Urinary Tract Infection in Outpatient Children and Adolescents: Risk Analysis of Antimicrobial Resistance

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ABSTRACT: **Background:** Urinary tract infection (UTI) is a common bacterial infection in children. Early treatment may prevent renal damage in pyelonephritis. The choice of empiric antibiotic treatment is based on knowledge of the local susceptibility of urinary bacteria to antibiotics. In Israel the recommended empiric oral antibiotic treatment are first or second generation cephalosporin, trimethoprim-sulfamethoxazole or amoxicillin-clavulanic acid.

Objectives: To describe resistance rates of urine bacteria isolated from children with UTI in the community settings. Identify risk factors for resistance.

Methods: A retrospective cross-sectional study of UTI in children aged 3 months to 18 years diagnosed with UTI and treated as outpatients in a large community clinic between 7/2015 and 7/2017 with a diagnosis of UTI.

Results: A total of 989 urinary samples were isolated, 232 were included in the study. Resistance rates to cephalexin, cefuroxime, ampicillin/clavulanate and Trimethoprim-Sulfamethoxazole were 9.9%, 9.1%, 20.7%, and 16.5%, respectively. Urinary tract abnormalities and recurrent UTI were associated with an increase in antibiotic resistance rates. Other factors such as age, fever, and previous antibiotic treatment were not associated with resistance differences.

Conclusions: Resistance rates to common oral antibiotics were low compared to previous studies performed in Israel in hospital settings. First generation cephalosporins are the preferred empiric antibiotics for febrile UTI for outpatient children. Amoxicillin/clavulanate is not favorable due to resistance of over 20% and the broad spectrum of this antibiotic. Care should be taken in children with renal abnormalities as there is a worrying degree of resistance rates to the oral first line antibiotic therapy.

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Urinary tract infection (UTI) is one of the most common bacterial infections in children, affecting 1–3% of girls and 1% of boys [1]. The incidence of UTI varies by gender, age, ethnicity, and circumcision status [1]. In girls, the first UTI usually occurs by the age of 5 years, with peaks during infancy and toilet training. In boys, most UTIs develop during the first year of life [1]. Colonic bacteria are the main cause of UTI, 75–90% of all infections are caused by *Escherichia coli*, followed by *Klebsiella* spp. and *Proteus* spp [1,2]. Among Gram-positive bacteria, *Enterococcus* and *Staphylococcus saprophyticus* may cause UTI, the latter found mainly in adolescent girls [1]. Fungi and viruses rarely cause UTI in children [1]. While most children have a good prognosis, a UTI can cause significant morbidity, including septicemia, hypertension, renal scarring, and end-stage renal disease [3,4]. Early antibiotic treatment, within 72 hours, is necessary to avoid renal injury [4]. Consequently, UTI is usually treated empirically. The choice of empirical therapy is based on knowledge of the susceptibility of local urinary bacteria to antibiotics [5].

Current data on the prevalence and patterns of antibiotic resistance of uropathogens in children treated as outpatients are limited. The recommended options for empiric oral antibiotic treatment for community acquired febrile UTI in children are first or second generation cephalosporin, trimethoprim-sulfamethoxazole (TMP-SMX), or amoxicillin/clavulanic acid [2,6,7]. The rate of Enterobacteriaceae resistant to antibiotics has increased in recent years [8]. Risk factors for resistance to narrow spectrum antibiotics include bowel and bladder dysfunction, hospitalization, recurrent infections, recent antibiotic exposure, and children receiving prophylaxis therapy with antibiotics [9-12]. The majority of *E. coli* isolates are now resistant to ampicillin [13], so this antibiotic is no longer appropriate for the empiric treatment of UTI. The prevalence of strains resistant to common first-line oral antibiotics such as TMP-SMX, first generation cephalosporins, and amoxicillin/clavulanic acid has increased worldwide [2], and specifically in the state of Israel [13]. This is of particular concern as the choice of an oral first-line antibiotic that will be effective, safe, and, in the case of children, palatable, is limited. The emergence of multi-drug

resistant (MDR) Enterobacteriaceae is a worrisome phenomenon, which currently extends beyond hospitals [14]. Recurrent UTI episodes and renal scarring were identified as significant risk factors for infection caused by extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae [8,11].

Different studies have investigated antibiotic resistance and risk factors for UTI in hospitalized children; however, there is a lack of data on community acquired UTI in children who are treated as outpatients. This study describes antibiotic resistance patterns of isolated urine bacteria and investigates potential risk factors associated with increased antimicrobial resistance patterns in outpatient children aged 3 months to 18 years diagnosed with UTI in community settings in Israel.

PATIENTS AND METHODS

This retrospective cross-sectional study of UTI in children aged 3 months to 18 years diagnosed with UTI and treated as outpatients in a large community clinic in Afula, Israel. The study was approved by the Helsinki Committee for community medicine of Clalit Meir Medical Center, Kfar Saba. All urine cultures from July 2015 to July 2017 were examined at the microbiology laboratory of Emek Medical Center, Afula, Israel. We excluded insignificant cultures (the growth of more than one bacterium, the growth of lower than standard quantity of colony forming units/ml [CFU], and the growth of bacteria considered contaminants). Samples taken less than 7 days apart were considered as a single episode. The main variable was resistance of organisms to the commonly used antibiotics. Urine samples were collected by urethral catheterization until the age of 3 years, and clean catch specimen collection by the midstream method in toilet trained children. Midstream clean catch sampling was also used in circumcised male infants. Urinalysis is the routine investigation in every child suspected of UTI. If leukocytes or nitrite were found in the urine sample, a urine culture was performed. In infants younger than 6 months of age urine culture is performed regardless of urinalysis findings. UTI was defined as the growth of > 10^3 CFU/ml in a sample obtained by transurethral catheterization or the growth of > 10^5 CFU/ml in a clean catch midstream sample. Disc diffusion method was used on cultures to perform antimicrobial susceptibility testing using a panel of antimicrobial substances and depending on the recognized causative pathogen. Interpretation of susceptibility tests was according to the Clinical and Laboratory Standards Institute (CLSI) criteria [15]. Further data were collected by reviewing medical files.

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA). Categorical variables were presented as percentages. Differences between subgroups were determined by Student's *t-test* or Wilcoxon 2-sample test. Analysis of association of categorical variants was done using chi-square test or Fisher's exact test. A P value < 0.05 was considered statistically significant.

RESULTS

A total of 989 urine cultures were analyzed; 757 samples did not meet the inclusion criteria and were excluded. The 232 urine samples were taken from children between the age of 3 months and 18 years, 219 females and 13 males. Of these samples, 52 were from children between 3 months and 3 years, 98 were from children between the ages of 3 and 10 years, and 82 samples were from children between 10 and 18 years old. The most common causative agent was *E. coli* (78.1%), followed by *Proteus* (11.2%), *Klebsiella pneumoniae* (3.9%), and *Enterococcus* spp. (3.4%).

The overall resistance rates to the various treatments were: amoxicillin/clavulanic acid (20.7%), first and second generation cephalosporins (9.9%, 9.1%, respectively), nitrofurantoin (16.9%), and TMP-SMX (16.5%).

We compared the antibiotic resistance patterns of the first-episode UTI group (n=147) to the recurrent UTI group (n=85). Resistance rates to amoxicillin/clavulanic acid were found to be significantly higher in the recurrent UTI group compared to the first-episode UTI group (29.4% vs. 15.6%, P = 0.01). In both groups we saw no significant differences in resistance rates to other antibiotics [Table 1].

Antibiotic resistance patterns were analyzed in three age groups: group I: 3 months–3 years (n=52), group II: 3–10 years (n=98), and group III: 10–18 years (n=82). The results show resistance patterns of amoxicillin/clavulanic acid (23.1%, 19.4%, 20.7%, in each group respectively, P = 0.87), cephalexin (13.5%, 10.2%, 7.3%, P = 0.51), cefuroxime (11.5%, 9.2%, 7.3%, P = 0.71), gentamicin (2.0%, 3.2%, 2.5%, P = 0.91), nitrofurantoin (16.0%, 19.1%, 15.0%, P = 0.75), and TMP-SMX, (24.0%, 17.0%, 11.3%, P = 0.16).

We examined the antibiotic resistance patterns in febrile children (> 38°C; n=73) and non-febrile children (n=159). We found the following antibiotic resistance rates: amoxicillin/clavulanic acid (26.0%, 18.2%, P = 0.17), cephalexin (11%, 9.4%, P = 0.72), cefuroxime (9.6%, 8.8%, P = 0.85), gentamicin (1.4%, 3.2%, P = 0.43), nitrofurantoin (11.4%, 19.5%, P = 0.14), and TMP-SMX (15.7%, 16.9%, P = 0.83), respectively [Table 2].

We examined the patterns of antibiotic resistance in children who were prescribed antibiotic therapy in the last two years (n=151) and children who were not prescribed antibiotic therapy (n=81). We found the following antibiotic patterns: amoxicillin/clavulanic acid (21.2%, 19.8%, P = 0.80), cephalexin (9.3%, 11.1%, P = 0.65), cefuroxime (8.6%, 9.9%, P = 0.75), gentamicin (2.7%, 2.6%, P = 0.96), nitrofurantoin (15.0%, 20.1%, P = 0.27), and TMP-SMX (18.4%, 13.0%, P = 0.30), respectively [Table 3].

Table 1. Resistance patterns of all uropathogens in first-episode versus recurrent urinary tract infection to different antimicrobial agents

		First-episode urinary tract infection (147)		Recurrent urinary tract infection (85)		*P* value
		n	%	n	%	
Amoxicillin/ Clavulanic acid	S	124	84.4%	60	70.6%	0.01
	R	23	15.6%	25	29.4%	
Ampicillin	S	55	46.6%	32	43.2%	0.65
	R	63	53.4%	42	56.8%	
Cephalexin	S	133	90.5%	76	89.4%	0.79
	R	14	9.5%	9	10.6%	
Ciprofloxacin	S	136	96.5%	80	96.4%	0.98
	R	5	3.5%	3	3.6%	
Cefuroxime	S	135	91.8%	76	89.4%	0.54
	R	12	8.2%	9	10.6%	
Ceftriaxone	S	137	92.6%	77	91.7%	0.81
	R	11	7.4%	7	8.3%	
Gentamicin	S	136	96.5%	82	98.8%	0.29
	R	5	3.5%	1	1.2%	
Nitrofurantoin	S	115	81.6%	71	85.5%	0.29
	R	26	18.4%	12	14.5%	
Sulfamethoxazole/ Trimethoprim	S	117	83.0%	70	84.4%	0.79
	R	24	17.0%	13	15.6%	

R = resistant, S = susceptible

Table 2. Resistance patterns of all uropathogens in febrile versus non-febrile children to different antimicrobial agents

		Febrile children (n=73)		Non-febrile children (n=159)		*P* value
		n	%	n	%	
Amoxicillin/ Clavulanic acid	S	54	74.0%	130	81.8%	0.17
	R	19	26.0%	29	18.2%	
Ampicillin	S	31	42.5%	84	52.8%	0.14
	R	42	57.5%	75	47.2%	
Cephalexin	S	65	89.0%	144	90.6%	0.72
	R	8	11%	15	9.4%	
Ciprofloxacin	S	68	97.1%	148	96.1%	0.70
	R	2	2.9%	6	3.9%	
Cefuroxime	S	66	90.4%	145	91.2%	0.85
	R	7	9.6%	14	8.8%	
Ceftriaxone	S	66	90.4%	148	93.1%	0.48
	R	7	9.6%	11	6.9%	
Gentamicin	S	69	98.6%	149	96.8%	0.43
	R	1	1.4%	5	3.2%	
Nitrofurantoin	S	62	88.6%	124	80.5%	0.14
	R	8	11.4%	30	19.5%	
Sulfamethoxazole/ Trimethoprim	S	59	84.3%	128	83.1%	0.83
	R	11	15.7%	26	16.9%	

R = resistant, S = susceptible

We compared the antibiotic resistance patterns of urine cultures from children with anatomic or functional urinary tract abnormalities (e.g., hydronephrosis, vesicoureteral reflux, and duplicated collecting system) (n=19) and children with no urinary tract abnormalities (n=213). We found significant differences in resistance rates to cephalexin (26.3%, 8.5%, P = 0.01), cefuroxime (26.3%, 7.5%, P = 0.006), ceftriaxone (21.1%, 6.1%, P = 0.02), and ampicillin (73.7%, 48.4%, P = 0.03), while there was only an insignificant increase in resistance rates in children with urinary tract abnormalities to other antibiotics: amoxicillin/clavulanic acid (36.8%%, 19.2%, P = 0.07), gentamicin (5.3%, 2.4%, P = 0.46), and TMP-SMX (26.3%, 15.6%, P = 0.23), respectively [Table 4].

DISCUSSION

The appropriate use of empirical antibiotics is associated with concerns about antibiotic resistance patterns as well as safety issues, compliance, and cost. Consequently, the ability to predict the risk of resistance to empirical antibiotics is important. Resistance rate of 20% to an antibiotic has been considered an acceptable limit for an antibiotic to be used for empirical therapy [16].

The present study describes the antibiotic resistance patterns in community acquired UTI infection in children treated as outpatients in a community clinic. Our secondary aim was to identify risk factors that influence the antibiotic resistance patterns, particularly the most routinely used antibiotics in the community settings.

An earlier study of outpatient soldiers from Israel showed resistance rates of 9.7–16.7% for oral cephalosporins and 19.6% for TMP-SMX [17]. In the current study, we found similar resistance patterns. Among the suggested oral empiric antibiotics, first and second generation cephalosporins demonstrated the lowest overall resistance rates of urine bacteria followed by TMP-SMX and amoxicillin/clavulanic acid (9.9%, 9.1%, 16.5%, and 20.7%, respectively). Shaikh et al. [9] showed similar low resistance rates for first and second generation cephalosporins to *E. coli* pathogens, however not for non-*E. coli* pathogens. Thus, our results might reflect that the leading pathogen of UTI in our study was *E. coli*, which is consistent with the literature [1,2]. The low resistance profile to first generation cephalosporins as well as the relatively narrow spectrum and palatability make them the preferred choice for empiric treatment of febrile UTI in the community settings. There is no advantage in prescribing second generation cephalosporins. TMP-SMX is a good alternative. We do not recommend the empiric use of amoxicillin/clavulanic acid because of the resistance rate, which exceeds the desired 20%, and the adverse effects of broad-spectrum antibiotics.

Table 3. Resistance patterns of all uropathogens in children who were prescribed antibiotic therapy in the last two years (antibiotic prescription) versus children who were not prescribed antibiotic therapy in the last two years (no antibiotic prescription)

		No antibiotic prescription (n=81)		Antibiotic prescription (n=151)		*P* value
		n	%	n	%	
Amoxicillin/ Clavulanic acid	S	65	80.2%	119	78.8%	0.80
	R	16	19.8%	32	21.2%	
Ampicillin	S	41	50.6%	74	49.0%	0.82
	R	40	49.4%	77	51.0%	
Cephalexin	S	72	88.9%	137	90.7%	0.65
	R	9	11.1%	14	9.3%	
Ciprofloxacin	S	76	98.7%	140	95.2%	0.18
	R	1	1.3%	7	4.8%	
Cefuroxime	S	73	90.1%	138	91.4%	0.75
	R	8	9.9%	13	8.6%	
Ceftriaxone	S	73	90.1%	141	93.4%	0.38
	R	8	9.9%	10	6.6%	
Gentamicin	S	75	97.4%	143	97.3%	0.96
	R	2	2.6%	4	2.7%	
Nitrofurantoin	S	61	79.2%	125	85.0%	0.27
	R	16	20.1%	22	15.0%	
Sulfamethoxazole/ Trimethoprim	S	67	87.0%	120	81.6%	0.30
	R	10	13.0%	27	18.4%	

R = resistant, S = susceptible

Table 4. Resistance patterns of all uropathogens in children with no anatomic or functional urinary tract abnormalities versus children with anatomic or functional urinary tract abnormalities

Antimicrobial agent		No anatomic or functional urinary tract abnormalities (n=213)		Anatomic or functional urinary tract abnormalities (n=19)		*P* value
		n	%	n	%	
Amoxicillin/ Clavulanic acid	S	172	80.8%	12	63.2%	0.07
	R	41	19.2%	7	36.8%	
Ampicillin	S	110	51.6%	5	26.3%	0.03
	R	103	48.4%	14	73.7%	
Cephalexin	S	195	91.5%	14	73.7%	0.01
	R	18	8.5%	5	26.3%	
Ciprofloxacin	S	199	97.1%	17	89.5%	0.09
	R	6	2.9%	2	10.5%	
Cefuroxime	S	197	92.5%	14	73.7%	0.006
	R	16	7.5%	5	26.3%	
Ceftriaxone	S	199	93.9%	15	78.9%	0.02
	R	13	6.1%	4	21.1%	
Gentamicin	S	200	97.6%	18	94.7%	0.46
	R	5	2.4%	1	5.3%	
Nitrofurantoin	S	170	82.9%	16	84.2%	0.89
	R	35	17.1%	3	15.8%	
Sulfamethoxazole/ Trimethoprim	S	173	84.4%	14	73.7%	0.23
	R	32	15.6%	5	26.3%	

R = resistant, S = susceptible

We found a statistically significant increase in the recurrent UTI group in the resistance rate to amoxicillin/clavulanic acid (29.4% vs. 15.6%, $P = 0.01$). However, there was no correlation between recurrent episodes of UTI and the development of bacterial resistance to first and second generation cephalosporins. Sakran and colleagues [18] compared first episode UTI with recurrent infection in inpatient children younger than 18 years who were hospitalized in same city as our community clinic. They showed resistance rates of 37.39% and 5.71% to first and second generation cephalosporin, respectively, whereas, in children with recurrent UTI, the resistance rates were 48.9% and 17.5%, respectively. This finding might be due to differences in resistance patterns between inpatients and outpatients as a study conducted in the United States found that uropathogen resistance to many antibiotics including cefazolin and cephalothin was lower in the outpatient vs. inpatient setting [19].

By comparing antibiotic resistance in three age groups we showed that age was not related to antibiotic resistance. Our results also indicate that there was no statistically significant difference in antibiotic resistance between febrile UTI and non-febrile UTI, which is consistent with a study that reported that age, race, and fever were not associated with increased antibiotic resistance rates [9].

Our results show no significant difference in rates of antibiotic resistance in children who were prescribed antibiotics in the last two years vs. children who were not prescribed antibiotics in the last two years. Likewise, Brosh-Nissimov and co-authors [17] reported that prescription of antibiotics more than six months preceding the UTI infection in outpatients was not related to increased antibiotic resistance. Brosh Nissimov et al. [17] showed that fluoroquinolone and cephalosporin exposures less than 6 months preceding the culprit infection were highly predictive of further antibiotic resistance. Other studies also found that children who received one course of antibiotics in the past six months increased the chances of resistance to first generation cephalosporin and amoxicillin but two courses or more of antibiotics did not change the chances of resistance to narrow spectrum antibiotics [9,20]. Those studies were performed in hospital settings. We assume that the children in our study had less complex chronic diseases, most of them had not been exposed to resistant bacteria or to hospital acquired infections, and the antibiotics they were exposed to were relatively narrow spectrum, mainly amoxicillin.

We found statistically significant higher resistance rates to first generation cephalosporin (26.3% vs. 8.5%, $P = 0.01$) and second generation cephalosporin (26.3% vs. 7.5%, $P = 0.006$) in children with urinary tract abnormalities Furthermore, there was no significant increase in resistance rates to amoxicillin/clavulanic acid, gentamicin, and TMP-SMX. A few previous reports found that both nephrorologic pathology and vesicoureteral reflux are significant risk factors for developing MDR and community onset ESBL-producing *E. coli* urinary tract infections [20,21].

CONCLUSIONS

Our results suggest that antibiotic resistance rates in outpatient children are lower compared to resistance rates in other studies in inpatient children [13,18]. Among the first line empirical antibiotics first generation cephalosporin is an appealing option, regardless of recurrent UTI infections, age of the child, fever, and previous antibiotic treatments in the last 2 years. However, in children with urinary tract abnormalities other antibiotic treatment should be considered due to a higher rate of resistance to these antibiotics. In such cases, a once daily treatment with gentamycin is a suitable option.

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Capsule

Prosthetics provide room to grow

Children with congenital heart disease who require heart valve replacement often must undergo multiple high-risk surgeries because the replacement valve cannot grow as their heart grows. Inspired by this problem, **Hofferberth** and colleagues developed a prosthetic valve that mimics the geometry of the human venous valve, which maintains function despite large fluctuations in blood volume. The prosthesis, composed of polymeric leaflets attached to a stainless-steel stent, can be mechanically expanded using transcatheter balloon dilation to adapt to larger fluid volumes. Size-adaptable valves maintained function when implanted into growing lambs and could be mechanically expanded over 10 weeks.

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