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Changes in Antibiotic Susceptibility of Urinary Tract Pathogens in Pediatric Population by Years

Hayrettin Temel[1*], Meral Öner[2]

1 Istanbul Medipol University, School of Medicine, Department of Pediatrics, Istanbul, Turkey.
2 Gebze Fatih State Hospital, Department of Medical Microbiology, Kocaeli, Turkey.

Abstract

Background: Urinary tract infection is one of the most common infections in the community and is more common in children than adults. In this study, it was aimed to investigate the distribution of the isolated microorganisms from pediatric patients, their susceptibility status, and the change in resistance by years in order to help clinicians manage the empirical medical treatment.

Materials and Methods: 3337 children with a preliminary diagnosis of urinary tract infection who applied to Gebze Fatih State Hospital between January 2013 and December 2018 were included in the study. Urine culture results and antibiotic susceptibilities were analyzed retrospectively and examined over years.

Results: The susceptibility rates of *E. coli* species to ampicillin, trimethoprim-sulfamethoxazole, cefuroxime, and cefixime were 35.5%, 66.6%, 64.5%, and 68.8%, respectively. There was a significant decrease in antibiotic susceptibility of *E. coli* isolates for cefoxitin (p=0.04), ceftazidime (p<0.001), amikacin (p<0.001) and nitrofurantoin (p<0.001) by years. Susceptibility rates against amikacin (p=0.04) and nitrofurantoin (p<0.001) in Klebsiella isolates decreased significantly by years. There was a significant decrease in Pseudomonas isolates thereby years in the rate of susceptibility to ceftazidime (p=0.019). There was no significant change in susceptibility rates for any antibiotic in Proteus isolates by years (p>0.05 for each).

Conclusions: Cefixime was found that the most effective oral antibiotic against *E. coli*. The most effective antibiotics were fosfomycin and carbapenems in the Enterobacteriaceae group. The antibiotic resistance of causative pathogens has been shown to increase over the years. Therefore, the antibiotic susceptibilities of bacteria should be monitored periodically.

Key words: *Urinary infection; pediatric patients; antibiotics susceptibility.*

***Corresponding Author:** Hayrettin Temel M.D., Istanbul Medipol University School of Medicine Department of Pediatrics,İstanbul, Turkey. **Phone:** +90 212 460 77 77
E-mail: htemel@medipol.edu.tr **Received:** Apr, 2020. **Accepted:** Oct, 2020.

Introduction

Urinary tract infections (UTI) are a common and important clinical problem in children. The prevalence of UTI is approximately 7 percent in febrile infants and young children. This prevalence varies according to age, sex, ethnicity, and circumcision status. It is highest among uncircumcised boys who are younger than three months. UTI occurs in girls 2 to 4 times more than circumcised boys (1). It is reported that a person has this infection at least once in their lifetime (2-4).

UTI present with nonspecific symptoms and signs such as fever, irritability, poor feeding, and poor weight gain in infants and young children (5). Usually, the foul-smelling urine or gastrointestinal symptoms such as vomiting, diarrhea, poor feeding are not helpful in diagnosing UTI (1,6,7). The diagnosis is difficult due to the excess of nonspecific findings. In case of suspicion, simple tests are performed in the laboratory for differential diagnosis. Early diagnosis and treatment of urinary system infections are important for preventing renal scar formation and progressive renal damage in children (2-4,8).

The antibiotic treatment is started empirically in the case of suspected UTI. However, treatment options have been restricted in many countries due to the serious resistance to empirical antibiotics used in recent years (9). Today, the number of oral antibiotics preferred in empirical treatment is limited especially in children. Antibiotics recently added to the antibiotics in use are also limited in number. Resistance to antibiotics may vary by region depending on the frequency of use. Knowing the infection factors and these resistance patterns will help the clinician choose the appropriate treatment in UTI cases. Therefore, UTI factors should be revealed and antibiotic resistance status should be followed (8-11).

In our study, it was aimed to investigate the distribution of the agents isolated from pediatric patients, their susceptibility status, and the change in resistance by years in order to help clinicians manage the empirical medical treatment.

Materials and Methods

This study protocol was approved by the Ethics Committee of the Istanbul Medipol University (10840098-604.01.01-E.48093). A total of 3337 culture-positive patients of 14460 patients whose urine culture was carried out with a preliminary diagnosis of UTI who applied to Gebze Fatih State Hospital between January 2013 and December 2018 were included in the study. This hospital is a 200-bed second-line healthcare center serving an area covering an urban and rural population of about 400,000 inhabitants.

The time of onset of the findings, the most frequent admission complaints, acute phase reactants, complete urinalysis, urine culture, and the demographic characteristics of the patients were accessed from the hospital data and evaluated retrospectively. Urine culture and antibiotic susceptibility results were analyzed retrospectively. Duplicate cultures of the same patient on the same day were excluded.

The samples were taken from all patients who had a preliminary diagnosis of UTI regardless of outpatient and inpatient discrimination. While the urine sample was taken with a sterile urine bag in children under 2 years of age, the midstream urine method was preferred in older children. Samples were collected under sterile conditions and sent to the microbiology laboratory.

The urine samples were inoculated onto 5% sheep blood agar and MacConkey agar media and were incubated for 24 hours at 37˚C. Samples with grown above 100,000 colony forming units (CFU)/mL in culture were considered significant and evaluated. Conventional methods were used to identify the bacteria until 2016, and VITEK®2 Compact (Biomerieux, France) automated system was used after 2016. Antibiotic susceptibilities of the isolated strains were interpreted using the Kirby-Bauer disc diffusion method according to the Clinical Laboratory Standards Institute (CLSI) criteria until 2016. VITEK®2 Compact (Biomerieux, France) the automated system was used, and the susceptibility results were interpreted according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations. Antibiogram results were given in three groups as susceptible, moderately sensitive, and resistant.

Statistical analysis

Descriptive data were given as numbers and percentages. In calculating the changes in susceptibility rates by years, and Pearson's chi-square test was used for the susceptibility rate comparison for each antibiotic. The chi-square test was also used to compare the susceptibility rates between genders. P <0.05 values were considered statistically significant.

Results

The mean age of the patients was 72.0 ± 47.6 months (age range 0-190 months). A total of 2713 (81.3%) of the patients were female, and 624 (18.7%) were male. The most frequently isolated microorganisms were gram-negative bacteria (82.7%). (Escherichia coli (*E. coli*) (65.0%), *Klebsiella spp* (6.8%), and *Proteus* spp. (5.9%), Citrobacter spp. 34 (1%), *Morganella morganii* 28 (0.8%), Enterobacter spp. 21 (0.6%), *Serratia marcescens* 8 (0.2%), Acinetobacter baumannii complex 5 (0.1%), Pseudomonas spp. 68 (2.0%). The rate of gram-negative bacteria types in girls (84.3%) were significantly higher compared to boys (47.6%) except Proteus spp (p<0.001). The rates of Klebsiella (6.2%) and Proteus (4.3%) in girls were significantly lower compared to boys (16.4% and 18.9%, respectively) (p <0.001).

The most frequently isolated Gram-positive bacteria were methicillin-susceptible coagulase-negative staphylococci (MRCNS) 46 (1.4%) and methicillin-resistant coagulase-negative staphylococci (MRCNS) 180 (5.4%). *Staphylococcus aureus* 24 (0.7%), Streptococcus agalactiae 23 (0.7%), Beta-hemolytic streptococci 10 (0.3%), Enterococcus spp 64 (1.9%) and Candida species 17 (0.5%) were detected in the cultures. The number of UTI cases varied between 252.4 ± 32.4 (min 232-max 315) in the month and there was no significant difference between genders in terms of monthly UTI cases (p=0.810). The number of cases in warmest months (May-October months) and coldest months (November-April months) were 1588 (47.7%) and 1748 (52.4%), respectively. Additionally, there was no significant difference between the genders in terms of the number of cases in the warmest and coldest months (p=0.795).

The susceptibility rates of E. coli species to ampicillin, trimethoprim-sulfamethoxazole, cefuroxime, and cefixime were 35.5%, 66.6%, 64.5%, 68.8%, respectively. The most effective antibiotics were fosfomycin and carbapenems in the Enterobacteriaceae group. None of the gender differences were statistically significant in terms of antibiotic susceptibility rates in all bacterial species (p>0.05 for each). For some bacteria, the change in antibiotic susceptibilities by years was analyzed. Accordingly, there was a significant decrease in antibiotic susceptibility of E. coli isolates for cefoxitin (p=0.04), ceftazidime ($p<0.001$), amikacin ($p<0.001$) and nitrofurantoin ($p<0.001$) by years. Susceptibility rates against amikacin ($p=0.04$) and nitrofurantoin ($p<0.001$) in Klebsiella isolates decreased significantly by years. There was a significant decrease in Pseudomonas isolates thereby years in the rate of susceptibility to ceftazidime ($p=0.019$). There was no significant change in susceptibility rates for any antibiotic in Proteus isolates by years ($p>0.05$ for each) (Table 1).

Table 1. Antimicrobial susceptibility rates **(%)** of gram-negative microorganisms according to years.

Microorganisms	Years	n	AMP	TZP	CXM	FOX	CAZ	FIX	CRO	MEM	IPM	CN	AK	CIP	F	SXT	ERT	FOS
	2013	**236**	30.2	80.4	79.9	92.6	93	82.3	82.3	100	100	95.0	100	84.4	100	63.4	100	100
	2014	**255**	39.4	76.6	76.2	90,4	85.9	76.2	76.2	100	100	90.1	98.4	85.2	100	62	100	100
Escherichia coli	**2015**	**299**	35.5	73.1	81.3	75	83.2	74.2	79.5	100	100	88.5	100	86.4	98.2	63.4	100	100
n:2170	**2016**	**364**	36.4	72.9	74.5	86.2	76.4	75.6	75.8	100	99.6	86.2	96.1	86.4	95.5	64	99.4	100
	2017	**492**	34.7	72.6	66.7	89.9	70.9	68.0	69.1	99.6	99.8	84.1	89.9	87.4	93.3	65.4	99.6	99.1
	2018	**522**	36.4	72	62.9	76.6	68.5	67.4	68.1	99.4	100	82.4	85.2	87.7	95.7	69.2	99.4	99.4
	p*		0.738	0.80	0.17	**0.04**	**<0.001**	0.56	**<0.001**	0.097	0.79	0.73	**<0.001**	0.39	**0.018**	0.15	0.25	0.93
	2013	**6**	-	62.1	80	75.9	83.3	66.2	66.7	100	100	95.2	100	89.1	100	69.6	100	78.3
	2014	**17**	-	58.6	70.6	78.5	70.6	75.6	76.5	100	100	94.1	100	88.7	100	68.2	100	77.1
Klebsiella spp.	**2015**	**22**	-	56.5	68.2	75.9	76.2	66,2	68.2	100	100	92.3	100	88.4	94.1	67.1	100	76.5
n:228	**2016**	**53**	-	53.2	72.2	75.9	66.7	65.3	66.7	97.9	98,6	86,9	91.8	88.2	55.3	67.6	95.5	76.8
	2017	**71**	-	53	66.7	78.5	68.7	65.2	65.2	97.2	97.2	81.5	95.7	85.9	35.3	73.2	94.1	77.1
	2018	**59**	-	51	59.6	76.3	64.4	64.4	64.4	100	100	82.8	79.7	78.0	32.2	62.7	98.3	87.7
	p*		-	0.78	0.97	0.32	0.29	0.42	0.45	0.39	0,86	0.49	**0.04**	**0.82**	**<0.001**	**0,69**	**0.72**	**0.44**
	2013	**17**	23.5	61.1	94.1	95.1	94.1	99	100	100	100	10	100	98.2	-	64.1	100	98
	2014	**15**	66.7	60.2	93.3	94.8	93.3	94.2	93.3	100	100	95	93.3	97.9	-	63.4	100	99
Proteus spp.	**2015**	**15**	42.9	58.6	92.9	94.5	93.3	98	100	100		100	100	97.6	-	61.6	100	100
n:197	**2016**	**52**	46.2	57.1	83.3	94.3	89.4	89.2	93.9	98	76.7	100	97.9	97.5	-	59	97.9	100
	2017	**52**	52	56.6	92	98.0	98	98.0	98.0	100	40.8	100	98.1	90.4	-	40.4	100	84.0
	2018	**46**	43.5	55.4	95.1	100	95.7	93.3	93.5	100	9.5	76.7	87	76.1	-	47.8	100	90.2
	p*		0.623	0.87	0.265	0.094	0.849	0.65	0.69	0.58	0.19	0.64	0.39	0.46	-	0,27	0.77	0.64
	2013	**8**	-	40	-	-	100	-	-	100	100	74	75	100	-	-	-	-
	2014	**8**	-	35	-	-	100	-	-	100	100	84.2	100	100	-	-	-	-
Pseudomonas spp	**2015**	**11**	-	30	-	-	87.5	-	-	100	100	82.1	100	100	-	-	-	-
n:68	**2016**	**13**	-	25	-	-	45.5	-	-	90.9	90.9	76.1	90	81.8	-	-	-	-
	2017	**13**	-	23	-	-	83.3	-	-	75	75.0	57.1	66.7	75	-	-	-	-
	2018	**15**	-	15.4	-	-	86.7	-	-	100	93.3	56.8	93.3	100	-	-	-	-
	p*		-	0.12	-	-	**0.019**	-	-	0.09	0.06	0.58	0.27	0.09	-	-	-	-

* Pearson's Chi-square test is used (Significance; p<0.05) AMP: Ampicillin, TZP: Tazobactam-piperacillin, CXM: Cefuroxime, FOX: Cefoxitin, CAZ: Ceftazidime, FIX: Cefixime, CRO: Ceftriaxone, MEM: Meropenem, IPM: Imipenem, CN: Gentamycin, AK, Amikacin, CIP: Ciprofloxacin, F: Nitrofurantoin, SXT: Trimethoprim-sulphamethoxazole, ERT: Ertapenem, FOS: Fosfomycin.

There was no significant change in susceptibility rates in Gram-positive bacteria over the years (Table 2).

Table 2. Antimicrobial susceptibility rates of gram-positive microorganisms according to years

Microorganism	Years	n	AMP	GN	CIP	SXT	FOS	VA
	2013	**24**	42,6	93.4	90.0	90.9	52.2	100
	2014	**26**	39.1	92.8	100	76.9	51.8	100
Staphylococci spp	**2015**	**36**	38.5	92.4	100	75.8	49.4	100
n:250	**2016**	**41**	36.8	91.8	100	85.0	47.2	100
	2017	**60**	37.1	91.3	88.2	94.7	45.1	100
	2018	**65**	35.6	90.9	91.4	90.5	53.9	100
	p*		0.92	**-**	0.89	0.77	0.23	1.0
	2013	**3**	89.2	-	92.3	-	46.4	100
	2014	**5**	87.1	-	89.6	-	43.5	100
Enterococci spp.	**2015**	**6**	86.3	-	86.8	-	42.4	100
n:56	**2016**	**20**	85.7	-	85.7	-	41.6	100
	2017	**24**	93.1	-	75.9	-	40.5	100
	2018	**36**	80.0	-	85.7	-	40.8	96.7
p*			0.96		0.82		0.76	0.98

Since there is not enough data per year for other bacterial species, statistical analysis could not be performed.

Discussion

It is critical to start treatment empirically in UTI, especially in pediatric patients. The current and local susceptibility patterns because the antibiotic susceptibility profiles in bacteria vary both over time and from region to region is important to determine. In determining the treatment policy, it is much more determinant to know the local surveillance patterns of the bacteria that are infectious agents (12,13). In our study, a surveillance report was prepared, which included antibiotic susceptibility patterns and changes in susceptibility rates for all bacteria that were infectious in pediatric UTI cases of recent years. Most of the studies on the subject include patients who apply to tertiary hospitals. Second-line hospitals in our country cover the clinics where children most frequently apply for suspected UTI. The findings of our study are important since the empirical treatments given in these clinics may provide a ground for antimicrobial resistance that may develop in the future and should be directed towards the potential factor.

In our study, it was found that UTI cases were more common in girls than boys in accordance with the literature (79.4% vs. 20.6%). No significant changes were observed in the monthly and seasonal distribution of the cases. According to this data, UTI cases do not appear to be related to the season. This finding is compatible with previous studies (14). In accordance with the literature, gram-negative bacteria were isolated in more than 85% of UTI cases and the most frequently isolated species was *E. coli* (14).

In the studies conducted between 2006-2016 in our country, the susceptibility rate of E. coli isolates to ampicillin and trimethoprim-sulfamethoxazole have been reported in the range of 35-68%, 8-64%, respectively (15-21). In our study, the susceptibility rates of E. coli to ampicillin and trimethoprim-sulfamethoxazole were 35.5%, 66.6%, respectively. There were no significant changes for these susceptibility rates between 2013 and 2018 according to our study.

It has been reported that E. coli strains in UTI cases have gradually increased resistance rates to co-trimoxazole and ceftriaxone in our country, however, the high effect of imipenem, meropenem and amikacin still continues (15). Konca et al. reported that the most effective antibiotics in E. coli isolates were imipenem, meropenem, and amikacin with 100% susceptibility rates (14). If UTI not associated with sepsis, carbapenems should be preferred when E. coli isolates were ESBL. If UTI is with sepsis and ESBL is positive, then imipenem and meropenem can be used (14,15). In our study, the most effective antibiotics to E. coli isolates were imipenem (99.8%), meropenem (99.8%), fosfomycin (99.3%) and amikacin (92.8%).

It was reported that E. coli isolates showed a significant increase in resistance rates of ciprofloxacin, amikacin and cefixime over the years in a study. In this study, they found that the rate of resistance to nitrofurantoin decreased and there was no significant change in the resistance rates to other antibiotics (20). In another study, it was reported that E. coli isolates had increased resistance to cefoperazone and cephalothin over the years (22). In our study, although the high effect of amikacin seems to continue, it was found that while the susceptibility rate was close to 100% between 2012 and 2014, the susceptibility rates gradually decreased towards 2017 and this decrease was statistically significant ($p<0.001$). In E. coli isolates, it was also observed that there was a statistically significant decrease in the susceptibility rates of ceftazidime, cefoxitin, ceftriaxone and nitrofurantoin over the years, and there was no significant change in the susceptibility rates to co-trimoxazole and cefixime over the years. In our study, there was also a significant decrease in amikacin and nitrofurantoin susceptibility rates in Klebsiella isolates, but no significant change was observed in the susceptibility rates to cefuroxime, one of the frequently preferred antibiotics. In Proteus isolates, there was no significant change in the resistance rates to any antibiotics over the years. In P. aeruginosa isolates, there was a significant decrease in susceptibility rates to ceftazidime over the years, but no significant change was observed in the susceptibility rates to parenteral options in cases caused by this bacterium, which may occur more frequently in inpatients. These data also show that susceptibility patterns should be determined and announced periodically. In addition, there may be a very rapid resistance development to antibiotics which are still considered to be effective. The resistance rates for ampicillin from Canada, Europe and Africa were reported as 45%, 50% and 100%, respectively. It is known that high resistance rates may occur due to the widespread use of inappropriate antibiotics in developing countries (14). Compared to some international studies, our susceptibility rates were higher than the reports of developing countries and lower than those of developed countries (14,15,19,21). These data also support that the antibiotic susceptibility profiles of bacteria vary regionally and should be determined regularly.

The present study had some limitations. It was retrospective, the age range was wide, it was not possible to define it as the first or recurrent infection. Although the number of cases was high, many bacteria species other than *E. coli* were isolated in low numbers. This led to the fact that the susceptibility rates for these bacteria have not been very informative, and have restricted the performing of important analyzes such as resistance change over the years. However, our data covered 95% of UTI agents. Therefore, it can be a guide for antibiotics that will be preferred in empirical treatment for children in UTI.

Conclusion

Investigation of bacterial species distribution and susceptibility helps the clinician choose the appropriate treatment. Therefore, the susceptibility of bacteria to antibiotics should be monitored periodically. Antibiotics that can be used orally in children who are considered to have UTIs are limited. Resistance to these drugs may require hospitalization. It is recommended that antibiotics, which do not show a significant decrease in antibiotic sensitivity over the years, should be considered as the first option in empirical treatment.

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