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Original Article

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Trends in Antimicrobial Resistance and Demographics of Urinary Tract Infections Regarding Impacts of Urological Comorbidities in Children in a Single Institution Over a 4-Year Period

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ABSTRACT

Objective: This study aims to determine trends in antimicrobial resistance and demographics of urinary tract infections regarding the impacts of urological comorbidities in children.
Methods: Data of all children from newborn to age 18 years with culture-proven urinary tract infection between January 1, 2016, and December 31, 2019, were examined through institutional medical records. Samplings and antibiotic susceptibility tests were evaluated according to standard criteria.
Results: A total of 931 cases of urinary tract infection from 574 girls (80.70%) and 137 boys (19.30%), being 261 (36.7%) with a predisposing comorbidity for urinary tract infection were enrolled. Vesicoureteral reflux was the leading underlying disorder (5.90%). *Escherichia coli,* the major prevalent uropathogen (65.00%) was mostly cultured in girls (74.6%); amid non-*Escherichia coli* isolates in boys. The prevalence of *Klebsiella* spp. was higher among children with vesicoureteral reflux and in girls with neurogenic bladder. There was no significant trend in antimicrobial resistance rates to *Escherichia coli* throughout. Resistance rates of *Escherichia coli, Klebsiella* spp., and the other Enterobacterales to nitrofurantoin, aminoglycosides, and carbapenems were low. *Enterococcus* spp. and *Pseudomonas* spp. were mostly susceptible to antibiotics.
Conclusion: *Escherichia coli* is the principal etiological uropathogen causing urinary tract infection in children, and nitrofurantoin, aminoglycosides, or carbapenems emerged as options for empirical treatment.
Keywords: Antibiotic susceptibility pattern, antimicrobial resistance, children, Türkiye, urinary tract infection, urological comorbidities

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INTRODUCTION

Urinary tract infection (UTI) has been ranked among the most common bacterial infections diagnosed in children. An average of 50,000 children/year were admitted to hospitals with a UTI, constituting 1.8% of all pediatric hospitalizations. Girls are more likely to develop UTIs regarding their unique anatomy and behaviours compared to boys throughout their lifetime, excluding infancy.[1,2]

Urinary tract infection triggers inflammation in the urinary system that ultimately might cause permanent kidney damage, particularly when treatment is delayed.[1,2] However, culture and susceptibility test results are often unavailable until 48 hours following admission. Thus, the clinician challenges to start on prompt "best guess" empirical antimicrobial therapy to a child with suspected UTI, based upon decisions on likely pathogens and local resistance patterns just as obtaining sample for urine culture.[2] The use of inappropriate antibiotics delays effective treatment and increases the risk of antimicrobial resistance besides longer hospitalizations.[2] Moreover, discordant antibiotic therapy for UTI is worryingly common, occurring in 9% of children hospitalized for UTI.[2]

Even so, *Escherichia coli* has been the most prevalent isolated uropathogen; the incidence, clinical symptoms, and responsible organisms in pediatric UTIs vary from age to sex accordingly.[1,3] Remarkable geographic variations concerning bacteriological profile in UTIs and erratic trends of antibiotic resistance rates (RR) with time have become an escalating global health treatment.[4] Comorbid urological diseases might have impacts on the bacteriological profile indeed.[2-4] However, research, taking into account the impacts of comorbid urological disorders over prevalence of uropathogens and their resistance patterns in pediatric urinary infections, has still been limited.[2,5-8] Considering the overall picture, conducting regional studies regularly might be critical to ascertain the local trends in RRs of antimicrobials over time, subsequently to adjusting the up-to-date appropriate empirical antibiotic therapies.

MAIN POINTS

- *Escherichia coli* was the major responsible uropathogen in pediatric UTIs overall (65.00%); predominantly among girls; amid non-*Escherichia coli* in boys.
- Considering the co-morbid diseases associated with UTI individually, this study determined diverse bacteriological profiles in urine, with Klebsiella spp. being significantly more prevalent in those with VUR and NB; amid smaller proportions for "other *Enterobacterales*" and *Escherichia coli* among children with VUR.
- Despite the recommendations of European guidelines over empirical treatment, the RRs to AMP, AMC, TRS, CUR and CTR in *Escherichia coli*, and subsequently to AMC, CUR and TRS among *Klebsiella* spp. and other *Enterobacterales* UTI were quite high.
- NIT, carbapenems and aminoglycosides emerged as empiric treatment candidates for outpatients and those hospitalized, respectively.
- No resistance of Escherichia coli to carbapenems was detected, likely in Europe. However, it is crucial to endeavour to conserve lower RRs to carbapenems.
- Despite the higher RRs of *Escherichia coli* to AMI and GEN in this study, compared to European scores (1.3% and 7.1% respectively), aminoglycosides might be deemed as an empiric agent for paediatric *Escherichia coli* UTI.
- Carbapenems and aminoglycosides have emerged as appropriate candidates for empirical treatment of UTIs in children with VUR, those suffering from DV and in girls with NB. Additionally, LIN, TEI and VAN, has AMP might be considered for treatment of paediatric UTIs with VUR which might be stemmed from *Enteroccus* spp.
- No significant trend was observed for *Escherichia coli* throughout the period; amid increasing trends in the susceptibility rates of *Klebsiella* spp. to AMC, CTR.
- Due to the demographic variations related to non-*Escherichia coli* uropathogens as commonly reported, taking predisposing co-morbidities and gender differences into consideration might be worthy before starting a promising empirical treatment.

A retrospective study was carried out in our Paediatric Nephrology unit to identify uropathogenic patterns and antibiotic resistance trends in urine cultures of local children with and without comorbid urological disorders between 2016 and 2019 in Istanbul, Türkiye, to evaluate empirical treatment options for UTI and reinforce policies to combat antimicrobial resistance and related complications in children with UTI.

METHODS

Patients

In this research, all admissions from newborn to age 18 years with UTI to our Paediatric Nephrology clinic and subsequently treated in inpatient or outpatient settings between January 1, 2016, and December 31, 2019, were evaluated. Data analyses of all children with culture-proven UTI were examined through institutional medical records. Patients with and without comorbid illnesses facilitating UTI were analyzed individually. The institutional review board of Health Sciences University approved the study (date: September 26, 2019 and decision number is 62977267-000-12405). Written informed consent from the parent was obtained indeed.

Sampling, Urinary Tract Infection Diagnosis, and Antimicrobial Susceptibility Testing

Precisely, the decisive colony count threshold for a urine culture positive for UTI is related to its collection method, which is based on the contamination risk of specimens. However, requiring pyuria for diagnosis and even the use of an acceptable single colony count for all children are of latest controversial topics. Additionally, several studies have advocated that children with lower colony counts, compared to the traditional cut-off level for a positive culture which was over 10^5 CFU/mL might have true UTIs.[9-12] Subsequently, the European Association of Urology has concisely admitted in their 2022 recommendations over Paediatric Urology that what represents a significant UTI is still unclear.[9] As such, the debate over the definition of UTI is likely to evolve with new data due. In the meantime, this retrospective study adheres to the European Association of Urology/European Society for Paediatric Urology 2015 Guideline to determine the likely diagnosis.[1]

Urine specimens were obtained as clean-midstream-catch urine in older cooperative children and transurethral catheterization or suprapubic aspiration in the others.[1,9] Accordingly, this included significant bacteriuria with the recovery of at least 100,000 colony-forming unit per milliliter (CFU/mL) of a single uropathogen from a clean catch specimen, or at least 50,000 CFU/mL of a single uropathogen from a transurethral catheterization specimen, amid bacterial colony counts of $\geq 10^3$ CFU/mL in infants $<$ 4 months, or any uropathogenic bacteria from a supra-pubic aspirate.[1,9] Only the first positive urine culture obtained per patient on admission was included in the analysis to eliminate any possibility of recurrence. Polymicrobial cultures were excluded from the study to lock out contaminations.

Antibiotic susceptibility tests were performed by VITEK2 system (bioMérieux, Marcy L'etoile, France), according to European Committee on Antimicrobial Susceptibility Testing criteria.[13-15]

Statistical Analysis

The study data were analyzed using Statistical Package for the Social Sciences version 21.0. (IBM SPSS Corp.; Armonk, NY, USA).[16] Number of units (n), percentages (%), mean ± standard deviation (SD), and median (interquartile range) of the data were provided using descriptive statistics. Pearson's chi-square test and Fisher's exact test were used in evaluating categorical variables. Normal distributions of numeric variables were judged by Shapiro–Wilk normality test and Q-Q graphs. The mean values of variables between the 2 groups were compared using the independent sample t-test and Mann–Whitney U-test. Annual trends of antibiotic resistance were evaluated using linear regression analysis. A P value less than .05 was considered statistically significant.

RESULTS

A total of 931 cases of UTI were confirmed in urine cultures from 711 patients—574 girls (80.70%) and 137 boys (19.30%). The rate of UTI diagnosed in females was 81.10%. The mean of patient age for boys, girls, and the total patient age were 3.17 ± 3.99, 7.05 ± 4.83, and 6.31 ± 4.92 years, respectively (Table 1).

A predisposing comorbidity for UTI was determined in 261 children (36.7%)—165 girls (63.22%) and 96 boys (36.78%)—who had enrolled in the study (Table 1). The variety of underlying diseases for UTI and concerning data are provided in Table 2. Vesicoureteral reflux (VUR) was the leading underlying disorder with a rate of 5.90%, followed by dysfunctional voiding (DV) and neurogenic bladder (NB) with rates of 4.80 and 4.40%, respectively. However, posterior urethral valve was the least frequently observed entity (0.30%) (Table 2).

Microorganisms isolated from urine samples are shown in Figure 1. *Escherichia coli* was by far the most frequently isolated uropathogen throughout the study period (65.00%), followed by *Enterococcus* spp. and *Klebsiella* spp., with 11.90 and 10.50% of the total isolates, respectively (Figure 1). By comparison with the frequencies of bacterial isolates according to gender, *Escherichia coli* was isolated in 74.6% of urine cultures in girls ($P < .01$). However, *Enterococcus* spp., *Klebsiella* spp., other Enterobacterales, and *Pseudomonas* spp. were significantly more frequently isolated in urine specimens among boys (Figure 2).

The percentages of bacteria isolated from urine cultures of patients with comorbid diseases predisposing UTI are demonstrated in Table 3. Accordingly, the prevalence of *Escherichia coli* and other Enterobacterales isolated from urine samples of patients with VUR was significantly lower (P = .036), amid *Klebsiella* spp. isolates were significantly higher among children with VUR and in girls with NB (P = .004) (Table 3).

The trends in antibiotic RRs of *Escherichia coli, Klebsiella* spp., and the other Enterobacterales isolated from children with UTI between 2016 and 2019 are demonstrated in Table 4. However,

Table 1. Epidemiological Data Regarding Patients with UTIs

	Patients	Age (Year)	Patients with Comorbidities	UTI
	n (%)*	Mean ± SD	n (%)	n (%)
Female	574 (80.70)	7.05 ± 4.83	165 (63.22)	755 (81.10)
Male	137 (19.30)	3.17± 3.99	96 (36.78)	176 (18.90)
Total	711 (100)	6.31± 4.92	261 (100)	931 (100)

*Number of patients (percentage); SD, standard derivation.

Table 2. The Comorbidities Facilitating UTI

	Total	Female	Male	
Comorbidity	n (%)	n (%)	n (%)	P
VUR	42 (5.90)	25 (59.52)	17 (40.48)	<.001
DV	34 (4.80)	22 (64.71)	12 (35.29)	.015
NB	31 (4.40)	18 (58.06)	13 (41.94)	.001
AKRD	23 (3.20)	16 (69.57)	7 (30.43)	.168
NL	11 (1.50)	8 (72.73)	3 (27.27)	.498
CH	7 (1.00)	6 (85.71)	1 (14.29)	.737
PUV	2 (0.30)	0 (0.00)	2 (100)	.004

AKRD, atrophic kidney with renal damage; CH, congenital hydronephrosis; DV, dysfunctional voiding; NB, neurogenic bladder; NL, nephrolithiasis; PUV, posterior urethral valve; VUR, vesicoureteral reflux.

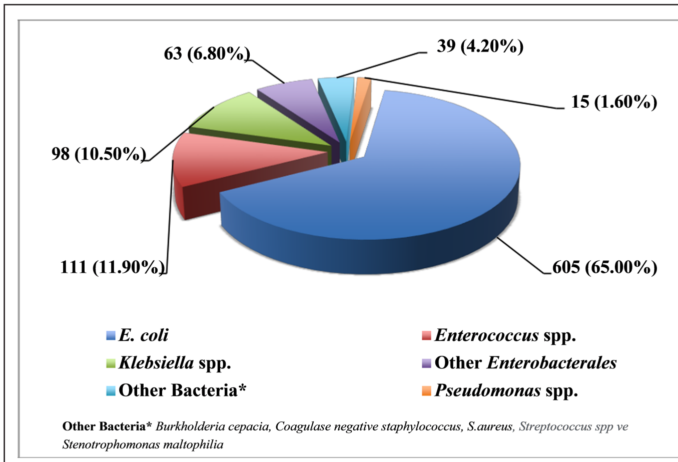

Figure 1. Microorganisms isolated from urine samples.

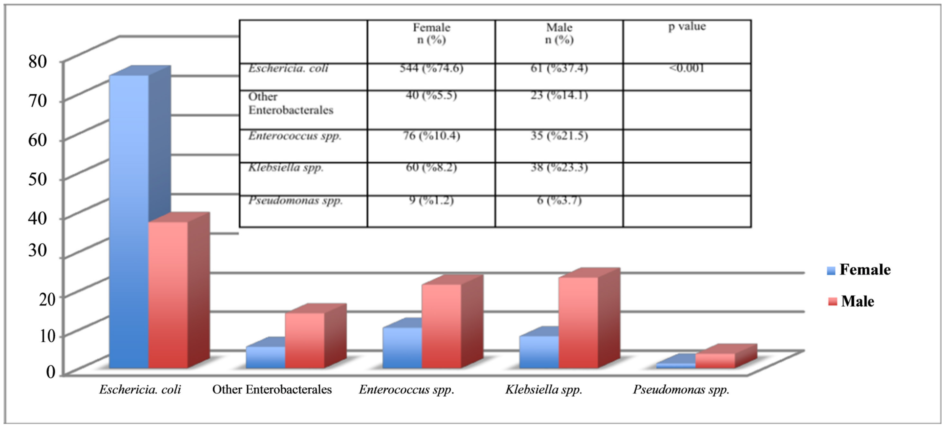

Figure 2. Frequency of microorganisms isolated from urine samples according to gender.

there was no statistically significant trend among antimicrobial RRs to *Escherichia coli* during the period. The resistance to nitrofurantoin (NIT) as a first-line choice for peroral use in *Escherichia coli* UTI was low throughout and lower than 1% in 2019 indeed (RRs = between 7.81 and 0.33%). Depending on the results in 2019, aminoglycosides (amikacin (AMI) and gentamicin (GEN) and carbapenems (meropenem and ertapenem) were among the parenteral agents with the lowest RRs, being a candidate for empirical antimicrobial treatment. Contrarily, RRs for second- and third-generation cephalosporins were remarkably high for *Escherichia coli* (30.53-46.99%) (Table 4).

For UTIs due to *Klebsiella* spp., the RRs for amoxicillin-clavulanate (AMC), ceftriaxone (CTR), and cefuroxime (CUR) declined significantly from 2016 to 2019, amid high RRs throughout. Based on the data from 2019, aminoglycosides and carbapenems were the most susceptible antibiotics likewise for *Escherichia coli* (Table 4).

There was no significant trend to the other Enterobacterales among antibiotics throughout**.** The RRs of aminoglycosides and carbapenems were low, whereas NIT outstood with markedly high RRs throughout (62.96-100%) (Table 4).

The variation in RRs of *Enterococcus* spp. during the period is illustrated in Table 5. The RRs of ampicillin (AMP) decreased from 25 to 15.69% during the period, but the decline was not statistically significant (*P* = .462). From 2018 onwards, *Enterococcus* spp. have been mostly susceptible to antimicrobials, but trime thoprim-sulfamethoxazole (TRS) (Table 5).

Pseudomonas spp. were susceptible to antibiotics, and no significant trend in RRs was determined between 2016 and 2019.

DISCUSSION

This study has found that *Escherichia coli* is the major responsible uropathogen in UTI during childhood, amid a higher rate of *Klebsiella* spp. isolates in urine among girls with NB. Nitrofurantoin, aminoglycosides, and carbapenems emerged as options for the empirical treatment of UTI in children. The fact that the RRs of *Escherichia coli* to AMP, AMC, TRS, CUR, and CTR were quite high, though commonly recommended in guidelines for empirical treatment of UTI in children, points out the importance of performing periodic local research to determine the demographic profile of microorganisms and their RRs.[1]

Table 3. The Percentages of Bacteria Isolated from Urine Cultures of Patients with Comorbid diseases Associated with UTI

	Escherichia coli	*Klebsiella* spp.	Other Enterobacterales	*Enterococcus* spp.	*Pseudomonas* spp.	*P*
VUR	47 (7.8%)	14 (14.3%)	1 (1.6%)	13 (11.7%)	2 (13.3%)	.036
DV	38 (6.3%)	10 (10.2%)	5 (7.9%)	8 (7.2%%)	1 (6.7%)	.297
NB	35 (5.8%)	16 (16.3%)	1 (1.6%)	7 (6.3%)	2 (13.3%)	.004
AKRD	29 (4.8%)	6 (6.1%)	00.0%)	7 (6.3%)	0 (0.0%)	.200
NL	19 (3.1%)	2 (2.0%)	3 (4.8%)	3 (2.7%)	0 (0.0%)	.178
CH	4 (0.7%)	3 (3.1%)	2 (3.2%)	2 (1.8%)	0 (0.0%)	.172
PUV	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	.078

AKRD, atrophic kidney with renal damage; CH, congenital hydronephrosis; DV, dysfunctional voiding; NB, neurogenic bladder; NL, nephrolithiasis; PUV, posterior urethral valve; VUR, vesicoureteral reflux.

Table 4. Trends in Antibiotic Resistance Rates of *Escherichia coli, Klebsiella* spp., and the other Enterobacterales

	Escherichia coli					*Klebsiella* spp.					Other Enterobacterales				
Antibiotics	2016 (%)	2017 (%)	2018 (%)	2019 (%)	*P*	2016 (%)	2017 (%)	2018 (%)	2019 (%)	*P*	2016 (%)	2017 (%)	2018 (%)	2019 (%)	*P*
AMI	12.50	26.87	25.30	3.43	.666	14.29	17.24	11.76	10.53	.272	0.00	15.38	7.69	6.06	.786
AMC	50.82	38.84	48.05	44.44	.752	57.14	50.00	43.75	37.84	.001	50.00	27.27	18.18	43.75	.755
CXI	13.56	12.50	16.00	15.09	.330	18.18	5.26	12.50	5.71	.366	66.67	33.33	8.33	16.13	.120
CIP	17.19	28.36	31.33	16.20	1.000	21.43	31.03	17.65	13.16	.351	0.00	15.38	30.77	21.88	.194
ERT	0.00	0.74	0.00	0.62	.631	14.29	0.00	11.76	0.00	.471	0.00	0.00	0.00	3.03	.225
FOS	0.00	0.81	2.67	0.00	.810	14.29	5.88	6.67	6.25	.251	0.00	30.77	9.09	19.23	.649
GEN	10.94	11.11	17.07	9.32	.958	21.43	34.48	29.41	13.16	.587	25.00	7.69	23.08	9.09	.540
MER	0.00	0.75	0.00	0.31	.932	14.29	0.00	11.76	0.00	.471	0.00	0.00	0.00	0.00	na
NIT	7.81	0.78	1.23	0.33	.197	57.14	40.74	12.50	25.00	.169	100.00	84.62	92.31	62.96	.163
PIT	28.13	28.15	28.92	15.89	.259	35.71	37.93	47.06	34.21	.897	0.00	0.00	8.33	9.68	.077
CTZ	42.86	32.33	42.17	34.06	.607	42.86	50.00	23.53	21.05	.169	0.00	0.00	0.00	18.18	.225
CTR	45.31	30.53	41.46	34.78	.597	50.00	44.00	23.53	21.05	.045	0.00	0.00	0.00	18.75	0.225
CUR	45.31	40.00	46.99	38.32	.565	57.14	48.28	29.41	21.62	.014	50.00	15.38	0.00	30.30	.549
TRS	41.27	32.33	37.80	25.71	.217	7.14	34.48	12.50	21.05	.786	25.00	23.08	45.45	42.42	.168
n*	64	136	83	322		14	29	17	38		4	13	13	33	

*Number of cases.
AMC, amoxicillin-clavulanate; AMI, amikacin; CTZ, ceftazidime; CIP, ciprofloxacin; CTR, ceftriaxone; CUR, cefuroxime; CXI, cefoxitin; ERT, ertapenem; FOS, fosfomycin; GEN, gentamicin; MER, meropenem; NIT, nitrofurantoin; PIT, piperacillin–tazobactam; TRS, trimethoprim-sulfamethoxazole.

Bacteriological profile and antibiotic RRs of uropathogens have been shown to differ geographically and with time, amid impacts of comorbid urological disorders. Conducting regional studies regularly is crucial to determine the current RRs of antimicrobials and the local trends in antibiotic susceptibilities over time, subsequently to adjusting the appropriate empirical agent. Several studies have been performed on this intriguing topic since the latest decade, despite limited research taking into account the impacts of comorbid urological disorders over the prevalence of uropathogens and their resistance patterns in pediatric urinary infections.[2,5-8] This study aims to discover the diversity of bacteriological profile in urine cultures of local children with and without comorbid urological disorders and the trends in RRs of antibiotics between 2016 and 2019 in Istanbul, Türkiye.

Table 5. Trends in Antibiotic Resistance Rates of *Enterococcus* spp.

	Enterococcus spp.				
Antibiotics	2016 (%)	2017 (%)	2018 (%)	2019 (%)	*P*
AMP	25.00	15.15	0.00	15.69	.462
CIP	33.33	15.15	7.14	10.00	.144
LIN	16.67	0.00	7.14	8.51	.673
TEI	83.33	91.67	0.00	0.00	.129
TRS	66.67	82.76	100.00	94.12	.124
VAN	16.67	3.23	7.14	10.42	.663
n*	12	33	14	51	

*Number of cases.
AMP, ampicillin; CIP, ciprofloxacin; LIN, linezolid; TEI, teicoplanin; TRS, trimethoprim-sulfamethoxazole; VAN, vancomycin.

In this study, the majority of uropathogens in urine specimens were isolated in females likewise in previous research (80.70%).[4,5,7,11] Shaikh et al[5] and Naseri et al[17] reported higher rates (91.0 and 89.1%, respectively), whereas a lower prevalence in girls (61%) was revealed by a recent study from Türkiye.[7] Contrarily, there are reports revealing preponderance of UTIs in boys indeed.[18,19] Majority of isolates reported in boys were from uncircumcised male infants < 2 years or febrile infants < 2 months; however, making a comparison regarding age was out of the scope of this research.[1,20]

In our study, VUR and bladder-related disorders (DV, NB) constituted the major predisposing comorbidities for UTI in children (Table 2). Friedman et al[21] reported VUR (50%) and congenital hydronephrosis (CH) (22.7%) as the principal underlying urinary tract anomalies in children with UTI. However, the prevalence of VUR and CH was 5.9 and 1%, respectively, in our research. The differences reported for the frequencies of the given comorbidities between studies might stem from the diversity of decisions for an indication for imaging. In another study, Naseri et al[17] revealed that 62.26% of the children with UTI had a normal urinary system. Diverse urinary tract disorders might have various impacts over the frequency of UTIs in children.

In our study population, all comorbid diseases associated with UTI were found predominantly in girls (Table 2). However, Naseri M et al[17] found a male predominance associated with urinary obstruction (male = 55%), amid a female predominance among children with VUR and NB (86.12 and 69.7%, respectively). Triggering intention for further etiological investigations, higher frequency of UTI in girls over 1 year of age might be responsible for the female predominance in the incidence of underlying urological anomalies in this study.

Escherichia coli was clearly the major responsible uropathogen in pediatric UTIs overall in this research (65.00%), likewise previously reported (Figure 1).[2,4,8,22] The prevalence of *Escherichia coli* was far higher among girls (74.6 vs. 37.4%, $P < .001$), whereas non-*Escherichia coli* uropathogens (*Klebsiella* spp., *Enterococcus* spp., and the other Enterobacterales) were mainly isolated in boys, likewise Erol et al's[8] results. Correlatively with our data, Edlin et al[23] had reported that *Escherichia coli* was the most common pathogen cultured, particularly among girls (83%), but *Enterococcus* (17%) and *Klebsiella* (10%) predominantly in boys.

In our study population, *Enterococcus* spp. ranked the second highest prevalence rate among isolated bacteria (11.9%) followed by *Klebsiella* spp. (10.5%), amid various frequency rates and sequences reported previously (Figure 1).[8,24] Several studies reported *Klebsiella* spp. and *Enterococcus* spp. as the second and third principal isolates in children with UTI, respectively, with diverse prevalence rates (ranging between 9.7 and 16.8% for *Klebsiella* spp. and about 10-5.4% for *Enterococcus* spp.); however, some other researchers found *Klebsiella* spp. as the second most isolated uropathogen likewise our results.[2,4,8,21,22] The discrepancy between and prevalence rates of uropathogens among diverse studies might be due to variations among study populations or regional characteristics.[4,7,21]

Considering the comorbid diseases associated with UTI individually, this study found that the bacteriological profiles in the urine of children have differed significantly. *Klebsiella* spp. were significantly more prevalent in children with VUR and NB as well, whereas other Enterobacterales and *Escherichia coli* were significantly less common among patients with VUR ($P = .036$) (Table 3). The predominance of *Klebsiella* spp. isolates in girls accounted for the higher prevalence of *Klebsiella* spp. in children with NB; however, such a relationship relating to gender was not determined in children with VUR.

Consistent with our results, previous studies indicated that non-*Escherichia coli* UTIs are associated with urinary tract anomalies among children.[17,21,25] Honkinen et al[25] pointed out the high prevalence of urinary tract abnormalities in hospitalized children with UTI caused by *Enterococcus* and *Klebsiella*. Shaikh et al[5] found *non-Escherichia coli* uropathogens being more prevalent in children with high-grade VUR, whereas Naseri et al referred to the high frequency of UTI due to *Pseudomonas* spp. in patients with NB.[21] It is worth calling attention to the fact that diverse non-*Escherichia coli* uropathogens have emerged in various research yet.[5,17,21,25] Hence, it might be critical to take variations related to underlying comorbidities and gender into consideration when starting an empiric antibiotic treatment for UTI.

It has been claimed that the choice of antimicrobial agent should be based on local antimicrobial sensitivity patterns for isolated dominant uropathogen (*Escherichia coli*) in the community because they are ever-changing and show major geographic variabilities.[1,11,26] This study has revealed that AMC, TRS, CTZ, CUR, and CTR constituted the highest RRs of *Escherichia coli* overall (Table 4). The RR of *Escherichia coli* to AMC has shown substantial geographic differences, being 14.3% in the Czech Republic amid a recently reported rate of over 40% from Türkiye, likewise our result.[7,27] The *Escherichia coli* RR to TRS in this study was consistent with a report from Korea (about 30%) but dramatically lower than an Iranian score (86.5%), underscoring the geographic diversity of antimicrobial sensitivity patterns.[3,22] Comparing with the relatively lower *Escherichia coli* RRs to second- and third-generation cephalosporins in Europe (15%), the rising trend in RRs to cephalosporins in our study might be quite worrisome (Table 4). Although cephalosporins, AMC and TRS, have been recommended for urogenital infections in guidelines in Europe, this study underlines the high RRs of *Klebsiella* spp. and other Enterobacterales, particularly for AMC, CUR, and TRS.[1] However, *Enterococcus* spp. and *Pseudomonas* spp. have been mostly susceptible to antimicrobials, but TRS for *Enterococcus* spp. The differences in RRs of antibiotics among various regions might be originated from diverse local antibiotic consumption policies. This study advocates that it is mandatory to specify current local antibiotic resistance patterns to determine appropriate "best guess" empiric treatment.

We had a tendency to start second-generation cephalosporins for empiric treatment in outpatient and CTR in hospitalized children with UTI. However, this study has indicated NIT for appropriate empiric treatment in outpatient, and carbapenems and aminoglycosides in hospitalized children with UTI caused by *Escherichia coli*. Fortunately, this research has determined no resistance of *Escherichia coli* to carbapenems, likewise in Europe.[27] Thus, we believe that it is critical to endeavor to conserve lower RRs to carbapenems. Despite higher RRs of *Escherichia coli* to AMI and GEN in this study, compared to European scores (1.3% and 7.1% respectively), aminoglycosides might remain to outstand as an option for appropriate empiric antibiotic treatment for pediatric *Escherichia coli* UTI in our region.[27]

Moreover, in view of the study results, carbapenems and aminoglycosides have emerged as appropriate candidates for empirical treatment of UTIs in children with VUR and particularly in girls with NB of which *Klebsiella* spp. appeared at the peak of the prevalence rates overall, likewise in other Enterobacterales UTIs in DV patients. It is worth underscoring that in addition to LIN, TEI, and VAN, AMP has remained to be an option for the treatment of pediatric UTIs due to *Enterococcus* spp. likewise in children with VUR (Tables 3-5).

In an attempt to account for the erratic patterns of antibiotic RRs of cultured bacteria throughout the period, no significant trend was observed for *Escherichia coli* in this research (Table 4). However, a recent Turkish report has called attention to the promising decline in the RR of *Escherichia coli* to CTR, amid upper trends to GEN and TRS between 2009 and 2014.[8]

However, we have found significant increasing trends in the susceptibility rates of *Klebsiella* spp. to AMC, CTR, and CUR, but the RRs have remained over 20% individually throughout. Nonetheless, no significant trend was observed in other antibiotics for *Klebsiella* spp. (Table 4). Gökçe et al[7] have indicated an increasing resistance trend of *Klebsiella* spp. for AMI ($P <$ .05), but a declining trend for NIT (I = .0001) contradicting with our results.

Moreover, *Enterococcus* spp. showed no significant trend in accordance with the RR of antimicrobials throughout, amid remaining sensitive to AMP (Table 5). Contradicting with our findings, Hrbacek et al[27] underlined the worrisome rising resistance of *Enterococcus* spp. to AMP in their study lately. No significant trend was determined in RR rates of antimicrobials to other Enterobacterales. We consider that antibiotic susceptibility trends show variations over time among regions and populations, and periodical local studies are mandatory to optimize antimicrobial treatments.

Study Limitations

The retrospective design of the study might be considered the major limitation of the study. Second, the uncertain circumcision status of boys and having limited knowledge about the clinical symptoms of patients might constitute the other principal limitations of the study.

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye , Haydarpasa Numune Health Application and Research Center institutional board (Date: September 26, 2019, Decision No: 62977267-000-12405).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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