Antimicrobial Resistance and Diagnostic Imaging in Infants Younger Than 2 Months Old Hospitalized With a First Febrile Urinary Tract Infection

A Population-based Comparative Study

Chih-Chuan Hsu, MD, Jeng-Dau Tsai, MD, PhD,†§ Min-Sho Ku, MD, PhD,†§ Shan-Ming Chen, MD, PhD,†§ Pei-Fen Liao, MD,†§ Tung-Wei Hung, MD,‡¶ Min-Ling Tsai, MMS,†‖ and Ji-Nan Sheu, MD, PhD*†§*

Background: Data on urinary tract infection (UTI) in infants ≤2 months of age are limited. We examined clinical characteristics, antimicrobial resistance, imaging findings and clinical outcomes in infants ≤2 months of age and children 2–24 months of age hospitalized with the first febrile UTI.

Methods: Children ≤24 months of age hospitalized with their first-diagnosed febrile UTI were prospectively studied. Renal ultrasonography, ^{99m}Tc-dimercaptosuccinic acid scanning and voiding cystourethrography were performed in all children.

Results: Of the 388 children analyzed (255 boys and 133 girls), 61 patients were ≤2 months of age, representing 15.7% of the whole population, whereas 327 patients were 2–24 months of age. *Escherichia coli* was the predominant bacterium, with similar antimicrobial resistance in the 2 groups, and associated *E. coli* bacteremia occurred in 9 patients (2.3%). Renal ultrasonography showed abnormal findings in 130 patients (33.5%), but there was no difference in the rate of abnormal findings between the groups. Vesicoureteral reflux (VUR) was present in 130 children (33.5%), including 93 (24%) with grades III–V VUR. VUR was more prevalent in the infants ≤2 months of age ($P = 0.007$), but there was no difference in the prevalence of grades III–V VUR between the groups. The incidence of renal scarring was 28.6% (111/388), and it did not differ between the groups.

Conclusions: There are similarities in clinical characteristics, antimicrobial resistance, imaging findings and clinical outcomes after a first UTI between the young infants ≤2 months and children 2–24 months of age. The same guidelines for the diagnosis and management after the first febrile UTI can be applied to children who are ≤24 months of age.

Key Words: antimicrobial resistance, infants younger than 2 months old, first febrile urinary tract infection, imaging, clinical outcomes

(*Pediatr Infect Dis J* 2016;35:840–845)

As febrile infants and young children usually present with nonspecific symptoms and signs, there are difficulties in assessing the localization and severity of illness. Urinary tract infection (UTI) is one of the common causes of unexplained fever and serious bacterial infections in febrile infants and young children.[1] The prevalence of UTI ranges from 5.3% to 13.6% in febrile infants ≤2 months of age,[2] suggesting that UTI is a relatively common cause of fever in this age group.

Childhood UTI is often associated with congenital urinary tract abnormalities, most commonly vesicoureteral reflux (VUR),[3] which may put infants and young children at high risk for acute pyelonephritis (APN), recurrent UTIs, subsequent renal scarring (RS)[3,4] and possible long-term medical problems.[5,6] In 2014, the recent the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial showed that antibiotic prophylaxis was effective in decreasing recurrent and symptomatic UTIs but not of RS in children with VUR,[7] suggesting that detection of VUR and prevention of recurrences in children are beneficial. Published guidelines do not specially address the evaluation after a first UTI in infants ≤2 months of age. In 2011, the American Academy of Pediatrics revised its recommendations for the diagnosis and management of the first UTI in febrile infants and children 2–24 months of age.[1] However, the guidelines excluded infants 0–2 months of age from consideration owing to limited data characterizing this age group.[1] In addition, many published studies on this age group have significant design or reporting flaws that may further cloud the clinical picture and limit their impact.[8–13]

We examined a defined group of infants ≤2 months of age hospitalized with their first-diagnosed community-acquired febrile UTI and compared them with young children 2–24 months of age on clinical characteristics, laboratory data, uropathogens and antimicrobial resistance, imaging findings and clinical outcomes.

PATIENTS AND METHODS

Patients and Study Design

This prospective cohort study evaluated young children ≤24 months of age who were admitted to an urban tertiary referral center and academic teaching hospital via the pediatric emergency department or outpatient department for a first-diagnosed community-acquired febrile UTI during a 6.5-year period. The hospital's Institutional Review Board approved the study protocol, and the parents of all of the participants provided informed consent.

Diagnosis of a first-episode febrile UTI was based on the following criteria: (1) fever with body temperature ≥38°C; (2) presence of pyuria [defined as ≥5 white blood cell (WBC) per high-power field] and/or abnormal dipstick urinalysis (a positive nitrite or leukocyte esterase test); (3) a positive urine culture, defined as any growth of a single bacterium in urine from a suprapubic bladder aspiration, $\geq 5 \times 10^4$ colony-forming units/mL collected from a transurethral catheterized specimen, or growth of a single microorganism $\geq 10^5$ colony-forming units/mL collected from the midstream clean-void urine specimen[1]; and (4) no previous history of

Accepted for publication January 22, 2016.
From the *Department of Pediatrics, Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan; †School of Medicine and ‡Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan; §Department of Pediatrics, ¶Department of Internal Medicine, and ‖Department of Pharmacy, Chung Shan Medical University Hospital, Taichung, Taiwan.
Supported by grants from the Chung Shan Medical University Hospital, Taichung, Taiwan (CSH-2011-C-015, CSH-2012-C-010 and CSH-2013-C-011) and National Science Council, Taipei, Taiwan (NSC93-2314-B-040-012).
The authors have no other funding or conflicts of interest to disclose.
C.-C.H. and J.-D.T. contributed equally to this study.
Address for correspondence: Ji-Nan Sheu, MD, PhD, Department of Pediatrics, Chung Shan Medical University Hospital, No. 110, Section 1, Jianguo North Road, Taichung 402, Taiwan. E-mail: cshy098@csh.org.tw.

ISSN: 0891-3668/16/3508-0840
DOI: 10.1097/INF.0000000000001184

UTI, urinary tract or neurologic abnormalities known to be associated with recurrent UTIs or renal damage. Bacteremia was defined as simultaneous isolation of an identical bacterial pathogen from urine and blood specimens.

All children were treated empirically with combined intravenous cefazolin (100 mg/kg/d) and gentamicin (7.5 mg/kg/d) for at least 3 days after admission according to the hospital's antibiotic policy. This regimen was later adjusted according to the results of the antimicrobial susceptibility tests for an overall treatment duration of 7–24 days.

Laboratory Investigations

Serum and urine indices for laboratory investigations, including WBC count, C-reactive protein (CRP), procalcitonin (PCT), serum creatinine, urinalysis and urine and blood cultures were taken from all patients on admission before the initiation of antibiotics treatment. Rapid and quantitative measurements of PCT values were performed using an enzyme-linked fluorescent assay in an automated instrument (VIDAS BRAHMS PCT, BRAHMS Diagnostica, Berlin, Germany) according to the manufacturer's instructions.[14]

Urine Cultures and Antimicrobial Susceptibility Tests

Urine samples were transferred immediately to the hospital's Department of Clinical Microbiology at room temperature. The identification of microbial growth and the determination of antimicrobial susceptibility testing were performed using the disk diffusion method according to the guidelines of the National Committee for Clinical laboratory Standard, with the recommended media and standard control strains.[15] Antimicrobial susceptibility was routinely tested for the following 15 antimicrobial agents: ampicillin, ampicillin/sulbactam, piperacillin/tazobactam, gentamicin, amikacin, cefazolin, ceftazidime, ceftriaxone, cefepime, ofloxacin, ciprofloxacin, ertapenem, meropenem, imipenem and trimethoprim/sulfamethoxazole (TMP/SMX).

Imaging Studies

All patients underwent complete diagnostic imaging, including renal ultrasonography (US), acute ^{99m}Tc-dimercaptosuccinic acid (DMSA) scanning and voiding cystourethrography (VCUG).

Renal US was performed within the first 3 days of admission. All abnormal US findings were recorded, including the anteroposterior diameter of the renal pelvis ≥5 mm and/or any grade of dilatation of the calyces or ureters irrespective of anteroposterior diameter; pelvic or ureteral wall thickening; absence of corticomedullary differentiation; renal hypoplasia; duplicated renal collecting system; and abnormal kidney size.[14]

A DMSA scan was performed within the first 5 days of admission to identify renal lesions. An abnormal acute DMSA scan suggesting APN was defined as the presence of focal or diffuse areas of decreased radioisotope uptake with preservation of the renal contour.[16–18] If there was an abnormal acute DMSA scan, a late DMSA scan was obtained at least 6 months after the acute infection to evaluate the presence of RS.[18] Previous studies showed that all children whose acute DMSA scan was normal had a normal late DMSA.[18] Thus, it was unnecessary and unethical to perform a late DMSA study on patients with previously normal scans. RS was defined as the presence of focal or generalized areas of persistent diminished radioisotope uptake at the same locations as in the acute DMSA scan and/or associated with loss of the contour of the kidney.[17,18] Primary clinical outcomes defined as the incidence of RS formation after a febrile UTI were measured.

A VCUG was performed 1–4 weeks after control of the acute infection. The VUR was graded I–V according to the International Reflux Study in children.[19] Interpretations of the DMSA and VCUG were made by 2 experienced nuclear medicine physicians and 2 radiologists in random order, and they were unaware of the patient's clinical and laboratory findings and blinded to the study's objectives.

Statistical Analyses

The unpaired 2-tailed Student's *t* test was used to compare continuous variables and was presented as mean and standard deviation. χ^2 test or Fisher exact test was used to compare categorical variables. Multivariate logistic analysis with a stepwise procedure was used to identify the potential predictors of RS. Results were expressed as odds ratio, 95% confidence interval and *P* values. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the software package SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL).

RESULTS

Clinical Characteristics

A total of 388 patients ≤24 months of age with the first febrile UTI, with complete diagnostic imaging and follow-up, were enrolled. They were divided into the young infant group (n = 61), who were ≤2 months of age, and the young children group (n = 327), who were ≤24 months but >2 months of age. The demographic and clinical characteristics of the patients are summarized in Table 1. The young infant group included 47 boys and 14 girls (mean age, 34.9 ± 14.1 days), representing 15.7% of the whole population, with a male-to-female ratio of 3.4:1. The young children group included

TABLE 1. Clinical Characteristics and Laboratory Findings of the Study Population (N = 388)

Variable	≤2 Mo of Age (N = 61)	2–24 Mo of Age (N = 327)	*P*
Age (mean ± SD)	34.9 ± 14.1 d	7.0 ± 5.0 mo	<0.001
Sex, male/female	47/14	208/119	0.060
Fever, maximum temperature (°C)	39.1 ± 0.6	39.4 ± 0.7	<0.001
Fever duration before admission (d)	1.3 ± 1.0	2.1 ± 1.3	<0.001
Fever duration after treatment (d)	1.3 ± 1.0	1.7 ± 1.7	0.044
WBC count (mm^3)	15,505 ± 5332	17,160 ± 7046	0.087
CRP (mg/dL)	6.96 ± 4.81	8.52 ± 6.63	0.083
PCT (ng/mL)	3.57 ± 6.41	3.77 ± 6.15	0.821
Escherichia coli / non-*E. coli* bacteria	53/8	283/44	0.943
Bacteremia	3 (4.9%)	6 (1.8%)	0.154

For comparison between groups, the χ^2 test or Fisher exact test was used for categorical variables (presented as number and percentage), and unpaired Student's *t* test for continuous variables (presented as mean and SD).

SD indicates standard deviation.

208 boys and 119 girls (mean age, 7.0 ± 5.0 months), with a male-to-female ratio of 1.7:1. All boys were uncircumcised in our study, as in customary in Taiwan.

The young infant group presented with a significantly lower maximum temperature ($P < 0.001$) and a shorter duration of fever before admission ($P < 0.001$) and after treatment ($P = 0.044$), compared with the young children group. The values of serum inflammatory markers, including WBC count, CRP and PCT were similar between the groups.

Uropathogens and Antimicrobial Resistance Patterns

The leading uropathogen among the 388 patients was *Escherichia coli,* which was isolated in urine cultures from 335 patients (86.3%), whereas 53 (13.7%) patients had other bacteria, including *Klebsiella*, *Proteus, Pseudomonas, Enterococcus* and *Citrobacter* species. Associated *E. coli* bacteremia occurred in 9 patients (2.3%; Table 1). *E. coli* predominated both in young infant and young children groups. Analysis of the *E. coli* isolates regarding sex predominance revealed no statistical difference in each group ($P = 0.179$ and $P = 0.916$, respectively).

The antimicrobial resistance rate of the *E. coli* isolated in our study to cefazolin and gentamicin was 24.2% and 13.1%, respectively, and they exhibited a high rate of antimicrobial resistance to ampicillin (75.8%) and TMP/SMX (55.8%). There were no differences in the antimicrobial resistance patterns between the 2 groups.

Imaging Findings

Abnormal US findings were detected in 130 patients (33.5%; Table 2). Abnormal US findings were more prevalent among boys 2–24 months of age ($P = 0.026$). Of the 388 patients, VUR (the maximum degree of reflux given if bilateral) was identified in 130 (33.5%); of those, 93 (24.0%) had grades III–V VUR, including 65 (69.9%) with concomitant abnormal US (Table 3). Only 5 of 40 children with grade IV VUR did not have any abnormal US findings, and no case of grade V VUR was missed on US. The prevalence of grades III–V VUR was 24% of the study, with a posttest probability of 10.7% for a negative test, meaning that the pretest probability (24%) decreased to 10.7% posttest probability. VUR of grades I to V was more prevalent in the young infant group (49.2% vs. 30.6%, $P = 0.007$); however, there was no difference in the prevalence of grades III–V VUR between the groups. When stratified by age and sex, grades III–V VUR were more prevalent in boys 2–24 months of age (77.3% vs. 55.9%, $P = 0.048$).

There were abnormal acute DMSA scans, suggesting APN, in 236 (60.8%) patients and normal acute DMSA scans, suggesting a lower UTI, in 152 (39.2%) patients. The incidences of APN were similar in both the young infant and young children groups and in boys and girls. APN was identified in 80.8% (105/130) of patients with VUR. In the study, patients with APN had significantly higher rates of VUR than those with a lower UTI (44.5% vs. 15.8%, $P < 0.001$); further, the rates of APN were more prevalent in patients with VUR (81.4% vs. 50.6%, $P < 0.001$). There were significant associations between APN and the severity of VUR grade (grades I–II vs. grades III–V) in both the young infant group ($P = 0.003$) and the young children group ($P < 0.001$). A slight predominance of non-*E. coli* bacteria (40.4%) other than *E. coli* (32.4%) was observed in children with VUR, but the difference was not statistically significant ($P = 0.331$).

TABLE 2. Results of Diagnostic Imaging Stratified by Age and Sex

	≤2 Mo of Age (N = 61)			2–24 Mo of Age (N = 327)			
Imaging findings	Boys (N = 47)	Girls (N = 14)	*P*	Boys (N = 208)	Girls (N = 119)	*P*	*P*
US findings							0.366*
Normal	26	11	0.212	131	90	0.026	
Abnormal	21	3		77	29		
Acute DMSA							0.647*
Normal	21	5	0.759	84	42	0.428	
Abnormal	26	9		124	77		
VCUG							0.007*
Normal	24	7	0.944	142	85	0.637	
VUR	23	7		66	34		0.632†
Grade I	2	0	1.000‡	0	1	0.048‡	
Grade II	3	2		15	14		
Grade III	2	3		18	13		
Grade IV	11	2		23	4		
Grade V	5	0		10	2		
Late DMSA							0.769*
Normal	34	11	0.742	148	84	0.914	
Renal scarring	13	3		60	35		0.099§
No VUR	3	0	1.000	21	19	0.105	
With VUR	10	3		39	16		1.000‖
Grades I–II	0	1	0.231	5	2	1.000	
Grades III–V	10	2		34	14		.

*Comparison of imaging findings between the young infant ≤2 months and young children 2–24 months of age groups.

†Comparison of VUR of grades I–II and grades III–V between the young infant ≤2 months and young children 2–24 months of age groups.

‡Comparison of VUR of grades I–II and grades III–V between boys and girls in the young infant ≤2 months and young children 2–24 months of age groups.

§Comparison of RS in patients with VUR and those without VUR between the young infant ≤2 months and young children 2–24 months of age groups.

‖Comparison of RS in patients with VUR of grades I–II and grades III–V between the young infant ≤2 months and young children 2–24 months of age groups.

TABLE 3. Abnormal US Findings for Identifying Children With VUR of Grades III–V (N = 388)

Abnormal US Findings	Presence of Grades III–V VUR: Yes	No	Total		
Yes	65	65	130	50%	Positive predictive value
No	28	230	258	89%	Negative predictive value
Total	93	295	388		
	70% Sensitivity	78% Specificity			

Abnormal US findings (at least 1 abnormal finding) included the anteroposterior diameter of the renal pelvis ≥5 mm and/or any grade of dilatation of the calyces or ureters irrespective of anteroposterior diameter; pelvic or ureteral wall thickening; absence of cortico-medullary differentiation; renal hypoplasia; duplicated renal collecting system, and abnormal kidney size.

Primary Clinical Outcomes

Of the 388 children, RS was present in 111 children (28.6%), and the incidence of RS did not differ between the 2 groups (Table 2). Seventy-seven (59.2%) of the 130 children with abnormal US findings had RS compared with 34 (13.2%) of 258 children with normal US findings ($P < 0.001$). Of the children with VUR, 52.3% (68/130) children had RS compared with 16.7% (43/258) children with no VUR ($P < 0.001$). Among children with no VUR or grades I–II VUR, 17.3% (51/295) had RS compared with 64.5% (60/93) of those with grades III–V VUR ($P < 0.001$). When stratified by age and sex, there were no associations of RS with age and sex regardless of the presence or grade of VUR (Table 2).

Risk Factor for RS

A multivariate analysis was performed to determine independent predictors of RS for patients after a febrile UTI (Table 4). After adjusting for confounding factors, the initial PCT value, abnormal US findings and the presence and grade of VUR were important predictors of RS.

DISCUSSION

In this study, the young infants ≤2 months of age represented 15.7% of children ≤24 months of age with a first febrile UTI, similar to a reported prevalence of 13.6% to 20.6%.[2,11–13] Males predominated (65.7%) in our study, especially in the young infant group (76.3%), in agreement with other reports.[2,11,12,20,21] Phimosis seems to be an important risk factor for UTI in male infants.[2,10–12,20,21] None of the boys in this study were circumcised at the time of UTI, similar to previous studies.[2,8,11,12,20,21]

The mean time of fever duration before admission and after treatment was 1.3 days and 1.3 days, respectively, for the young infant group and 2.1 days and 1.7 days, respectively, for the young children group, similar to the findings of a previous study.[11] The relatively shorter duration of fever before admission and after treatment in the young infant group may be partly explained by parental vigilance and alarm at the presence of fever in younger infants, which prompts the parents/providers to seek care more quickly than that for older children. Therefore, younger infants can obtain timely diagnosis and treatment.

Children ≤24 months of age are more likely to have APN than older children.[22,23] The incidence of APN (60.8%) in our study was similar between the 2 groups of patients during their acute febrile UTI, consistent with incidences of 51.5%–72.7% of APN in young children.[12,18,24,25]

In this study, the values of serum inflammatory markers like WBC count, CRP and PCT were similar between the 2 groups and were also similar to previously reported values of young children with a febrile UTI.[8,10–12,14,26–28] Our results demonstrate that initial PCT is a robust predictor for identifying children who had APN in the acute phase of UTI and those that developed late RS, in accordance with the findings of previous reports.[14,28] This suggests that PCT measurement has the potential to aid the clinical decision-making process regarding the acute management and follow-up of children after a febrile UTI.[14,28]

E. coli was the most common uropathogen causing the first febrile UTI in the young infant and young children groups of this study, and the rate of *E. coli* isolated and antimicrobial resistance patterns were similar between the 2 groups. There is growing concern about the resistance of *E. coli* to commonly recommended empiric antibiotics for childhood UTI like ampicillin and TMP/SMX.[29–31] *E. coli* showed a high rate of resistance to ampicillin (75.8%) and TMP/SMX (55.8%) in our study, consistent with previous reports of the rate of resistance to ampicillin (55.0%–82.0%) and TMP/SMX (30.0%–57.1%).[12,30–32] In contrast, resistance to the first and third generation cephalosporins and aminoglycosides was relatively low in this study, with resistance rates of 24.2% to cefazolin, 6.9% to ceftriaxone, 13.1% to gentamicin and 0% to amikacin, in accordance with recent reported resistance rates of 24.0%–46.3% to cefazolin, 12.9%–24.9% to gentamicin and 0%–1.1% to amikacin in Taiwan.[31–34] It is important to start empiric treatment of childhood UTI considering not only the most probable uropathogen

TABLE 4. Independent Risk Factors of Renal Scarring in Children Hospitalized After the First Febrile UTI, by Multivariate Logistic Analysis*

Variable	OR (95% CI)	*P*
Age (mo)		
≤2	1	
2–24	3.281 (0.820–13.131)	0.093
Sex		
Boys	1	
Girls	1.319 (0.574–3.029)	0.514
Biomarker		
CRP (mg/dL)	1.010 (0.946–1.079)	0.765
WBC count (mm^3)	1.000 (1.000–1.000)	0.721
PCT (ng/mL)	2.114 (1.740–2.568)	<0.001
VUR grade		
No	1	
I–II	6.433 (1.688–24.525)	0.006
III–V	9.522 (3.679–24.641)	<0.001
US findings		
Normal	1	
Abnormal	6.680 (2.860–15.605)	<0.001

*For multivariate regression analysis, a binary logistic regression model with stepwise procedure was used.

CI, confidence interval; OR, odds ratio.

but also its most likely antimicrobial susceptibility when selecting the antimicrobial agents. Although no standard antibiotic treatment exists, our findings imply that the antibiotic policy with a combination of cefazolin and gentamicin is an appropriate treatment for our children ≤24 months of age with a first community-acquired febrile UTI.

Associated *E. coli* bacteremia occurred in 3 infants (4.9%) of the young infant group, consistent with results of 0%–12.8% of young infants with a UTI.[2,8–10,12,13] Despite the small number of subjects with UTI-associated bacteremia, the clinical course in all children was uneventful with no extrarenal complications, consistent with previous reports of such patients.[8,10–12,18]

UT anomalies are reported to affect 20% to 50% of young children with UTI,[3,12,35] of which VUR is the most common finding. Abnormal US findings were detected in 33.5% of children in this study, consistent with other findings of 8%–47.4%.[8–13] Despite different criteria being used to define US abnormalities in each study, most patients had normal US findings. In this study, the negative predictive value of US for grades III–V VUR indicates that approximately 11% of patients with normal US findings would have had a misdiagnosis when they actually had grades III–V VUR (Table 3). Although a normal US cannot exclude high-grade VUR, most grades IV and V VUR are detected on US.[12,36–38] Our findings are in agreement with previous reports of identifying most grades IV–V VUR on US,[12,36–38] indicating that when US findings are normal in children after a UTI, the risk of missing grades IV–V VUR is low. Therefore, we suggest a less aggressive diagnostic approach like US in the first management of children after a first UTI to identify the high-risk group for whom a further imaging workup is necessary.

An increased incidence of urinary tract anomalies, most commonly VUR, in boys is an explanation for the male predominance of UTI during the first 2 months of life.[38,39] Our results identify a significant rate (49%) of any VUR in infants ≤2 months of age regardless of sex, similar to the reported prevalence of 21%–75% of anatomic abnormalities in this age group,[9,11–13,38,39] suggesting that children with urinary tract abnormalities may have a higher prevalence for UTI earlier in life. Therefore, others' and our findings are in disagreement with recent Vachharajani et al[8] recommendations that VCUG may not be required in all infants under the age of 2 months after a UTI.

Our results show that 28.6% of this study had RS, and the primary clinical outcomes were similar between the 2 groups. We selected RS as the primary clinical outcomes because RS is more likely to cause long-term medical complications and possibly affect renal function. In addition, selecting RS as the clinical outcomes allowed us to demonstrate whether the presence and degree of VUR could lead to the development of RS. Our findings suggest that abnormal US findings and the presence and grade of VUR, especially grades III–V VUR, are important risk factors for the development of RS, consistent with the recent studies,[6,24,40–42] indicating that VUR is a clinically significant condition.[6,40–43]

This study has several strengths. Data were collected using strict protocols from a single center. By using rigorous methodology, this study has applied a consistent strategy for managing children with a first-episode febrile UTI. To date, this study represents the largest cohort from a single center on the measurement of PCT as a biomarker and predictor in children with a febrile UTI.[28] Moreover, children with an abnormal acute DMSA were followed-up to identify those who developed RS, not performed in previous studies.[8–13]

Nonetheless, this study has several limitations. First, it only enrolled hospitalized children ≤24 months of age with their first-episode febrile UTI. This may create selection bias. The current findings may not be immediately generalized or extrapolated to outpatients with UTI, those with afebrile UTI and patients with recurrent UTIs. Second, this study had strict criteria and only enrolled subjects who had completed imaging workup of US, acute and late DMSA scanning and VCUG. This may prevent further generalizations of the findings. Finally, the number of reported cases of young infants ≤2 months of age may be too small to make a firm conclusion. Further prospective studies with larger cohorts are warranted.

In conclusion, there are important similarities like male predominance, similar results of inflammatory markers and antimicrobial resistance patterns, comparable incidence of APN and UTI-associated urinary tract abnormalities, as well as uneventful clinical courses and similar clinical outcomes between the first-diagnosed febrile UTI in young infants ≤2 months of age and those in young children 2–24 months of age. Our findings suggest that abnormal US findings and the presence and grade of VUR are important predictors of RS. Therefore, diagnostic imaging of the urinary tract in children after their first febrile UTI is essential. We suggest that the same guidelines for the diagnosis and management after the first febrile UTI can be applied to all children who are ≤24 months of age.

REFERENCES

1. 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;128:595−610.
2. Lin DS, Huang SH, Lin CC, et al. Urinary tract infection in febrile infants younger than eight weeks of age. *Pediatrics*. 2000;105:E20.
3. Stefanidis CJ, Siomou E. Imaging strategies for vesicoureteral reflux diagnosis. *Pediatr Nephrol*. 2007;22:937−947.
4. Rushton HG. The evaluation of acute pyelonephritis and renal scarring with technetium 99m-dimercaptosuccinic acid renal scintigraphy: evolving concepts and future directions. *Pediatr Nephrol*. 1997;11:108–120.
5. Lahdes-Vasama T, Niskanen K, Rönnholm K. Outcome of kidneys in patients treated for vesicoureteral reflux (VUR) during childhood. *Nephrol Dial Transplant*. 2006;21:2491–2497.
6. Shaikh N, Ewing AL, Bhatnagar S, et al. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics*. 2010;126:1084–1091.
7. RIVUR Trail Investigators. Antimicrobial prophylaxis for children with vesicoureteral reflux. *N Engl J Med*. 2014;370:2367–2376.
8. Vachharajani A, Vricella GJ, Najaf T, et al. Prevalence of upper urinary tract anomalies in hospitalized premature infants with urinary tract infection. *J Perinatol*. 2015;35:362–366.
9. Wang SF, Huang FY, Chiu NC, et al. Urinary tract infection in infants less than 2 months of age. *Acta Paed Sin*. 1994;35:294–300.
10. Dayan PS, Hanson E, Bennett JE, et al. Clinical course of urinary tract infections in infants younger than 60 days of age. *Pediatr Emerg Care*. 2004;20:85–88.
11. Kanellopoulos TA, Salakos C, Spiliopoulou I, et al. First urinary tract infection in neonates, infants and young children: a comparative study. *Pediatr Nephrol*. 2006;21:1131–1137.
12. Ismaili K, Lolin K, Damry N, et al. Febrile urinary tract infections in 0- to 3-month-old infants: a prospective follow-up study. *J Pediatr*. 2011;158:91–94.
13. Bonadio W, Maida G. Urinary tract infection in outpatient febrile infants younger than 30 days of age: a 10-year evaluation. *Pediatr Infect Dis J*. 2014;33:342–344.
14. Liao PF, Ku MS, Tsai JD, et al. Comparison of procalcitonin and different guidelines for first febrile urinary tract infection in children by imaging. *Pediatr Nephrol*. 2014;29:1567–1574.
15. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing: seventeenth informational supplement. CLSI document. M100-S17. Wayne, PA: Clinical and Laboratory Standards Institute; 2007.
16. Sun HL, Wu KH, Chen SM, et al. Role of procalcitonin in predicting dilating vesicoureteral reflux in young children hospitalized with a first febrile urinary tract infection. *Pediatr Infect Dis J*. 2013;32:e348–e354.

17. Sheu JN, Wu KH, Chen SM, et al. Acute 99mTc DMSA scan predicts dilating vesicoureteral reflux in young children with a first febrile urinary tract infection: a population-based cohort study. *Clin Nucl Med*. 2013;38:163–168.
18. Hoberman A, Wald ER, Hickey RW, et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics*. 1999;104(1 pt 1):79–86.
19. Lebowitz RL, Olbing H, Parkkulainen KV, et al. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. *Pediatr Radiol*. 1985;15:105–109.
20. Tsai JD, Huang CT, Lin PY, et al. Screening high-grade vesicoureteral reflux in young infants with a febrile urinary tract infection. *Pediatr Nephrol*. 2012;27:955–963.
21. Lee MD, Lin CC, Huang FY, et al. Screening young children with a first febrile urinary tract infection for high-grade vesicoureteral reflux with renal ultrasound scanning and technetium-99m-labeled dimercaptosuccinic acid scanning. *J Pediatr*. 2009;154:797–802.
22. Tappin DM, Murphy AV, Mocan H, et al. A prospective study of children with first acute symptomatic E. coli urinary tract infection. Early 99mtechnetium dimercaptosuccinic acid scan appearances. *Acta Paediatr Scand*. 1989;78:923–929.
23. Ditchfield MR, de Campo JF, Nolan TM, et al. Risk factors in the development of early renal cortical defects in children with urinary tract infection. *AJR Am J Roentgenol*. 1994;162:1393–1397.
24. Hansson S, Dhamey M, Sigström O, et al. Dimercapto-succinic acid scintigraphy instead of voiding cystourethrography for infants with urinary tract infection. *J Urol*. 2004;172:1071–3; discussion 1073.
25. Herz D, Merguerian P, McQuiston L, et al. 5-year prospective results of dimercapto-succinic acid imaging in children with febrile urinary tract infection: proof that the top-down approach works. *J Urol*. 2010;184(4 suppl):1703–1709.
26. Garin EH, Olavarria F, Araya C, et al. Diagnostic significance of clinical and laboratory findings to localize site of urinary infection. *Pediatr Nephrol*. 2007;22:1002–1006.
27. Shaikh N, Hoberman A, Rockette HE, et al. Identifying children with vesicoureteral reflux: a comparison of 2 approaches. *J Urol*. 2012;188: 1895–1899.
28. Leroy S, Fernandez-Lopez A, Nikfar R, et al. Association of procalcitonin with acute pyelonephritis and renal scars in pediatric UTI. *Pediatrics*. 2013;131:870–879.
29. Prelog M, Schiefecker D, Fille M, et al. Febrile urinary tract infection in children: ampicillin and trimethoprim insufficient as empirical mono-therapy. *Pediatr Nephrol*. 2008;23:597–602.
30. Saperston KN, Shapiro DJ, Hersh AL, et al. A comparison of inpatient versus outpatient resistance patterns of pediatric urinary tract infection. *J Urol*. 2014;191(5 suppl):1608–1613.
31. Cheng CH, Tsai MH, Huang YC, et al. Antibiotic resistance patterns of community-acquired urinary tract infections in children with vesicoureteral reflux receiving prophylactic antibiotic therapy. *Pediatrics*. 2008;122:1212–1217.
32. Wu CY, Chiu PC, Hsieh KS, et al. Childhood urinary tract infection: a clinical analysis of 597 cases. *Acta Paediatr Taiwan*. 2004;45:328–333.
33. Tseng MH, Lo WT, Lin WJ, et al. Changing trend in antimicrobial resistance of pediatric uropathogens in Taiwan. *Pediatr Int*. 2008;50:797–800.
34. Wu JH, Chiou YH, Chang JT, et al. Urinary tract infection in infants: a single-center clinical analysis in southern Taiwan. *Pediatr Neonatol*. 2012;53:283–288.
35. Ring E, Zobel G. Urinary infection and malformations of urinary tract in infancy. *Arch Dis Child*. 1988;63:818–820.
36. Preda I, Jodal U, Sixt R, et al. Value of ultrasound in evaluation of infants with first urinary tract infection. *J Urol*. 2010;183:1984–1988.
37. Kovanlikaya A, Kazam J, Dunning A, et al. The role of ultrasonography in predicting vesicoureteral reflux. *Urology*. 2014;84:1205–1210.
38. Goldman M, Lahat E, Strauss S, et al. Imaging after urinary tract infection in male neonates. *Pediatrics*. 2000;105:1232–1235.
39. Burbrige KA, Retic AB, Colodny AH, et al. Urinary tract infection in boys. *J Urol*. 1984;132:541–542.
40. Swerkersson S, Jodal U, Sixt R, et al. Relationship among vesicoureteral reflux, urinary tract infection and renal damage in children. *J Urol*. 2007;178:647–651; discussion 650.
41. Orellana P, Baquedano P, Rangarajan V, et al. Relationship between acute pyelonephritis, renal scarring, and vesicoureteral reflux. Results of a coordinated research project. *Pediatr Nephrol*. 2004;19:1122–1126.
42. Shaikh N, Craig JC, Rovers MM, et al. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. *JAMA Pediatr*. 2014;168:893–900.
43. Coulthard MG. Vesicoureteric reflux is not a benign condition. *Pediatr Nephrol*. 2009;24:227–232.