included some children with congenital renal dysplasia, this reflects the spectrum of renal parenchymal abnormalities observed in practice. Furthermore, because identification of children with dysplasia could be potentially helpful, detection of such children using the prediction rules presented could be considered an advantage rather than a limitation.

We chose scarring and not VUR as our primary outcome variable because scarring is more likely to affect renal function. In addition, selecting scarring as the primary outcome allowed us to show the degree to which various grades of VUR affect long-term renal scarring.

Conclusions

To our knowledge, this study is the first to combine individual patient data from multiple studies (9 studies including 1280 children) to identify variables predictive of renal scarring. Because we included studies that were conducted at a time when VCUG was routinely recommended, we were able to assess the additional predictive ability of 3 increasingly invasive models. We found that using a simple model with only 3 clinical variables provided a reasonable screening strategy. The 21.7% of children identified as high risk through this strategy would include 44.9% of all children who scar. Early identification of children at risk for renal scarring using the prediction rules developed in this study could help clinicians deliver specific treatment and follow-up for this small subgroup in the future. One small study suggested that treatment with corticosteroids in children with febrile UTI may decrease renal scarring.[63] This conclusion is being further evaluated in a larger trial.[64] In addition, more aggressive follow-up (eg, antibiotic prophylaxis, imaging, and timely treatment of recurrent UTI) may prevent further renal damage. Although little evidence exists that supports the efficacy of these measures at this time, several ongoing studies promise to provide useful data in the near future.[65] We are hopeful that data from this study, along with emerging data from longitudinal and biomarker studies, can be used to develop individualized care plans for children with a first UTI.

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