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Early Antibiotic Treatment for Pediatric Febrile Urinary Tract Infection and Renal Scarring

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IMPORTANCE Existing data regarding the association between delayed initiation of antimicrobial therapy and the development of renal scarring are inconsistent.

OBJECTIVE To determine whether delay in the initiation of antimicrobial therapy for febrile urinary tract infections (UTIs) is associated with the occurrence and severity of renal scarring.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study that combined data from 2 previously conducted longitudinal studies (the Randomized Intervention for Children With Vesicoureteral Reflux trial and the Careful Urinary Tract Infection Evaluation Study). Children younger than 6 years with a first or second UTI were followed up for 2 years.

EXPOSURE Duration of the child's fever prior to initiation of antimicrobial therapy for the index UTI.

MAIN OUTCOMES AND MEASURES New renal scarring defined as the presence of photopenia plus contour change on a late dimercaptosuccinic acid renal scan (obtained at study exit) that was not present on the baseline scan.

RESULTS Of the 482 children included in the analysis, 434 were female (90%), 375 were white (78%), and 375 had vesicoureteral reflux (78%). The median age was 11 months. A total of 35 children (7.2%) developed new renal scarring. Delay in the initiation of antimicrobial therapy was associated with renal scarring; the median (25th, 75th percentiles) duration of fever prior to initiation of antibiotic therapy in those with and without renal scarring was 72 (30, 120) and 48 (24, 72) hours, respectively (P = .003). Older age (OR, 1.03; 95% CI, 1.01-1.05), Hispanic ethnicity (OR, 5.24; 95% CI, 2.15-12.77), recurrent urinary tract infections (OR, 0.97; 95% CI, 0.27-3.45), and bladder and bowel dysfunction (OR, 6.44; 95% CI, 2.89-14.38) were also associated with new renal scarring. Delay in the initiation of antimicrobial therapy remained significantly associated with renal scarring even after adjusting for these variables.

CONCLUSIONS AND RELEVANCE Delay in treatment of febrile UTIs and permanent renal scarring are associated. In febrile children, clinicians should not delay testing for UTI.

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In children with febrile urinary tract infections (UTIs), a delay in the initiation of antimicrobial therapy has been hypothesized to increase the risk and extent of renal scarring. This hypothesis has been examined in 6 previous studies with conflicting results[1-6]; 4 studies[2-4,6] suggest that delay in initiation of antimicrobial therapy and the extent or severity of renal scarring are associated, whereas 2 studies[1,5] found no such association. The latter 2 studies differed from the other studies in that they included only a subset of children with febrile UTIs (ie, those with photopenia on an early dimercaptosuccinic acid [DMSA] scan), which limits their usefulness in testing this hypothesis.

Our objective was to determine, in a well-characterized sample of children with febrile UTIs, whether delay in the initiation of antimicrobial therapy was associated with the occurrence and severity of renal scarring and to determine whether these associations persisted after adjusting for potential confounding factors.

Key Points

Question Is delay in the initiation of antimicrobial therapy for urinary tract infections in children associated with the occurrence of new renal scarring?

Findings In this cohort study, delay in the initiation of antimicrobial therapy was significantly associated with renal scarring and remained so after adjusting for potential confounding variables (age, race, ethnicity, infecting organism, history of urinary tract infection, interim urinary tract infection, and study group). Median delay in initiation of antibiotic treatment in those with and without renal scarring was 72 and 48 hours, respectively.

Meaning In febrile children, clinicians should not delay testing for urinary tract infections.

Methods

To evaluate the question posed in this study, we used data from 2 longitudinal studies (the Randomized Intervention for Children With Vesicoureteral Reflux [RIVUR] trial and the Careful Urinary Tract Infection Evaluation Study [CUTIE] study). Children in these studies were aged 2 to 72 months, presented following their first or second UTI at primary and subspecialty care settings throughout the United States, and were prospectively followed up for 2 years. The methods for these studies have been previously reported.[7-9] Briefly, children with vesicoureteral reflux were enrolled in the RIVUR (n = 607) trial whereas those without vesicoureteral reflux were enrolled in the parallel CUTIE study (n = 195). Not all sites participating in the RIVUR trial participated in the CUTIE study. The follow-up and data collection forms in both studies were identical with the exception that children in the RIVUR trial received (1) a study drug (antimicrobial prophylaxis or placebo), (2) a DMSA scan at the 12-month follow-up visit, and (3) a voiding cystourethrogram at the 24-month follow-up visit. Institutional review boards at all participating sites approved the RIVUR and CUTIE study protocols, and written informed consent was obtained from the parents of all participating children. At the time of enrollment in the studies, we asked parents about the duration of their child's fever (in hours as a continuous variable) prior to initiation of antimicrobial therapy for the index UTI. Delay in the initiation of therapy was defined as the duration of time between the onset of fever and the start of antimicrobial therapy. In both studies, children had a technetium Tc 99m DMSA renal scan at baseline and a late DMSA scan either at the 24-month follow-up visit or 3 to 4 months after being withdrawn from the study owing to recurrent UTIs (ie, met predetermined criteria for treatment failure). We defined new renal scarring as the presence of areas of photopenia plus contour changes on a late DMSA scan that were not present on the baseline scan. The extent of renal scarring was quantified using the system developed by the RIVUR trial steering committee in which the renal parenchyma is divided into 13 segments.[8] The studies used SAS, version 9.3, for the analysis (SAS Institute Inc).

For this analysis, we excluded children with no fever (temperature <38°C), children with missing information about delay in the initiation of therapy, and children who did not have a late DMSA scan. We used the Wilcoxon rank sum test to compare the median delay in the initiation of antimicrobial therapy in children with and without evidence of renal scarring and the Kruskall-Wallis test to examine the association between delay in the initiation of antimicrobial therapy and the number of segments affected. We fitted logistic models with renal scarring as the dependent variable. Predictor variables were delay in the initiation of antimicrobial therapy, age, sex, race/ethnicity, vesicoureteral reflux, bladder and bowel dysfunction, parental education, public assistance, history of UTI (no prior UTIs vs 1 prior UTI), type of infecting organism (*Escherichia coli* vs other), interim UTIs between enrollment and time of DMSA scan, treatment group, and height of fever at the time of the index UTI (temperature <39°C vs ≥39°C). Univariable models were considered first, and covariates with association significant at a 0.20 level and covariates considered important (ie, treatment group and study) were included in constructing the multivariable model. We also constructed alternate models using different criteria (eg, with and without interim UTIs included or using $P < .10$ for inclusion) to assess the robustness of our findings.

Results

Of the 802 children enrolled in the RIVUR and CUTIE studies, we excluded 132 children who were afebrile at the time of presentation for the index UTI, 12 children with missing duration of fever, and 176 children with missing late DMSA scans, leaving 482 children. Dimercaptosuccinic acid scans were obtained 200 to 1060 days after an index UTI. The mean (SD) time between the index UTI and enrollment was 58 (29) days. Compared with children who were excluded, those included in the study were significantly younger (median age 11 months for included children vs 16 months for excluded children) and significantly more likely to have vesicoureteral reflux (78% [375 of 482] vs 72% [232 of 320]), not to have a history of UTIs (94%

Table 1. Demographic and Clinical Characteristics of 482 Children With Febrile Urinary Tract Infection According to Delay in the Initiation of Antimicrobial Therapy

Characteristics	Overall (n = 482)	Duration of Fever Prior to Treatment, No. (%)		*P* Value
		<48 h (n = 304)	≥48 h (n = 178)	
Age, mo				
2-11	259 (54)	191 (63)	68 (38)	<.001
12-35	135 (28)	67 (22)	68 (38)	
36-72	88 (18)	46 (15)	42 (24)	
Sex				
Male	48 (10)	32 (11)	16 (9)	.59
Female	434 (90)	272 (89)	162 (91)	
Race				
White	375 (78)	234 (77)	141 (79)	.47
Nonwhite	101 (21)	67 (22)	34 (19)	
Missing	6 (1)	3 (1)	3 (2)	
Ethnicity				
Hispanic	74 (15)	47 (15)	27 (15)	.94
Non-Hispanic	406 (84)	256 (84)	150 (84)	
Missing	2 (0)	1 (0)	1 (1)	
Parental education				
High school graduate or lower	139 (29)	87 (29)	52 (29)	.89
Greater than high school	340 (71)	215 (71)	125 (70)	
Missing	3 (1)	2 (1)	1 (1)	
Public assistance				
Yes	166 (34)	107 (35)	59 (33)	.72
No	312 (65)	196 (64)	116 (65)	
Missing	4 (1)	1 (0)	3 (2)	
Highest reflux of both ureters				
0	107 (22)	69 (23)	38 (21)	.63
1	33 (7)	18 (6)	15 (8)	
2	147 (30)	88 (29)	59 (33)	
3	155 (32)	102 (34)	53 (30)	
4	37 (8)	25 (8)	12 (7)	
Missing	3 (1)	2 (1)	1 (1)	
No. of UTIs prior to the index UTI				
0	453 (94)	287 (94)	166 (93)	.61
1	29 (6)	17 (6)	12 (7)	
Infecting organism				
Escherichia coli	442 (92)	283 (93)	159 (89)	.15
Non-*Escherichia coli*	40 (8)	21 (17)	19 (11)	
Highest temperature reported within 24 h of index UTI				
<39°C	131 (27)	98 (32)	33 (19)	.001
≥39°C	351 (73)	206 (68)	145 (81)	
Bladder and bowel dysfunction				
No or not toilet trained	433 (90)	274 (90)	159 (89)	.75
Yes	46 (10)	28 (9)	18 (10)	
Missing	3 (1)	2 (1)	1 (1)	
Interim UTIs				
No	390 (81)	249 (82)	141 (79)	.47
Yes	92 (19)	55 (18)	37 (21)	
Treatment group and study				
CUTIE	107 (22)	69 (23)	38 (21)	.79
RIVUR				
Placebo	195 (40)	125 (41)	70 (39)	
Active	180 (37)	110 (36)	70 (39)	

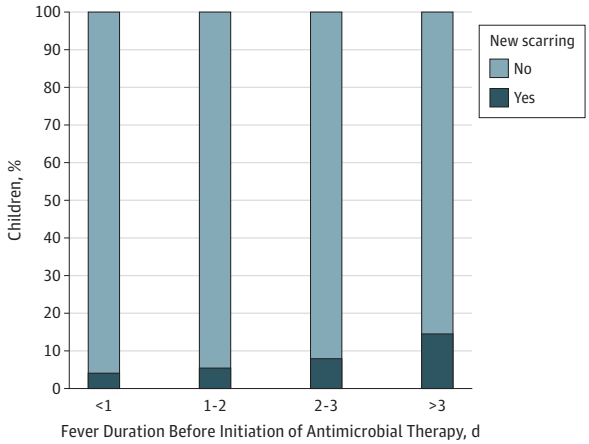
Abbreviations: CUTIE, Careful Urinary Tract Infection Evaluation Study; RIVUR, Randomized Intervention for Children With Vesicoureteral Reflux; UTI, urinary tract infection.

[453 of 482] vs 86% [275 of 320]), and not to be toilet trained at the time of enrollment (82% [393 of 482] vs 69% [215 of 320]). The demographic and clinical characteristics of the sample are further described in **Table 1**. Children included in the study were more likely to have a delay in the initiation of antimicrobial therapy (median of 56.3 hours in included children compared with 50.3 hours in excluded children), although this association was not significant.

A total of 35 children (7.2%) had new renal scarring on the outcome DMSA scan. Delay in the initiation of antimicrobial therapy and renal scarring were associated; the median (25th, 75th percentiles) duration of fever in those with and without renal scarring was 72 (30, 120) and 48 (24, 72) hours, respectively (P = .003). The proportion of children with new renal scarring increased with increasing duration of fever before initiation of antimicrobial therapy (**Figure**). **Table 2** presents the univariate association of covariates and new renal scarring, and **Table 3** presents the results of the multivariable logistic regression analysis. Because bladder and bowel dysfunction status and age were highly correlated, we only included age in the multivariable model. Delay in the initiation of antimicrobial therapy remained significantly associated with renal scarring even after adjusting for age (OR, 1.03; 95% CI, 1.01-1.05), race (OR, 0.62; 95% CI, 0.20-1.89), ethnicity (OR, 5.24; 95% CI, 2.15-12.77), infecting organism (OR, .57; 95% CI, 0.20-1.63), previous UTI (OR, 0.97; 95% CI, 0.27-3.45), and interim UTIs (OR, 6.44; 95% CI, 2.89-14.38). For every hour that antimicrobial therapy is delayed, we expect the odds of new renal scarring to increase by 0.8%. In all alternate models considered, delay in initiation of antimicrobial therapy and new renal scarring remained significant.

The association between delay in initiation of therapy and number of segments with renal scarring (OR, 1.005; 95% CI, 1.001-1.01; P = .03) became nonsignificant (P = .12) after adjusting for potential confounders. Only height of fever (OR, 4.13; 95% CI, 1.72-9.94; P = .002), and interim UTIs (OR, 1.95; 95% CI, 1.05-3.64; P = .04) remained significantly associated with the number of segments with renal scarring.

Figure. Percentage of Children With New Renal Scarring According to Delay in the Initiation of Antimicrobial Therapy



Discussion

In children with a febrile UTI, we found that delay in initiation of antimicrobial therapy was associated with the development of renal scarring. After adjusting other covariates, we estimate that a delay of 48 hours or more would increase the odds of new renal scarring by about 47%. The concordance of our finding with previous studies[2-4] that included similar patients and the robustness of our main finding even after controlling for other potential confounding factors (including interim UTIs, previous UTIs, and age) strongly support the hypothesis that delay in the initiation of antimicrobial therapy and the development of renal scars are related. Data from experimentally induced pyelonephritis in animals provide further support. Miller and Phillips[10] injected bacteria into kidneys of rats and waited 8, 24, 48, 72, 96, and 120 hours before initiating antibiotic treatment; the extent of renal scarring as evidenced on gross pathology and delay in the initiation of antimicrobial therapy were strongly associated. Studies performed by Ransley and Risdon[11] and Glauser et al[12] had similar findings.

Although 1 large study by Hewitt et al[5] failed to find an association between delay in the initiation of antimicrobial therapy and development of renal scars, this study only included children with pyelonephritis confirmed by DMSA. In our view, this is a limitation. Because an acute-phase DMSA scan is not usually obtained in clinical practice, findings from this study cannot be extrapolated to all children with a febrile UTI. Furthermore, even if early antibiotic treatment does not reduce rates of renal scarring once the renal parenchyma is involved (and can be visualized on a DMSA scan), early treatment could still be effective by reducing the risk of renal parenchymal involvement in the first place. If so, one would expect a study that included only children with known renal involvement to find no association between delay in the initiation of antimicrobial therapy and renal scarring even if the 2 were causally linked. A second study by Doganis et al[1] also failed to find an association between delay in the initiation of antimicrobial therapy and the occurrence of renal scarring, likely because the association between treatment delay and renal scarring was only examined in the subset of patients who already had renal involvement. Of note, the latter study found that children in whom antimicrobial therapy was delayed had a substantially higher risk of acute pyelonephritis, which supports the hypothesis that the detrimental effect of treatment delay occurs before pyelonephritis is detectable on a DMSA scan. The later 2 studies also differed from our study in that they included a very high proportion of boys. Because boys are substantially more likely to have congenital lesions that could be mistaken for acquired renal scarring[13] and because neither study examined the incidence of new renal scarring, it may have been more difficult for these studies to detect an association between treatment delay and renal scarring.

Several limitations are notable. First, we asked parents about the duration of fever before initiation of antimicrobial therapy at the enrollment visit, which occurred, on average, 58 days after the index UTI. Therefore, parental recollection

Table 2. New Renal Scarring According to Selected Clinical and Demographic Characteristics

Characteristics	Renal Scarring, No./No. (%) (n = 35)	OR (95% CI)	*P* Value
Age, mo			
2-11	11/259 (4)	0.23 (0.10-0.54)	.003
12-35	10/135 (7)	0.42 (0.18-1.00)	
36-72	14/88 (16)	1 [Reference]	
Sex			
Male	2/48 (4)	1 [Reference]	.39
Female	33/434 (8)	1.89 (0.44-8.15)	
Race			
White	31/375 (8)	2.19 (0.75-6.34)	.15
Nonwhite	4/101 (4)	1 [Reference]	
Missing	0/6 (0)		
Ethnicity			
Hispanic	11/74 (15)	2.78 (1.30-5.56)	.01
Non-Hispanic	24/406 (6)	1 [Reference]	
Missing	0/2 (0)		
Parental education			
High school graduate or lower	11/139 (8)	1.13 (0.54-2.38)	.74
Greater than high school	24/340 (7)	1 [Reference]	
Missing	0/3 (0)		
Public assistance			
Yes	11/166 (7)	0.85 (0.41-1.79)	.67
No	24/312 (8)	1 [Reference]	
Missing	0/4 (0)		
Highest reflux of both ureters			
None	5/107 (5)	0.56 (0.21-1.48)	.24
Any	30/372 (8)	1 [Reference]	
Missing	0/3 (0)		
Infecting organism			
Escherichia coli	29/442 (7)	0.40 (0.15-1.02)	.06
Non-*Escherichia coli*	6/40 (15)	1 [Reference]	
No. of prior UTIs			
0	31/453 (7)	0.46 (0.15-1.40)	.17
1	4/29 (14)	1 [Reference]	
Highest temperature reported within 24 h of index UTI			
<39°C	8/131 (6)	0.78 (0.35-1.77)	.55
≥39°C	27/351 (8)	1 [Reference]	
Bladder and bowel dysfunction			
No or not toilet trained	27/433 (6)	0.32 (0.13-0.74)	.01
Yes	8/46 (17)	1 [Reference]	
Missing	0/3 (0)		
Duration of fever prior to treatment, h[a]			
≤24	8/194 (4)	0.26 (0.11-0.63)	.02
>24-28	6/112 (5)	0.34 (0.13-0.90)	
>48-72	6/74 (8)	0.52 (0.19-1.42)	
>72	15/104 (14)	1 [Reference]	
Interim UTIs			
No	17/390 (4)	0.19 (0.09-0.38)	<.001
Yes	18/92 (20)	1 [Reference]	
Treatment group and study			
CUTIE	5/107 (5)	0.58 (0.20-1.66)	.51
RIVUR			
Placebo	16/195 (8)	1.06 (0.50-2.24)	
Active	14/180 (8)	1 [Reference]	

Abbreviations: CUTIE, Careful Urinary Tract Infection Evaluation Study; OR, odds ratio; RIVUR, Randomized Intervention for Children With Vesicoureteral Reflux; UTI, urinary tract infection.

[a] Data were collected as a continuous variable.

Table 3. Results of the Multivariable Model for New Renal Scarring

Predictors	Contrast	Adjusted Odds Ratio (95% CI)	*P* Value
Age	1-mo increase	1.03 (1.01-1.05)	.01
Race	Nonwhite vs white	0.62 (0.20-1.89)	.40
Ethnicity	Hispanic vs other	5.24 (2.15-12.77)	<.001
Infecting organism	*Escherichia coli* vs other	0.57 (0.20-1.63)	.29
Duration fever prior to treatment	1-h increase	1.008 (1.002-1.015)	.009
History of UTI	No vs yes	0.97 (0.27-3.45)	.96
Treatment group and study	RIVUR active vs other	1.94 (0.87-4.33)	.11
Interim UTIs	Yes vs no	6.44 (2.89-14.38)	<.001

Abbreviations: OR, odds ratio; RIVUR, Randomized Intervention for Children With Vesicoureteral Reflux; UTI, urinary tract infection.

of the duration of fever before treatment may not have been precise. However, only 12 children were excluded from the analysis because their parents were unable to estimate the duration of fever prior to treatment. In addition, we asked about delay in the initiation of antimicrobial therapy before the outcome was determined (ie, before the baseline DMSA scan was performed). Accordingly, it is unlikely that the imprecision in the data could explain differences observed in children with and without renal scarring. A second limitation is that children included in the study were younger and were more likely to have vesicoureteral reflux than children who were excluded. Nevertheless, no significant differences in time to antimicrobial therapy were noted between children who were included and children who were excluded. Finally, the number of children with new renal scarring was relatively low, limiting our confidence in the multivariate models.

Our findings have several implications. First, because prompt testing and treatment appeared to be associated with a reduced risk of renal scarring, clinicians should not delay testing in febrile children who could potentially have a UTI. Some authors have suggested that testing for UTIs should be delayed until fever has been present for at least 4 to 5 days.[14] Careful examination of the American Academy of Pediatrics guidelines[15] and other available diagnostic algorithms[16] reveals that many febrile children meet criteria for testing before the 48-hour mark. For example, 1 meta-analysis found that white female children younger than 2 years who had a fever for more than 24 hours had a probability of UTI that was higher than the testing threshold for most clinicians.[16] Second, parents of children who are at high risk for febrile UTI recurrences (eg, children with vesicoureteral reflux, bladder bowel dysfunction, or previous UTIs) should be counseled to bring their child promptly for evaluation of subsequent febrile illnesses. Third, our data do not support the notion frequently held by clinicians that the risk of renal scarring is higher in younger children. In fact, this very notion may be partly responsible for the higher likelihood of treatment delay and associated renal scarring in older children.

Conclusions

A growing body of evidence suggests that delay in treatment of febrile UTIs and permanent renal scarring are associated. These data may help clinicians make more informed decisions regarding the need for diagnostic testing for UTIs in children presenting with fever.

ARTICLE INFORMATION

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REFERENCES

1. Doganis D, Siafas K, Mavrikou M, et al. Does early treatment of urinary tract infection prevent renal damage? *Pediatrics*. 2007;120(4):e922-e928.

2. Falakolaflaki B, Jamshidi MR. Risk factors for renal scarring in children with first pyelonephritis. *Pediatr Nephrol*. 2013;28(8):1379.

3. Oh MM, Kim JW, Park MG, Kim JJ, Yoo KH, Moon G. The impact of therapeutic delay time on acute scintigraphic lesion and ultimate scar formation in children with first febrile UTI. *Eur J Pediatr*. 2012;171(3):565-570.

4. Coulthard MG, Lambert HJ, Vernon SJ, Hunter EW, Keir MJ, Matthews JN. Does prompt treatment of urinary tract infection in preschool children prevent renal scarring: mixed retrospective and prospective audits. *Arch Dis Child*. 2014;99(4):342-347.

5. Hewitt IK, Zucchetta P, Rigon L, et al. Early treatment of acute pyelonephritis in children fails to reduce renal scarring: data from the Italian Renal Infection Study Trials. *Pediatrics*. 2008;122(3):486-490.

6. Smellie JM, Poulton A, Prescod NP. Retrospective study of children with renal scarring associated with reflux and urinary infection. [comment]. *BMJ*. 1994;308(6938):1193-1196.

7. Hoberman A, Greenfield SP, Mattoo TK, et al; RIVUR Trial Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med*. 2014;370(25):2367-2376.

8. Keren R, Carpenter MA, Hoberman A, et al. Rationale and design issues of the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) study. *Pediatrics*. 2008;122(suppl 5):S240-S250.

9. Keren R, Shaikh N, Pohl H, et al. Risk factors for recurrent urinary tract infection and renal scarring. *Pediatrics*. 2015;136(1):e13-e21.

10. Miller T, Phillips S. Pyelonephritis: the relationship between infection, renal scarring, and antimicrobial therapy. *Kidney Int*. 1981;19(5):654-662.

11. Ransley PG, Risdon RA. Reflux nephropathy: effects of antimicrobial therapy on the evolution of the early pyelonephritic scar. *Kidney Int*. 1981;20(6):733-742.

12. Glauser MP, Lyons JM, Braude AI. Prevention of chronic experimental pyelonephritis by suppression of acute suppuration. *J Clin Invest*. 1978;61(2):403-407.

13. Wennerström M, Hansson S, Jodal U, Stokland E. Primary and acquired renal scarring in boys and girls with urinary tract infection. *J Pediatr*. 2000;136(1):30-34.

14. Newman DH, Shreves AE, Runde DP. Pediatric urinary tract infection: does the evidence support aggressively pursuing the diagnosis? *Ann Emerg Med*. 2013;61(5):559-565.

15. Roberts KB; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595-610.

16. Shaikh N, Morone NE, Lopez J, et al. Does this child have a urinary tract infection? *JAMA*. 2007;298(24):2895-2904.