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Follow-up after infants younger than 2 months of age with urinary tract infection in Southern Israel: epidemiologic, microbiologic and disease recurrence characteristics

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ABSTRACT

Background: The timing of most recurrences after neonatal urinary tract infection is during the first year of life, with peak incidence 2–6 months after the initial infection. Information on the microbiologic characteristics of recurrent urinary tract infection episodes in relation to the microbiology of the initial episodes is limited.
Objectives: To analyze the epidemiologic/microbiological characteristics of 1st and recurrent urinary tract infection in infants <2 months of age.
Methods: A retrospective study including all infants <2 months of age with urinary tract infection admitted during 2005–2009 and followed till the age of 1 year.
Results: 151 neonates were enrolled (2.7% of all 5617 febrile infants <2 months of age admitted). The overall incidence of urinary tract infection occurring during the first 2 months of life was 151/73,480 (0.2%) live births during 2005–2009 in southern Israel (2.1 cases/1000 live births). One pathogen was isolated in 133 (88.1%); *Escherichia coli*, *Klebsiella* spp., *Enterococcus* spp., *Morganella morganii*, *Proteus* spp., and *Enterobacter* spp. represented the most common pathogens (57.9%, 12.2%, 7.9%, 6.7%, 6.1%, and 5%, respectively). Trimethoprim/sulfamethoxazole, ampicillin, and cefuroxime-axetil were the most commonly recommended prophylactic antibiotics (45%, 13.2%, and 8%, respectively). Twenty-three recurrent urinary tract infection episodes were recorded in 20 (13.2%) patients; 6/23 (26%) were diagnosed within one month following 1st episode. *E. coli* was the most frequent recurrent urinary tract infection pathogen (12/23, 52.2%). No differences were recorded

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in *E. coli* distribution between first urinary tract infection vs. recurrent urinary tract infection. Seventeen (74%) recurrent urinary tract infection episodes were caused by pathogens different (phenotypically) from those isolated in 1st episode. Recurrent urinary tract infection occurred in 25.0%, 8.3%, and 0 patients recommended trimethoprim/sulfamethoxazole, cefuroxime-axetil, or amoxicillin prophylaxis, respectively.

Conclusions: (1) The study determined the incidence of urinary tract infection in febrile infants <2 months of age in Southern Israel; (2) *E. coli* was responsible for the majority of first and recurrent urinary tract infection; (3) recurrent urinary tract infection was caused mostly by pathogens different than the pathogens isolated at initial episode.

Introduction

The incidence of urinary tract infections (UTI) is 3–4.6% in neonates, 0.7–5.9% in infants up to 1 year of age, 1–3% at the age of 1–5 years and 0.71–2.3% at school age.[1,2] Approximately 7–8% of girls and 2% of boys will develop an UTI during the first 8 years of life.[3] The most common pathogen is *Escherichia coli*, causing up to 70–90% of all UTIs.[4,5]

Diagnosis of UTI is of major importance, particularly in young ages, because the infection may represent, potentially, the first sign of a congenital defect of the urinary tract. Early diagnosis and treatment are considered to prevent complications such as renal scarring, deteriorating renal function, and hypertension, especially in young infants and children <5 years of age.[6] The most common abnormality diagnosed by imaging investigation is vesico-uretheral reflux (VUR).[6–9] The rate of VUR in children <1 year of age is between 18–35%.[6,8,9] It is known today that severe VUR may be associated with development of renal scars by up to 4–6 times more than a low grade VUR and 8–10 times more likely than in patients without VUR.[6,8,9]

The timing of most UTI recurrences after neonatal UTI is during the first year of life, with peak incidence 2–6 months post infection.[10] In general, UTI recurrence occurs in 30–40% of the children with UTI and around 60% of them will have the recurrence during the first two years of life. In a retrospective study completed between 1978 and 1984 and including 262 children <1 year of age followed for three years after the first episode, 35% boys and 32% girls developed recurrent UTI and the recurrent UTI incidence was higher in children with higher (III–V) degrees of reflux.[11]

Information on the microbiologic characteristics of the recurrent UTI episodes in relation to the microbiology of the initial episodes is limited. The objectives of our study are to describe and characterize the 1st UTI episode in infants <2 months of age admitted at our center during 2005–2009, to determine the incidence of UTI in this population in Southern Israel, to establish the rates of recurrent UTI episodes until the age of 1 year and the microbiologic characteristics of these episodes, and to discuss the appropriate antibiotic treatment policies for the treatment and prophylaxis of UTI in infants.

Patients and methods

This was a retrospective study performed during 2005–2009 and including all the infants <2 months of age admitted to the pediatric departments of the Soroka University Medical Center with the diagnosis of UTI proven by urine culture (obtained by supra-pubic aspiration or bladder catheterization). Our hospital is the only primary and tertiary medical center in Southern Israel and takes care of a population of approximately 1 million patients, out of them around 250,000 children.[3]

Infants <2 months of age, following the hospitalization with UTI, were discharged with the recommendation for antibiotic prophylaxis and for imaging investigations of the urinary tract during the period of two months following the original UTI episode, according to the available recommendations.[6,8] The medical records of the admitted infants, laboratory findings from the bacteriological laboratory and imaging data from the radiology department and the nuclear medicine institute, were searched. Age, sex and ethnicity of the infants with UTI were documented. All urine cultures were obtained (at the initial and also the recurrent UTI episode) by catheterization or suprapubic aspiration. The recovered urine cultures pathogens were considered true uropathogens according to treatment physicians and additional recommendations by the pediatric infectious disease unit of the hospital. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans* were not considered true uropathogens in single pathogen or mixed pathogens-UTI cases without an additional renal anatomic abnormality.

A comparative analysis of the microbiological factors responsible for the first and for the recurrent UTI episodes was performed. The antibiotic coverage and duration of treatment of UTI were documented. The timing of the UTI recurrence was analyzed in relation to the initial UTI episode. Anatomical abnormalities diagnosed during the first episode of UTI were documented as well as all imaging finding completed during the follow-up period. When VUR diagnosis was present, its severity degree was reported.

The antibiotic prophylaxis policy was not well defined at the pediatric department during the study period, leaving at the physicians' decision the specific antibiotic to be administered. However, the local guidelines recommended antibiotic

prophylaxis for all infants <2 months of age with first UTI episodes until the completion of imaging studies.

The recommended imaging studies during the study period included the completion of an ultrasound (US) examination during hospitalization or after hospitalization in all cases of infants <2 months of age with UTI and performance of a voiding cystourethrogram (VCUG) after 6–8 weeks following the discharge from the hospital. Additional investigations, like Technetium-Dimercaptosuccinic (DMSA) scan, in specific cases, were performed according to nephrologist's recommendations.

The study was approved by the ethics committee of the hospital.

Statistical analysis

Data were recorded using the Access Microsoft Office software. Statistical analysis was performed using the SPSS 16.0 software. Contingency table analysis for comparing rates between unmatched samples was performed using the Chi-square or Fisher's exact test, as appropriate. Student's independent samples *t*-test or ANOVA were used to compare continuous variables.

Results

Overall, 151 infants <2 month of age diagnosed with the 1st UTI episode in life, were enrolled. These infants represented 2.7% of all 5617 infants <2 months of age admitted at the pediatric departments during the study years (22/1129 [1.9%], 34/1205 [2.8%], 45/1302 [3.4%], 24/1217 [2.0%], and 26/1029 [2.5%] during 2005, 2006, 2007, 2008, and 2009, respectively).

The overall incidence of UTI occurring during the first two months of life was 151/73,480 (0.2%) live births during 2005–2009 in the Negev area of Southern Israel, representing an incidence of 2.1 cases/1000 live births. The respective numbers for each year of the study were: 1.5, 2.4, 3.1, 1.6, and 1.7/1000 live births during 2005, 2006, 2007, 2008, and 2009 respectively.

The mean ± standard deviation age (in days) at UTI diagnosis was 42.26 ± 31.25 days for the whole study population; no differences were recorded in the mean age at first UTI diagnosis between male and female neonates (38.24 ± 15.8 vs. 42.26 ± 31.25, $p = 0.06$). There were 85 (56.3%) male patients (all circumcised) and 102 (67.5%) patients of Moslem Bedouin ethnicity.

One hundred and twenty (79.5%) young infants with UTI did not suffer from any previous pathologic conditions. The remaining 31 (21.5%) were diagnosed with various anomalies, of them 9 (5.9%) with renal anomalies (6 with hydronephrosis).

Concomitant pathologies were diagnosed at the time of UTI diagnosis in 25 (16.6%) patients with UTI; pneumonia and bronchiolitis were diagnosed concomitantly in 8 (5.3%) cases each and bacterial meningitis in 5 (3.3%).

Microbiology

One pathogen was isolated in 133 (88.1%) UTI episodes. *Escherichia coli*, *Klebsiella* spp., *Enterococcus* spp., *Morganella morganii*, *Proteus* spp., and *Enterobacter* spp. were the most frequently isolated pathogens (53.3%, 10.6%, 5.2%, 5.2%, 4.5%, and 3.9% of all episodes, respectively) – Table 1. Mixed infection caused by two organisms considered as true UTI pathogens was recorded in 18 (11.9%) episodes, with *E. coli* isolated in 6/18 (33.3%) episodes. In the two patients with mixed UTI with recovery of *P. aeruginosa* and *S. aureus* (together with *Klebsiella* spp. and *Enterococcus* spp., respectively), both isolates were considered as true uropathogens due to the concomitant presence of renal tract anatomic anomalies (moderate hydronephrosis and VUR degree IV, respectively).

Table 1 – Pathogen distribution: 151 episodes of first UTI occurring in 151 neonates <2 months of age.

Pathogens	*n* (%)
(1) Pathogen	133 (88.1)
Escherichia coli	85 (56.3)
Klebsiella spp.	16 (10.6)
Enterococcus spp.	8 (5.2)
Morganella morganii	8 (5.2)
Proteus spp.	7 (4.5)
Enterobacter spp.	6 (3.9)
Citrobacter spp.	2 (1.3)
Serratia marcescens	1 (0.6)
(2) Pathogens (mixed infection)	18 (11.9)
Escherichia coli + *Enterococcus* spp.	3 (1.9)
Escherichia coli + *Klebsiella* spp.	2 (1.3)
Escherichia coli + *Proteus* spp.	2 (1.3)
Escherichia coli + type b *Haemophilus influenzae*	1 (0.6)
Escherichia coli + *Morganella morganii*	1 (0.6)
Escherichia coli + *Acinetobacter* spp.	1 (0.6)
Klebsiella spp. + *Enterococcus* spp.	1 (0.6)
Klebsiella spp. + *Pseudomonas* spp.	1 (0.6)
Morganella morganii + *Enterococcus* spp.	1 (0.6)
Morganella morganii + *Klebsiella* spp.	1 (0.6)
Enterobacter spp. + *Enterococcus* spp.	1 (0.6)
Enterobacter spp. + *Proteus* spp.	1 (0.6)
Proteus spp. + *Enterococcus* spp.	1 (0.6)
Enterococcus spp. + *Staphylococcus aureus*	1(0.6)

Overall, there were 169 uropathogens, of them 95 (57.9%) *E. coli* isolates. *Klebsiella* spp., *Enterococcus* spp., *M. morganii*, *Proteus* spp., and *Enterobacter* spp. represented the most common UTI pathogens isolated (in decreasing frequency) following *E. coli* (12.2%, 7.9%, 6.7%, 6.1%, and 5% of all pathogens, respectively).

No statistical differences were recorded between *E. coli*-UTI cases recorded in male vs. female patients (68.2% vs. 56%, $p = 0.5$). Significantly more *E. coli*-UTI cases were recorded in Bedouin patients compared with Jewish patients (70.6% vs. 46.9%, $p = 0.005$).

Antibiotic prophylaxis following the first UTI episodes

Trimethoprim/sulfamethoxazole (TMP/SMX) was the most common prophylactic antibiotic recommended (68, 45% of all enrolled patients) in the study patients following the first UTI episodes. Amoxicillin and cefuroxime-axetil were the next most common prophylactic antibiotic recommended (20 [13.2%] and 12 [8%] of all enrolled patients). Forty-five (29.8%) of the patients enrolled in the study did not receive

Table 2 – Epidemiologic, microbiologic, and therapeutic characteristics: 20 patients (23 episodes) with UTI recurrence.

No.	M/F	Age at recurrence (months)	Renal background pathology	Pathogen in 1st episode	Pathogen in 2nd episode	Antimicrobial prophylaxis after first UTI
1	F	12		*E. coli*	*E. coli*	TMP/SMX
2	M	1		*Proteus* spp.	*C. albicans*	TMP/SMX
3	F	2		*Proteus* spp.	*P. aeruginosa*	TMP/SMX
4	F	3		*E. coli*	*Citrobacter* spp.	TMP/SMX
5	M	2		*Enterobacter* spp. + *Enterococcus* spp.	*E. coli*	TMP/SMX
6	F	2		*E. coli*	*Enterobacter* spp.	NA
7	M	2		*E. coli*	*Klebsiella* spp.	NA
8	M	3		*E. coli*	*E. coli*	TMP/SMX
9	F	3		*E. coli*	*E. coli*	Cefuroxime-axetil
10	M	6		*E. coli*	*E. coli*	TMP/SMX
11	F	4		*M. morganii*	*E. coli*	TMP/SMX
12	M	7		*E. coli*	*E. coli*	TMP/SMX
13	M	6		*E. coli*	*E. coli*	TMP/SMX
14	F	11		*Proteus* spp.	*E. coli*	NA
15	M	11	Hydronephrosis	*Enterobacter* spp.	*Enterococcus* spp.	TMP/SMX
16	M	10	Hydronephrosis	*Enterobacter* spp.	*Enterobacter* spp.	TMP/SMX
17	M	4		*E. coli*	*E. coli*	NA
18.1	M	7		*Klebsiella* spp.	*Proteus* spp.	TMP/SMX
18.2		9		*Klebsiella* spp.	*E. coli*	TMP/SMX
19.1	M	3	Congenital megaurether, UVJ obstruction, hydronephrosis	*Klebsiella* spp.	*S. aureus*	TMP/SMX
19.2		7		*Klebsiella* spp.	*C. albicans*	TMP/SMX
19.3		10		*Klebsiella* spp.	*E. coli*	TMP/SMX
20	M	12		*Klebsiella* spp.	*Klebsiella* spp.	NA

TMP/SMX, trimethoprim/sulfamethoxazole; NA, not administered; UVJ, urethero-vesicular junction.

any recommendation for antibiotic prophylaxis following the initial UTI episode.

Imaging studies

US was performed in 83 (54.9%) patients; 68 (81.9%) of these examinations were reported as normal. The abnormal findings diagnosed in 15 (18.1%) patients included: mild to severe hydronephrosis in all cases, one megaureter and one case suspected of nephrolithiasis. VCUG was performed in 66 (43.7%) and was diagnosed as normal in 52 (78.8%); VUR of degrees IV–V was found in three patients.

Recurrent UTI (Table 2)

Recurrent UTI episodes were recorded in 20/151 (13.2%) patients. One patient developed two UTI recurrences during the first year of life and one patient developed three UTI recurrences within the first year of life. Recurrent UTI was recorded in 13 males and seven female patients; 6/23 (26%) recurrent UTI episode were diagnosed within one month following the discharge after the first UTI episode. Three of the patients with recurrent UTI had a previously diagnosed renal abnormality (all three with hydronephrosis, one of them with urethero-vesicular obstruction)

Five of the patients with recurrent UTI did not receive any antibiotic prophylaxis following the first UTI episode. There were 23 uropathogens; no mixed pathogens recurrent UTI episodes were recorded. *E. coli* was the most frequent UTI pathogen recovered in recurrent UTI (12/23, 52.2% of all recurrent UTI episodes). No differences were recorded in the representation of *E. coli* among all the pathogens isolated in the first UTI episodes compared with the recurrent UTI episodes (95/151, 62.9% vs. 12/23, 52.2%, $p = 0.30$).

Seventeen (74%) of the 23 episodes of recurrent UTI were caused by pathogens different (phenotypically) from the pathogen isolated at the first UTI episode. In two of these episodes, the initial and recurrent UTI pathogen was *E. coli* with a different antibiotic susceptibility profile. Six (26%) of the 23 episodes of recurrent UTI were caused by the same (phenotypically) pathogens as those causing the first UTI episode: four *E. coli*, one *Klebsiella* spp. and one *Enterobacter* spp.

Recurrent UTI episodes occurred in 17/68 (25.0%), 1/12 (8.3%), and 0/20 of patients receiving initial prophylaxis with TMP/SMX, cefuroxime-axetil, or amoxicillin, respectively.

Antibiotic susceptibilities of uropathogens isolated at the initial and recurrent UTI episode (Table 3)

At the initial UTI episode, the antibiotic resistance of *E. coli* isolates to the most commonly used oral antibiotics was 57.9%, 13.5%, 9.9%, and 5.4% for ampicillin, amoxicillin/clavulanic acid, TMP/SMX, and cefuroxime-axetil. The respective numbers for the two most commonly used IM/IV antibiotic drugs were 3.9% and 2.1% for ceftriaxone and gentamicin. The antibiotic resistance of *Klebsiella* spp. isolates to the most commonly used oral antibiotics was 90.0%, 21.4%, 14.3%, and 6.3% for ampicillin, amoxicillin/clavulanic acid, cefuroxime-axetil, and TMP/SMX. The respective numbers for the two most commonly used IM/IV antibiotic drugs were 6.3% and 4.8% for ceftriaxone and gentamicin. All 11 *M. morganii* isolates were resistant to ampicillin. All 13 *Enterococcus* spp. isolates were susceptible to ampicillin.

Table 3 – Antibiotic non-susceptibilities[*] of the most frequently uropathogens isolated at the initial and the recurrent UTI episodes.

Antibiotic	Organism											
	E. coli *n* (%)		*Klebsiella* spp. *n* (%)		*M. morganii* *n* (%)		*Proteus* spp. *n* (%)		*Enterobacter* spp. *n* (%)		*Enterococcus* spp. *n* (%)	
	UTI episode timing											
	I[**] *n* = 95	II[**] *n* = 12	I *n* = 21	II *n* = 2	I *n* = 11	II *n* = 0	I *n* = 11	II *n* = 1	I *n* = 8	II *n* = 2	I *n* = 14	II *n* = 1
Ampicillin	55/95 (57.9)	7/12 (58.3)	18/20 (90)	2/2 (100)	11/11 (100)		7/11 (63.6)	2/2 (100)	7/8 (87.5)	2/2 (100)	0/13	1/1 (100)
TMP/SMX	7/71 (9.9)	0/10	1/16 (6.3)	0/2	2/8 (25)		0/5	1/1 (100)	0/6	–	2/10 (20)	–
Cefuroxime	5/92 (5.4)	0/10	3/21 (14.3)	1/2 (50)	1/10 (10)		0/11	0/1	1/7 (14.3)	2/2 (100)	3/10 (30)	–
Ceftriaxone	3/77 (3.9)	2/12 (100)	1/16 (6.3)	0/1	2/9 (22.2)		1/11 (9.1)	–	0/7	2/2 (100)	3/8 (37.5)	–
Gentamicin	2/94 (2.1)	0/12	1/21 (4.8)	–	3/11 (27.3)		0/11	0/1	0/8	0/2	2/13 (15.4)	0/1
Amoxicillin/clavulanic acid	5/37 (13.5)	4/5 (80)	3/14 (21.4)	–	1/4 (25)		4/9 (44.4)	–	1/1 (100)	1/1 (100)	3/7 (42.9)	–
Ciprofloxacin	3/29 (10.3)	0/1	2/5 (40)	–	1/3 (33.3)		2/5 (40)	–	0/1	–	6/7 (85.7)	–

[*] Antibiotic susceptibilities for some antibiotic drugs not determined for all pathogens.
[**] I, initial UTI episode; II, recurrent UTI episode.
TMP/SMX, trimethoprim/sulfamethoxazole.

The antibiotic resistance of the 12 *E. coli* isolates recovered in R-UTI patients was 58.3%, 0%, and 0% for ampicillin, TMP/SMX, and cefuroxime-axetil, respectively. Four of the five *E. coli* isolates examined showed resistance to amoxicillin/clavulanic acid. The respective numbers for the two most commonly used IM/IV antibiotic drugs were 16.6% and 0 for ceftriaxone and gentamicin.

Discussion

The most recently published information on the diagnosis and management of an initial UTI episode in febrile infants and young children are included in the last (2011) technical report of the subcommittee of UTI of the American Academy of Pediatrics.[7] A meta-analysis was performed on a final amount of 159 relevant publications and revealed a consistent UTI prevalence of 5% among infants and young children 2–24 months of age with fever without obvious source. Evidence was found that delay in the institution of appropriate treatment of pyelonephritis increases the risk of renal damage. A prevalence of VUR of 18–35% among infants/young children with UTI was reported. The report emphasized that normal prenatal US findings may not be sufficient to obviate the need for additional studies if a UTI occurs in infancy and that the accumulated evidence was not supporting antimicrobial prophylaxis to prevent UTI when VUR is found through VCUG. Finally, performance of VCUG after the first UTI for children between 2 and 24 months of age was not recommended anymore.[7] The following (2011) guidelines of the American Academy of Pediatrics did not support the use of antimicrobial prophylaxis to prevent febrile recurrent UTI in infants without grade I–IV VUR.[9] VCUG was not recommended anymore routinely after the first UTI, but is still indicated if renal and bladder ultrasonography reveals hydronephrosis, scaring, or other finding suggestive of either high grade VUR or obstructive uropathy and in other atypical or complex clinical circumstances. The performance of VCUG, however, is recommended in the presence of a recurrence of febrile UTI.[9]

Few data exist in the literature regarding UTIs occurring in infants <2 months of age. The major purpose of our retrospective study was to analyze the epidemiological, microbiological, imaging, and therapeutical aspects of the first episodes of UTI in infants <2 months of age and to follow these infants until the age of one year, in order to track the occurrence of recurrent UTI episodes and to study the appropriateness of current imaging and antibiotic therapeutic guidelines. The major findings of this study were: (1) the UTI incidence was 2.1 cases/1000 live births among infants <2 months of age in Southern Israel; (2) *E. coli* was responsible for the majority of first and also recurrent UTI episodes; (3) no differences were recorded in the percentages of *E. coli* among the pathogens isolated at the first and the recurrent UTI episodes; (4) the adherence to diagnostic imaging guidelines for infants <2 months of age with first UTI episodes was partial; (5) recurrent UTI episodes were recorded in relatively few (13.2%) patients and were caused mostly by pathogens phenotypically different than the pathogen isolated at the initial episode; (6) while high rates of resistance to ampicillin were recorded among the *E. coli* and *Klebsiella* spp. isolates in the first UTI episode and among *E. coli* isolates at UTI recurrence, the resistance rate of these pathogens to TMP/SMX and cefuroxime-axetil were low.

We calculated in our study an UTI incidence of 2.1/1000 live births among infants aged 0–2 months living in the Negev area of Southern Israel and a prevalence of 2.7% cases of first UTI episode in life among febrile infants <2 months admitted at the pediatric departments of our hospital during the study years. The prevalence rates are lower than the figures published in the medical literature (reporting a rate of around 5%).[1,4,5,8] The incidence rate reported in our study should be considered reliable, because all our findings are reported in this study as population-based, taking into consideration that the Soroka University Medical Center is the only medical center treating infants and children in the Negev area of southern Israel.

E. coli was responsible for the majority of cases of first UTI. Our data are similar to data previously published in the literature showing a representation of *E. coli* among first UTI episodes of 60–89%.[8,12,13] The current guidelines for the treatment of neonatal UTI take into consideration these finding but may often be inappropriate for hospitalized infants with non-*E. coli* UTI, caused in general by pathogens resistant to antibiotics and therefore more difficult to treat.[13] The *E. coli* isolates recovered from our patients at the first UTI episode, although resistant, in most patients, to ampicillin and also in a considerable number of cases to amoxicillin/clavulanic acid, showed a favorable antibiotic susceptibility profile vs. TMP/SMX, cefuroxime, ceftriaxone, and gentamicin. Furthermore, the resistance rates of *Klebsiella* spp. to TMP/SMX were also very low. Therefore, and not in accordance with the published literature, TMP/SMX may represent, at least in older children, an acceptable first line empiric antibiotic in the treatment of UTI in young infants.

The R-UTI rates recorded in our study reached 13.2% following an initial UTI episode occurring during the first two months of life. Most prior studies have shown much higher recurrence rate (20–48%) of UTI 6–12 months after an initial UTI episode.[7,9,14] Interestingly, only a few of the patients developing R-UTI episodes in our study had a previously diagnosed renal pathology. The influence of the antibiotic prophylactic treatment administered after the first UTI episode could not be clearly determined in our study. However, 25% of the patients receiving prophylaxis with TMP/SMX developed R-UTI episodes (despite low resistance to this antibiotic drug) while no cases of recurrent UTI were diagnosed in patients receiving amoxicillin prophylaxis (despite an unfavorable susceptibility profile of the most frequently isolates pathogens recovered in this study). The effectiveness of long-term prophylactic antibiotic treatment is yet unclear.[6,7,8,9] Williams et al.[15] showed that long-term antibiotic prophylaxis is effective in preventing UTI recurrences, but this effect was not sustained after the interruption of the antibiotic treatment. Shah et al. determined that prophylactic antibiotic is recommended for children <8 years of age with VUR and frequent symptomatic recurrences of UTI (≥2 UTI episodes over a 6-month period) and in young children <18 months of age with acute pyelonephritis without any diagnosed reflux using ^{99m}Tc-DMSA scan.[16] On the other hand, Garin et al. determined that the presence of VUR of mild or moderate degree does not increase the risk for R-UTI, pyelonephritis, or kidney

scarring and there is no reason for prophylactic antibiotic.[17] Conway et al.[10] reported rates of 0.007 episodes per person-year of primary UTI up to the age of one year and 0.12 episodes per person-year of recurrent UTI. The authors found that the risk factors for recurrence of UTI included white race, age of 4–5 years, and a VUR of degrees 4–5. Prophylactic antibiotic treatment was not associated with a decrease in the risk of UTI recurrence, but was a risk factor for development of antimicrobial resistance among children with recurrent UTI.[10] In 2014, in a two-year, multisite, randomized, placebo-controlled trial involving 607 children with VUR (80.4% with grade II or III VUR) diagnosed after a first or second febrile or symptomatic urinary tract infection, antimicrobial prophylaxis with TMP/SMX was associated with a substantially reduced risk of recurrence (50%) but not of renal scarring.[18]

We could establish in this study that the overall etiology of the recurrent UTI episodes was similar to that of the initial UTI episode in terms of *E. coli* and non-*E. coli* organisms representation and also, importantly, that the majority (64%) of the recurrent UTI episodes were caused by pathogens different than those isolated at the first UTI episode. Our last findings, based on similarity between the antimicrobial profiles of the isolates, were not definitively confirmed by genetic tests demonstrating unequivocally this similarity, and this is one of the limitations of our study.

The imaging guidelines in use at the pediatric division of our hospital during the study period recommended the performance of US examination during hospitalization or shortly after hospitalization in all cases of UTI in young infants, a VCUG examination after 6–8 weeks following the discharge from the hospital. These guidelines were implemented only partially in the enrolled patients.

In conclusion, our study showed that *E. coli* was responsible for the majority of first UTI in neonates and also in the recurrent UTI episodes of these patients. We could not find any differences in the percentages of *E. coli* and non-*E. coli* organisms between the first and the recurrent UTI episodes. Recurrent UTI episodes were recorded in relatively few patients and were caused mostly by pathogens phenotypically different than the pathogen isolated at the initial episode.

Conflicts of interest

The authors declare no conflicts of interest.

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