Characteristics of First Urinary Tract Infection With Fever in Children

A Prospective Clinical and Imaging Study

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Background: Our objective is to provide the clinical characteristics, uropathogen frequencies, and antimicrobial resistance rates of first urinary tract infection (UTI) diagnosed in febrile Belgian children. The ability of noninvasive ultrasound to detect renal abnormalities and vesicoureteral reflux (VUR) in these patients was also assessed.

Methods: We prospectively followed (median, 20 months) 209 children treated for first febrile UTI. Renal ultrasound (US) and voiding cystourethrography examinations were performed in all patients.

Results: Among these children, 63% were females and 37% were males, and 75% of them had their first UTI before the age of 2 years. The most common causative agent was *Escherichia coli* (91% of cases) with high rate resistance to ampicillin (58%) and trimethoprim/sulfamethoxazole (38%). Of these children, 25% had evidence of VUR (15 boys and 38 girls). VUR was of low grade in 85% of cases. The overall performance of renal US as a diagnostic test to detect significant uropathies excluding low-grade VUR was excellent; the sensitivity attained 97% and the specificity 94%.

Conclusion: Girls represent 63% of cases with first UTI. For 91% of UTIs, *Escherichia coli* is held responsible with a high rate of resistance to ampicillin and trimethoprim/sulfamethoxazole. US is an excellent screening tool that allows avoidance of unjustified voiding cystourethrography studies.

Key Words: urinary tract infection with fever, first episode, voiding, cystourethrography, vesicoureteral reflux, ultrasonography.

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Urinary tract infection (UTI) is one of the most common infections diagnosed in outpatients and hospitalized pediatric patients, with 8% of girls and 2% of boys experiencing at least one UTI by the age of 7 years.[1] Renal ultrasonography (US) and voiding cystourethrography (VCUG) examinations have been standard diagnostic tools for children with first UTI to identify possible structural or functional abnormalities of the urinary tract, such as vesicoureteral reflux (VUR). These abnormalities were thought to be important to detect as they have been suspected to predispose the child to repeated episodes of pyelonephritis and potentially irreversible renal damage.[2,3]

There is growing concern regarding the resistance of uropathogens to antibiotics, because of the increasing number of failures of empiric treatments administered according to national and international guidelines for children.[4]

The major aim of this prospective study was to describe the characteristics and the clinical evolution of first UTI that was diagnosed by systematic screening in the emergency department of febrile Belgian children in whom UTI was considered a possibility on clinical grounds. The second aim of this study was to characterize the frequencies of uropathogens and their antimicrobial resistance rates to evaluate the options for empiric antibiotic therapy for UTI in Belgian children. Finally, we investigated the diagnostic performance of renal US to detect significant congenital abnormalities of the urinary tract that might predispose children to recurrent infections.

METHODS

Between July 2006 and July 2008, we prospectively collected data on 209 children (median age of 10 months; 0.2–204 months) who were diagnosed with a clinically proven first episode of UTI at the emergency department of our hospital. These patients were followed at least for 1 year.

Sample of urine was collected from all febrile children admitted to the emergency department with high suspicion of UTI. UTI was suspected in the presence of at least a combination of 2 of the following criteria: C-reactive protein $\geq$4.0 mg/dL, leukocytosis $\geq$15,000/mm^3, signs of systemic infection with deteriorated health condition; vomiting and poor feeding in infants; and back pain and chills in older children.

We defined a positive urinalysis as a trace or greater result for leukocyte esterase and/or nitrite on dipstick or as the presence of $\geq$35 leukocytes/μL of un centrifuged urine. UTI was confirmed in those children having growth of $\geq$100,000 colony-forming units per milliliter in urine culture. In urine samples obtained by suprapubic aspiration, any growth of enteric Gram-negative pathogens was considered significant.

All urine samples from children younger than 24 months were obtained by suprapubic aspiration or a single bladder catheterization. Urine samples from older children were obtained by clean catch or bladder single catheterization.

All febrile patients with UTI were treated, according to a predefined local antibiotic protocol, parenterally with cefotaxime and amikacin in young infants (0–3 months of age), and with ampicillin and amikacin when aged 4 months to 1 year. Children older than 1 year were treated parenterally with temocillin (6-alpha-methoxy-ticarcillin). Treatment was adapted to antibiogram

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results. Oral treatment was started after 48 hours of apyrexia. The total duration of treatment was of 2 weeks.

According to the standard of care in our institution, all febrile children with a first episode of UTI are evaluated with an US examination of the urinary tract during hospitalization, and a routine VCUG is performed at least 1 month after the first UTI. The criteria for abnormal US included pelvic anteroposterior diameter ≥7 mm, calyceal or ureteral dilatation, pelvic or ureteral wall thickening, absence of the corticomedullary differentiation, and signs of renal dysplasia (small kidney, thinned or hyperechogenic cortex, and cortical cysts).[5] The US examinations were performed by the same trained pediatric radiologists using adapted equipment, with high-resolution curvilinear and linear transducers with settings optimized for pediatric patients. VUR was graded by means of the International Reflux Study Committee classification.[6]

Characterization of the pathogens and antibiotic susceptibility testing was performed according to standardized procedures in the laboratory of the Department of Microbiology of our institution.

The study protocol was reviewed and approved by the Ethics committee of our institution. The study was designed as a quality control of current center practice according to treatment and diagnostic work-up protocols routinely applied to all febrile patients admitted with UTI to our institution. For this reason, written informed consent was not requested from the parents of children who contributed data to the present study. To guarantee data confidentiality, data were anonymized, birthdates were deleted after the age had been calculated, and the data file was conserved on a password protected laptop computer.

Categorical data are shown as proportions and expressed as percentage. Continuous data are shown as medians with minimal and maximal figures. The diagnostic performance of renal US to detect VUR was assessed against the conventional standard of VCUG. Sensitivity was defined as the proportion of patients with positive VCUG who had positive renal US, specificity as the proportion of patients with negative VCUG who had negative renal US. The positive predictive value was the proportion of patients with positive renal US who had positive VCUG and the negative predictive value as the proportion of patients with negative renal US who had negative VCUG. All descriptive statistical analysis was done using STATA 7.0 for Windows (Stata Corporation, College Station, TX).

RESULTS

During this prospective 2-year inclusion period, 245 consecutive febrile children (272 episodes) were treated for UTI in our hospital in Brussels. Of them, 209 (85%) had first UTI.

Among the 209 children with first UTI, 132 (63%) were girls and 77 (37%) were boys. The median follow-up period was of 20 months (12–40 months) and 35 (16%) patients were lost to follow-up.

Demographics and initial clinical data are summarized in Table 1. In all, 157 children (75%) had their first UTI before the age of 2 years.

All but 11 (5%) of these children had available antenatal US examination data. Only 17 of 198 (9%) of them had known congenital abnormalities of the kidney and urinary tract (CAKUT) (Table 1).

The most common pathogen that caused UTI was *Escherichia coli*, which grew in 189 (91%) cultures. Frequencies of other pathogens were as follows: *Klebsiella pneumoniae*, 8 (4%); *Proteus mirabilis,* 6 (3%); *Enterobacter* spp., 2 (1%); *Citrobacter* spp., 1 (0.5%); *Streptococcus faecalis,* 1 (0.5%); and *Pseudomonas aeruginosa*, 0 (0%).

TABLE 1. Demographics and Initial Clinical Data

Data	Total (%)
Gender	
Male	77 (37%)
Female	132 (63%)
Age distribution (mo)	
0–3	43 (21%)
4–12	77 (37%)
13–24	37 (18%)
25–36	13 (6%)
>36	39 (19%)
Duration of fever at entry (d)	
<1	37 (18%)
1–2	90 (43%)
2–3	37 (18%)
>3	45 (22%)
Level of CRP (mg/dL)	
<4	43 (21%)
4–10	72 (34%)
>10	94 (45%)
Antenatal US examinations results	
Available data	198 (95%)
CAKUT	17 (9%)
High-grade reflux	6 (3%)
Pyeloureteral junction obstruction	5 (2.5%)
Duplex kidneys	2 (1%)
Dysplastic kidneys	2 (1%)
Posterior urethral valves	1 (0.5%)
Primary megaureter	1 (0.5%)

CAKUT indicates congenital abnormalities of the kidney and/or urinary tract; CRP, C-reactive protein.

Resistance to ampicillin and trimethoprim/sulfamethoxazole among *E. coli* isolates was 58% and 36%, respectively. Table, Supplemental Digital Content 1, http://links.lww.com/INF/A693, shows the frequency of resistance to other selected antibiotics. Nitrofurantoin, temocillin, and amikacin were the most active agents against *E. coli* (0% resistant isolates), followed by cephalosporins of second and third generation (1.5%), gentamicin (2.5%), ciprofloxacin (2.5%), and amoxicillin/clavulanic acid (8%). Amikacin and temocillin were also the most active agents against *K. pneumoniae* and *P. mirabilis*; none of these isolates were found to be resistant to these antimicrobial agents.

Extended-spectrum beta-lactamase (ESBL) production was observed in 3 (1.5%) isolates (3 *E. coli*). The antimicrobial resistance rates among ESBL-producing isolates against temocillin, amikacin, and gentamicin were 0%, 0%, and 33%, respectively. All the ESBL producers were obtained from children aged <6 months. Moreover, before entry, none of these patients had received antibiotic therapy for any reason and only one had significant CAKUT.

Associated bacteremia occurred in 7 children (3.5%). There were 3 boys and 4 girls with a median age of 6 months (0.2–150 months). CAKUT was present in only one boy (posterior urethral valves). The median duration of fever at the time of diagnosis was of 1 day (range, <1–4 days). The median level of C-reactive protein was of 10.7 mg/dL (4–33.7 mg/dL).

A renal US was obtained within 48 hours of the diagnosis of UTI in all 209 children. Of these, 170 (81%) did not show any structural abnormality; the findings on US are shown in Table 2. VCUG was performed in all children, at least 1 month after diagnosis. Fifty-three children (25%) had evidence of VUR (15 boys and 38 girls). In 45 (85%) cases of VUR, the reflux was classified as grade I, II, or III (low-grade) (Table 2).

Only 18 of 53 (34%) patients with VUR on VCUG had an abnormal renal US examination. This was largely because of a low sensitivity of renal US to detect low-grade reflux (11/45, sensitiv-

TABLE 2. Association Between the Presence of CAKUT and Abnormal Renal Ultrasound Examination in Febrile Children Hospitalized for a First Urinary Tract Infection

CAKUTs	Total	US After UTI	
		Abnormal	Normal
Total	209 (100%)	39	170
Low-grade VUR	45 (21%)	11	34
High-grade VUR	8 (4%)	7	1
Mild hydronephrosis	7 (3%)	7	0
PUJO	5 (2%)	5	0
Duplex kidney	3 (1.5%)	3	0
Primary megaureter	2 (1%)	2	0
Renal dysplasia	2 (1%)	2	0
PUV	2 (1%)	2	0
Any CAKUT	74 (35%)	39	35
Any CAKUT excluding low-grade VUR*	29 (14%)	28	1
None	135 (65%)	0	135

*The overall performance of renal US as a diagnostic test to detect CAKUT excluding low-grade VUR: Sensitivity: 28/29 = 97%, Specificity: 169/180 = 94%, PPV: 28/39 = 72%, NPV: 169/170 = 99%.

CAKUT indicates congenital abnormalities of the kidney and/or urinary tract; VUR, vesicoureteric reflux; PUJO, pyeloureteral junction obstruction; PUV, posterior urethral valves.

ity 24%). However, 7 of 8 (88%) patients with grade IV–V VUR had abnormal renal US suggesting renal pathology. VUR of grade IV–V was more likely to occur among children with important abnormal ultrasonographic findings such as renal dysplasia and calyceal dilatations.

The overall performance of renal US as a diagnostic test to detect significant CAKUT excluding low-grade VUR was excellent; the sensitivity attained was 97% and the specificity 94% (Table 2).

Twenty-three children (11%), 19 girls and 4 boys, have had recurrence of infection during follow-up period. In 12 of them (52%), the urinary tract was normal on imaging work-up. In contrast, 8 children had low-grade VUR, 2 had high-grade VUR, and 1 had a complex duplex kidney. The median age of occurrence of first UTI in these children was 6 months (from 2 to 64 months). The median time of occurrence of first recurrence was 7 months (from 0.1 to 30 months).

DISCUSSION

Most UTIs in children are caused by Gram-negative aerobic bacilli. *E. coli* is the most common organism isolated, accounting for up to 80% of infections.[7] This comprehensive data analysis in children with UTIs in a pediatric hospital setting in Belgium shows that *E. coli* remains the predominant organism causing UTIs and was isolated in 91% of cases. This is in accordance with the pattern of bacterial strains isolated from patients with community-acquired UTIs reported in other regions of the world in recent years.[8,9]

There is growing concern regarding the increasing *E. coli* resistance to first-line antibiotics such as ampicillin and trimethoprim/sulfamethoxazole.[10,11] This worrisome problem was also observed in Belgium. As shown in the current study, resistance rates to ampicillin and trimethoprim/sulfamethoxazole were high (58% and 36%, respectively). In addition, rising resistance patterns to amoxicillin/clavulanic acid are also observed in Europe. Chakupurakal et al[12] have recently found in the United Kingdom that *E. coli* UTIs were uniformly susceptible to amoxicillin/clavulanic acid in 2002, but the resistant pattern changed in 2008, with 48% of *E. coli* UTIs being resistant. Our findings are less impressive (8% resistance rate to amoxicillin/clavulanic acid) but resistance should be taken into consideration in daily clinical practice.

Because antibiotic resistance is an important factor, we would like to emphasize that urine culture and antibiotic susceptibility testing should be routinely performed in pediatric patients with UTI. This attitude is not common among general practitioners even in developed countries like Holland.[13] We also believe that the local/regional policies for the choice of first-line antibiotic treatment for complicated UTI in children should be reviewed regularly according to local resistance rates. Gram-negative aerobic bacilli seem to have extremely low resistance to temocillin. Temocillin is the 6-α-methoxy derivative of ticarcillin. The potential weaknesses of temocillin, explaining its limited previous use, are a lack of activity against Gram-positive organisms, anaerobes, and *Pseudomonas*.[14] These uropathogens were isolated in less than 1% of our patients. Despite its narrow spectrum, temocillin seems to be an excellent first-line therapy for UTI in children as it efficiently treats almost all bacteria isolated from the urinary tract in our series, even including ESBL + strains.

Debate is offered in the literature concerning imaging of the urinary tract in children with UTI.[15] The arguments in favor of early evaluation of children with documented UTI include that up to 40% of those undergoing VCUG may have VUR.[16] In addition, 60% to 80% of children with VUR may have recurrent infection within 18 months of presentation.[17] Only 25% of our patients with UTI presented VUR on VCUG with 85% of them having low-grade VUR. Furthermore, relapses were seen in only 11% of patients within a median period of 7 months after presentation.

VUR is surrounded by several myths that are currently being vigorously debated.[18,19] The concept of VUR predisposing to UTI and renal scarring is on the basis of the notion that the majority of urinary infections are ascending in origin. This is thought to be particularly important in VUR where the presence of intrapelvic reflux will carry the bacteria into the renal parenchyma causing potential scars.[20] However, clinical studies report that renal scarring may also occur in 62% of kidneys in the absence of demonstrable reflux.[21] Nevertheless, there is a widely held belief that UTI and VUR are important and that reflux is often considered as the main risk factor for recurrent UTI and renal scarring.[18,22]

With a vast majority of children with UTI having a low risk of recurrence, as shown in our study, a major question is the extent to which these children are submitted to unnecessary and invasive investigations. A prospective multicenter study suggested that in febrile children less than 2 years of age with UTI, US was not required because of the widespread use of prenatal US, and the authors stated that VCUG was the only imaging test which makes sense in this context.[23] Our data indicate that antenatal US examinations results are often not available at entry. In addition, and not surprisingly, we demonstrated that when US examination was normal in children after a first UTI with fever, the risk of missing a significant renal abnormality was extremely low. In children with normal US, a certain number of low-grade VUR are missed. However, it is now evident that the recurrence rate seen among patients with low-grade VUR is similar to that observed among patients without VUR.[24] It is therefore reasonable to consider that the risk of missing low-grade reflux would be outweighed by the benefit of avoiding unnecessary invasive examinations in the majority of these patients.[24] All children with high-grade VUR had hydronephrosis and/or signs of dysplasia visualized on US and would have been scheduled for more complete investigation. We believe, in common with other authors,[25,26] that US should remain the first-line examination in febrile children with a first UTI. The presence or absence of abnormal US represents the key for deciding about VCUG studies.

CONCLUSION

In summary, the present study shows the following:

1. Girls represent 63% of all cases with first UTI in the pediatric population.
2. Seventy-five percent of children have their first UTI before the age of 2 years.
3. *E. coli* is responsible for 91% of all UTIs with a high rate of resistance to ampicillin and trimethoprim/sulfamethoxazole.
4. Twenty-five percent of the children have evidence of VUR. VUR is of low grade in 85% of them.
5. Most cases of significant CAKUTs including high-grade VUR are detected by US. Therefore, the presence or absence of abnormal US represents the key for deciding about VCUG studies.
6. Eleven percent of children have recurrence of infection during follow-up period. Half of these patients have strictly normal urinary tract on imaging work-up.

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