Identifying Children with Vesicoureteral Reflux: A Comparison of 2 Approaches

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Purpose: Various screening approaches have been proposed to identify the subgroup of children with urinary tract infection who have vesicoureteral reflux. However, few studies have compared the sensitivity of screening approaches in a representative population of young children. We compared the sensitivities of the top-down (^{99m}technetium dimercaptosuccinic acid renal scan to screen) and biomarker based (C-reactive protein level at presentation) approaches in identifying children with vesicoureteral reflux.

Materials and Methods: We calculated the sensitivity of the 2 screening approaches in detecting vesicoureteral reflux and subsequently high grade (III or greater) vesicoureteral reflux in children.

Results: The top-down and C-reactive protein based approaches missed 33% and 29% of cases of high grade vesicoureteral reflux, respectively.

Conclusions: The sensitivity of the top-down approach for detecting high grade vesicoureteral reflux was lower than previously reported. Further study of novel methods to identify children at risk for renal scarring is warranted.

Key Words: urinary tract infections, pyelonephritis, vesico-ureteral reflux

Abbreviations and Acronyms

CRP = C-reactive protein

DMSA = ^{99m}technetium dimercaptosuccinic acid

ESR = erythrocyte sedimentation rate

UTI = urinary tract infection

VCUG = voiding cystourethrogram

VUR = vesicoureteral reflux

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ALTHOUGH prevention of permanent renal scarring represents the ultimate goal of any management strategy for childhood urinary tract infection, controversy exists regarding how this goal should be achieved. Because vesicoureteral reflux increases the risk of renal scarring,[1] the prevailing management approach in the United States has been the bottom-up approach, which has focused on identifying and treating the subset of children with vesicoureteral reflux (see figure). Children younger than 2 years with urinary tract infection undergo voiding cystourethrography to determine the presence and severity of vesicoureteral reflux, which then is managed by antimicrobial prophylaxis, surgery or both.[2]

Acute pyelonephritis, rather than VUR, is a prerequisite for development of scarring. Accordingly, identification of children with upper tract involvement has been suggested as a better approach. Recent studies suggest that children with UTI who have renal involvement are at increased risk for febrile reinfection and new scarring,[3–7] which has led some experts to advocate routine performance of DMSA renal scan early after a UTI episode as the first-line imaging test in children with UTI.[8,9] VCUG is then reserved for children with evidence of acute pyelonephritis on the acute phase DMSA scan. This top-down approach has been recommended based on earlier reports of the high sensitivity of DMSA scanning in detecting high grade VUR (see figure).

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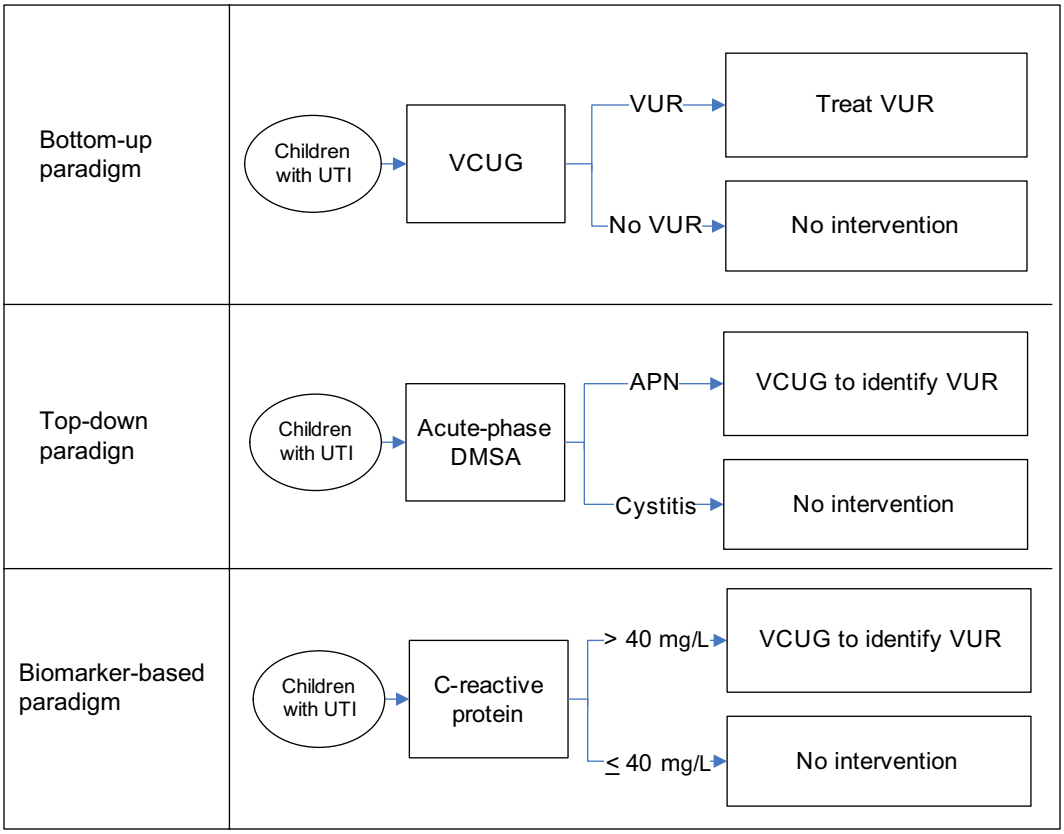

Proposed approaches for management of febrile urinary tract infection in children. *APN,* acute pyelonephritis.

An alternative screening approach would include assessment of biomarker levels (laboratory tests) at presentation to determine the need for VCUG. In this 2-step approach the level of a biomarker, not DMSA scanning, would be used to identify children likely to have acute pyelonephritis (see figure). We used data from a cohort of children we previously studied to compare the sensitivity of the top-down approach and a biomarker based approach in detecting VUR.

METHODS

We used data collected in a randomized controlled trial comparing oral vs intravenous antibiotic administration in 309 children 1 to 24 months old with a first febrile UTI.[10] In that study, which received institutional review board approval, we followed a large representative cohort of children with UTI who were carefully characterized (comprehensive imaging and laboratory evaluation at baseline). Children with previously diagnosed abnormalities of the urinary tract were excluded. All urine was collected by bladder catheterization, and a positive culture was defined by the presence of a single pathogen at 50,000 cfu/ml or greater. At diagnosis we measured total white blood cell count, bands (immature neutrophils), polymorphonuclear cell count, CRP and ESR. Acute pyelonephritis was defined by the presence of photopenia on DMSA scan obtained within 7 days of diagnosis of urinary infection, and vesicoureteral reflux was diagnosed using contrast VCUG obtained 4 to 6 weeks after diagnosis of urinary infection.[11,12]

We calculated the sensitivity of the top-down and biomarker based approaches in identifying VUR and subsequently high grade (III or greater) VUR in children. As a measure of performance for each screening strategy, we determined the number of imaging tests required for each screening approach, which relates to specificity but provides information that is more readily interpretable. We calculated the total number of imaging tests per child by adding the number of VCUGs and DMSA scans that would have been performed with each screening strategy. We did not consider the number of ultrasounds in our calculations because ultrasounds do not use ionizing radiation.

To identify the best biomarker based approach, we first examined the univariate and multivariate association between each of the 5 biomarkers assessed and the presence of acute pyelonephritis using logistic regression models. In constructing multivariable models we included only biomarkers that were significantly associated (using $p < 0.15$, as is customary) with acute pyelonephritis on univariate analysis. We evaluated the accuracy of models by examining the area under the receiver operator characteristic curve, and we regarded a model with an area under the curve of more than 0.80 as being highly predictive. We used stepwise logistic regression to identify parsimonious models with reasonable accuracy. Cutoff values for C-re-

Table 1. *Biomarker levels in patients with and without pyelonephritis*

	Acute Pyelonephritis	No Acute Pyelonephritis	p Value
Peripheral white blood cell count (10^3/mm^3)	22.2	17.3	<0.001
Polymorphonuclear cell count (10^3/mm^3)	53.9	46.5	<0.001
% Immature neutrophils (bands)	7.4	7.8	0.67
C-reactive protein (mg/l)	119.1	38.1	<0.001
Erythrocyte sedimentation rate (mm/hr)	47.5	28.0	<0.001

active protein were determined by examining the implications of each cutoff in the detection of pyelonephritis.

RESULTS

Of the 309 children in the original cohort 308 were included in this analysis.[10] One child had clear evidence of renal scarring at baseline (with clear change in renal contour on acute DMSA scan) and was excluded from all subsequent analyses. Three children enrolled in the original study did not undergo randomized treatment. These children were included in the analysis.

Mean ± SD patient age was 8.4 ± 5.7 months, and 275 patients (89%) were female. Of the 301 children with VCUG available 115 (38%) had evidence of VUR, of which 43% demonstrated grade III or IV reflux. Almost all children (305) had an acute phase DMSA scan available, with 115 (38%) being normal. Two children (0.6%) had hydronephrosis on renal ultrasound. A total of 60 children (19.4%) had missing C-reactive protein values.

Univariate associations between biomarker values and acute pyelonephritis are shown in table 1. The 4 variables with $p < 0.15$ on univariate analysis (white blood cell count, polymorphonuclear cell count, CRP and ESR) were entered into a multivariate model and stepwise logistic regression was performed. Two variables were removed from the model, resulting in a model with ESR and CRP that had an area under the curve of 0.85 and $p < 0.001$. The addition of baseline clinical variables (age, gender, race, maximum temperature recorded at home, temperature at presentation, reported duration of fever before diagnosis and duration of fever after diagnosis) did not improve the model significantly. A model including CRP alone had nearly the same predictive capacity (area under the curve 0.84, $p < 0.001$). A C-reactive protein of greater than 40 mg/l represented a reasonable tradeoff between sensitivity (86%) and specificity (62%).

The sensitivities of the top-down and CRP based approaches in detecting VUR and subsequently high grade (III or greater) VUR are compared in table 2. Specificity values are not presented in the table because, as expected for screening, the top-down and biomarker based strategies had similarly low specificities (42% and 34%, respectively). The top-down and CRP based approaches missed 33% and 29% of cases of high grade VUR, respectively. The CRP based approach resulted in the least number of imaging tests being performed.

DISCUSSION

This is the largest known study to date evaluating the accuracy of the top-down approach using DMSA renal scanning to identify children with VUR or high grade VUR. We found that the top-down approach not only failed to identify 33% of children with high grade reflux, but also increased the number of imaging tests required compared to the traditional bottom-up approach. Accordingly, DMSA scanning seems ill suited as a first-line imaging modality to detect VUR.

Apart from its poor sensitivity, DMSA renal scanning as a screening test is limited because it entails 1) a visit to a tertiary medical center, 2) placement of an intravenous line, 3) routine sedation at some centers and sedation of uncooperative children at others, 4) higher health care expenditures (approximately $1,000 per scan) and 5) higher exposure to radiation.[13] The impact of radiation exposure from routine DMSA scan may not be trivial. Not only are children more sensitive to radiation than adults,[14] but also, because of the location of the kidneys, radiation to the gonads is inevitable in girls (the majority of children with UTI). In addition, because it usually takes several days to schedule a DMSA renal scan, the results cannot be used to tailor initial treatment for UTI. Finally, in children with previous UTIs differentiation of prior renal scarring from acute pyelonephritis may be difficult. It is noteworthy that voiding cystourethrography has many of the same shortcomings. Indeed, these shortcomings are an important motivator for the development of novel biomarker based strategies.

Table 2. *Sensitivity and number of radiographic tests using ionizing radiation*

	Top-Down Approach	CRP Based Approach*
Sensitivity in detecting VUR	70	71
Sensitivity in detecting high grade (III or greater) VUR	67	71
No. radiographic tests per child undergoing imaging	1 or 2	1
Mean radiographic tests per child†	1.6	0.7

* CRP greater than 40 mg/l had sensitivity of 86% for detecting pyelonephritis and 100% for detecting scarring.

† Bottom-up approach would require 1 imaging test (ie 1 VCUG) per child.

Table 3. *Sensitivity of top-down approach in detecting VUR and high grade VUR in published studies*

	No. Pts	Age (yrs)	Representative of General Pediatric Population with UTI	No. Pts with High Grade VUR (%)	Sensitivity in Detecting VUR (%)	Sensitivity in Detecting High Grade VUR (%)
Current study	308	Younger than 2	Yes	51 (16.6)	70	67
Fouzas et al[17]	296	Younger than 2	Yes	46 (15.5)	Not reported	70
Herz et al[16]	121	Younger than 11	No	56 (46.2)	80	88
Lee et al[15]	220	Younger than 2	No*	43 (19.5)	70	88
Preda et al[18]	290	Younger than 1	Yes	27 (9.3)	85	96
Tseng et al[9]	142	Younger than 2	No†	21 (14.7)	88	100
Hansson et al[8]	303	Younger than 2	Yes	36 (11.9)	66	81

* Retrospective convenience sample of children referred for imaging.
† Only children followed for 5 years at a urology clinic were included in study.

Six other studies to date have examined the top-down approach, and most have demonstrated higher sensitivities (table 3). The higher sensitivity of DMSA renal scans in some of these studies compared to our study is likely related to 1) differences in study design (retrospective studies are more prone to bias), 2) selection bias (relatively high risk cases are more likely to show abnormal VUR and DMSA studies), 3) followup bias (only higher risk cases that are likely to have abnormal VCUG and DMSA scans are likely to be followed), 4) differences in imaging procedures used (eg cyclic VCUG is more sensitive for VUR) and 5) differences in characteristics of the children included.[9,15–17] It is noteworthy that the 2 studies with the highest reported sensitivities for high grade VUR were also the ones with the smallest number of children with high grade reflux (and thus expected to provide the least precise sensitivity estimates).[9,18]

At first glance the CRP based approach appears promising because it significantly reduces the number of imaging tests required and accurately predicts renal involvement (CRP greater than 40 mg/l was detected in 86% of children with acute pyelonephritis), and the results are available at diagnosis. However, like the top-down approach, the CRP based approach missed approximately a third of children with high grade VUR. Thus, CRP does not appear to be a viable strategy to screen children for VUR or high grade VUR. Nevertheless, these data demonstrate the promise of biomarker based strategies in reducing the use of imaging tests in children with UTI.

This study has several limitations. Our results apply only to children younger than 2 years with a febrile UTI. Also, many children (60) had missing CRP values, which limited our ability to fully assess the accuracy of CRP as a screening test. Additionally, several biomarkers that have been identified since we conducted our study (eg procalcitonin, interleukin-6 and interleukin-8) were not included in this analysis.

Perhaps most importantly, in this study we only addressed the question of whether the top-down and CRP based approaches were sensitive in detecting VUR and subsequently high grade (III or greater) VUR. Although neither approach was sensitive in detecting VUR, detection and treatment of VUR may not be the most effective approach to reduce renal scarring in children with UTI. While the role of antimicrobial prophylaxis for children with VUR or pyelonephritis has been the subject of several recent and ongoing studies,[19–22] the important question of whether the benefits of screening outweigh the risks remains unanswered.[23] Many prospective studies are needed to answer these broader questions. We are hopeful that the increasing availability of proteomic and genomic techniques will help identify novel and effective screening approaches for young children with UTI.

CONCLUSIONS

In this study the sensitivity of the top-down approach for detecting high grade VUR was lower than previously reported. Similarly, the sensitivity of a CRP based approach was suboptimal. Neither DMSA scanning nor a CRP based approach is an effective screening strategy for detecting VUR. Further study of novel methods to identify children at risk for renal scarring is warranted.

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