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Comprehensive analysis of antibiotic resistance in Enterobacteriaceae from outpatient urine cultures: Implications for empirical therapy

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ABSTRACT

OBJECTIVE: Urinary tract infections (UTIs) are among the most common bacterial infections. The misuse of antibiotics is one of the factors contributing to the global increase in antimicrobial resistance (AMR), making the management of UTIs more challenging. Our study aims to evaluate the causative agents of UTIs and the factors influencing resistance, as well as to identify antibiotics that can be used in the outpatient treatment of patients diagnosed with UTIs.

METHODS: This retrospective study was conducted by collecting urine sample results between 2015–2023. The culture results of the urine samples and the results of the antibiotic sensitivity tests of the Enterobacteriaceae isolates were analyzed. Antimicrobial susceptibilities of the isolates were defined using the VITEK®2 Compact system (bioMérieux, Marcyl'Etoile, France) and PheonixTM (Becton-Dickinson, NJ, USA). All sensitivity statuses were determined according to EUCAST standards. Data analysis was conducted using SPSS software version 23.

RESULTS: 1842 culture results were included. 71.5% of the included samples were from women, and the average age of the cases was 63±18. The most commonly grown agent in urine cultures is Escherichia coli. The resistance profile of the Enterobacteriaceae to antibacterial agents was examined, and it was found that the highest resistance rates were against ampicillin (77.92%), cefazolin (52.36%), ciprofloxacin (49.5%), and trimethoprim/sulfamethoxazole (45.5%), while the lowest resistance rates were against meropenem (4.9%), amikacin (7.6%), fosfomycin (11.4%), and nitrofurantoin (11.6%). Comparing resistance rates before and after 2019, a significant increase in resistance to amikacin and nitrofurantoin was observed ($p \leq 0.001$). It was found that resistance rates were higher in urine samples from male cases.

CONCLUSION: Our study revealed that patients should be carefully evaluated in terms of the necessity of culture requests and patients should be informed about culture requests due to the high rate of non-growth and contamination in urine culture results. The high rates of antimicrobial resistance were detected, and the outpatient treatment options of UTI patients are narrowing which can increase hospital admission rates. Our study is important because it shows that nitrofurantoin and fosfomycin can be included in the outpatient and empirical treatment of UTI patients.

Keywords: Antimicrobial resistance; antimicrobial therapy; Enterobacteriaceae; urinary tract infection.

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Urinary tract infections (UTIs) are prevalent across all age groups and rank among the most commonly encountered medical conditions that necessitate outpatient treatment. Among the different bacteria that cause UTIs, gram-negative bacteria such as Enterobacteriales, which is a family of bacteria, are frequently encountered as the causative agents [1]. UTIs have a global impact, affecting millions of people and causing a decline in quality of life while imposing substantial economic burdens. In some instances, UTIs can manifest as severe and complicated cases that require hospitalization, underscoring the importance of effectively treating these infections as a crucial objective in healthcare delivery [2].

Oral antibiotics are widely used and preferred drugs in the treatment of UTIs. Their popularity stems from their low cost, ease of administration, and the ability to treat patients in an outpatient setting. Oral drugs from various antibiotic classes can be utilized for UTIs treatment; however, the development of resistance and side effects makes selecting the appropriate drug challenging [3].

Treatment guidelines offer recommendations for managing urinary tract infections and propose several treatment options. These options commonly involve the use of antibiotic agents like nitrofurantoin, trimethoprim-sulfamethoxazole (TMX-SXT), or fosfomycin. The choice of the most suitable treatment agent depends on individual cases, considering various factors or actual prescribing behaviors may exhibit substantial variability. It is crucial to acknowledge that treatment recommendations should not be applied indiscriminately to every patient due to factors including local resistance rates, sensitivities, or comorbidities [4, 5]. However, initial antibacterial agents should rely on susceptibility data specific to the local and regional area. It is also suggested to select the most suitable and most targeted effective antibiotic to tackle the increasing problem of resistance arising from the incorrect application of broad-spectrum antibiotics [6, 7].

Due to the potential delay in obtaining urine sample results, clinicians may opt to initiate empirical antibiotic therapy before receiving the culture results to avoid a potential loss of workforce productivity while ensuring timely treatment initiation. This situation can lead to antibiotics being prescribed inappropriately or suboptimally [8].

The growing prevalence of antibiotic-resistant uropathogens in UTIs presents a significant challenge due to two main factors: the increasing occurrence of resistance and the limited availability of oral treatment options. Drug-resistant uropathogens Enterobacteriaceae are increasingly reported in community-based studies [7, 9]. Understanding local rates of resistance utilizing local surveillance is crucial for developing better empirical approaches to prescribing practices. The objective of the research is to assess the variety of microorganisms isolated from urine samples in our institution, aiming to identify their resistance frequencies in outpatients and to find alterations in the frequency of antimicrobial resistance over time. As a secondary objective, we focused on identifying the risk factors that impact antibiotic resistance patterns, specifically focusing on the commonly prescribed antibiotics in community settings.

Highlight key points

- A significant portion of the urine cultures produced negative or contaminated outcomes, leading to the suggestion for conducting repeat cultures.
- Escherichia coli was the predominant bacteria isolated from the urine samples, followed by Klebsiella species.
- The resistance rates to first-line antimicrobials, ranging from 3% to 80%, amikacin, and nitrofurantoin were observed to be significantly increased over the years.
- Older age and years were significant risk factors for AMR. The male has higher rates of antibiotic resistance in urine samples.
- For outpatient and empirical treatment of UTIs, nitrofurantoin, and fosfomycin might be favorable choices, while the use of ampicillin and cotrimoxazole should be avoided.

MATERIALS AND METHODS

Specimen Collection and Culture

Our study is conducted as a cross-sectional and retrospective by collecting urine samples of cases who applied to the large community infectious diseases outpatient clinic and all urine cultures from January 2015 to January 2023 were examined in the Department of Microbiology in Research and Training Hospital. The eligibility criteria for sample inclusion in this study were: 1) The patients aged ≥18 years, 2) Positive significant results (growth of >105 colony-forming units (CFU)/ml in urine culture), 3) Presence of any Enterobacteriaceae spp. isolates, and 4) Samples from patients who applied to the outpatient clinic. Samples were excluded from the study if these met the listed criteria: 1) The patients ≤18 years, 2) Samples with no growth or insignificant results, 3) Samples with bacterial growth other than Enterobacteriaceae spp., and 4) Samples from inpatients. Additionally, hospital records were used to obtain socio-demographic details. The results are reported by the STROBE guidelines. The study was approved by the Ankara Etlik City Hospital Clinical Research Ethics Committee (date: 05.04.2023, number: AESH-EK1-2023-061). This was a retrospective data study, so the ethics committee waived informed consent. Our study was conducted following the principles of the Declaration of Helsinki.

Urine specimens were cultured on 5% sheep blood agar (produced by bioMérieux, Marcy l'Etoile, France) and eosin methylene blue agar (produced by bioMérieux, Marcy l'Etoile, France) and incubated for 18-24 hours at 35 °C. Antibiotic susceptibility results of bacteria defined as Enterobacteriaceae were analyzed. Insignificant cultures (the growth of more than one bacterium, the growth of lower than <105 standard quantity of CFU/ml, and microorganisms considered as contaminants) were excluded. A single urinary culture from every patient was evaluated for this study.

Identification of Bacteria and Assessing Antibiotic Resistance

Bacteria were identified with conventional methods, VITEK® 2 Compact (bioMérieux, Marcy l'Etoile, France), PheonixTM (Becton-Dickinson, NJ, USA), and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Bremen, Germany). To determine the antimicrobial agent sensitivity of the isolated strains, we used the VITEK® 2 Compact system (by bioMérieux, Marcy l'Etoile, France) and PhoenixTM (from Becton-Dickinson, NJ, USA), following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines for each year. We assessed the susceptibility of the Enterobacteriaceae isolates against various antimicrobials such as ampicillin, ceftazidime, cefotaxime, cefepime, piperacillin, ciprofloxacin, gentamicin, nitrofurantoin, cefoxitin, TMX-SXT, fosfomycin, imipenem, meropenem, and amikacin.

Data and Statistical Analyses

The analysis of data was conducted with IBM Statistical Package for the Social Sciences Statistics Software, version 23 (SPSS, IBM Corp, Armonk, NY, USA). Descriptive statistics of patients having positive urine cultures were presented by calculating means and standard deviations (SD). Categorical variables were presented as percentages. To assess differences between the groups, Chi-square or Fisher's exact test was used for categorical data, and the t-test was applied for continuous data. To calculate the rates of antimicrobial susceptibility or resistance for each organism and drug, we divided the quantity of susceptible or resistant organisms by the overall number of organisms subjected to testing. To determine the correlation between resistance to each antibiotic and various factors like age, gender, and year, a logistic regression model was utilized. The Wald test (enter method) was used in the model. Statistical significance was assigned to p values lower than 0.05.

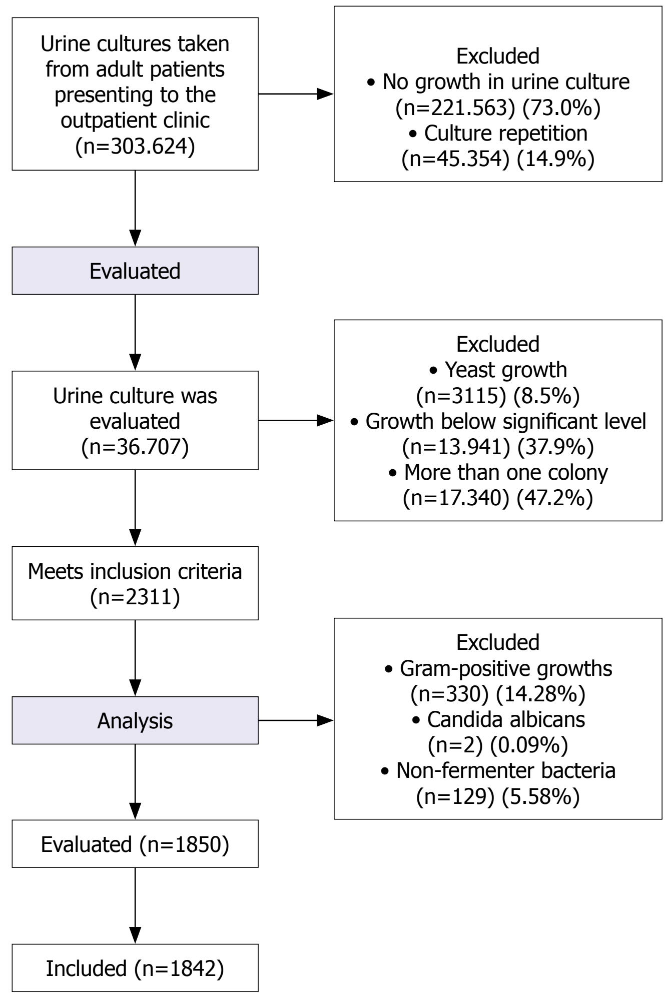

Figure 1. Evaluation algorithm of urine culture samples from 2015 to 2023.

RESULTS

In total, 303,624 urine culture results were evaluated from patients who visited the outpatient clinic during the study period, regardless of their clinical symptoms. Of these, 73% had a negative urine culture, while the remaining 82,061 urine cultures were positive. In 55.3% of these was considered contamination and repeat cultures

Table 1. Distribution of bacteria from urinary isolates

	Gram-negative bacteria				Gram-positive bacteria	
	n (%)		n (%)			n (%)
Enterobacteriace	1850 (80.1)	Non-fermenting bacteria	129 (5.58)	Gram-positive bacteria		330 (14.28)
Escherichia coli	1335 (57.77)	*Pseudomonas* spp	101 (45.37)	*Enterococcus* spp		178 (7.70)
Klebsiella spp	330 (14.28)	*Achromabacter* spp	2 (0.09)	*Coagulase-negative staphylococcus*		92 (3.98)
Morgenalla morgagni phyticus	18 (0.78)	*Acinetobacter*	18 (0.78)	*Staphylococcus sapro*		7 (0.30)
Serratia spp	22 (0.95)	*Stenotrophomonas maltophilia*	6 (0.26)	*Staphylococcus aeureus*		15 (0.65)
Proteus spp	54 (2.4)	*Burkholderia* spp	2 (0.09)	*Staphylococcus agalactia*		38 (1.64)
Enterobacter spp	71 (3.07)					
Citrobacter spp	19 (0.82)					
Salmonella spp	1 (0.04)					

Results were presented as count (n) and percentages.

were recommended. Results of quantitative cultures were reported in CFU/ml, with 2,311/45,380 (5.1%) urine cultures showing positive outcomes ≥105 CFU/ml. Antibiotic susceptibility was assessed in 2,311 urine cultures, and based on the inclusion criteria, 1,842 cultures were selected for the study (Fig. 1). Among the included samples, 71.5% (1317) belonged to females, and the participants' average age was reported as 63±18 years.

The most common bacteria extracted from the urine samples was Escherichia coli (n=1335, 57.77%), followed by Klebsiella spp. (n=330, 14.28%), Enterobacter spp. (n=71, 3.07%), Proteus spp. (n=54, 2.34%), Serratia spp. (n=22, 0.95%), Citrobacter spp. (n=19, 0.82%) and Morganella morganii (n=18, 0.78%). Resistance profiles against antibacterial agents were examined in the Enterobacteriaceae species, and the highest resistance rates were observed against ampicillin (n=1334, 77.92%), cefuroxime(n=109, 60.6%), cefixime (n=597, 52.4%), cefazolin (n=211, 52.36%), ciprofloxacin (n=833, 44.0%), and TMX-SXT (n=816, 45.2%), while the lowest resistance rates were observed against meropenem (n=50, 2.8%), amikacin (n=50, 2.8%), fosfomycin (n=155, 11.2%), and nitrofurantoin (n=140, 11.4%) (Table 1, 2).

Table 2 details resistance rates to first-line antimicrobials, ranging from 3% to 80%, and univariate analyses of susceptible controls and resistant isolates (intermediate susceptibility and resistant isolates were grouped). We compared the antibiotic resistance patterns of samples before to after 2019 (n=1719 vs. n=592). Resistance rates, to amikacin (4.96% vs. 14.98%, $p \leq 0.001$), and nitrofurantoin (9.96% vs. 21.14%, $p \leq 0.001$) were observed to be significantly increased. We found no significant differences in resistance rates to other antibiotics. We investigated the antibiotic resistance patterns in females and males and observed higher rates of antibiotic resistance in male urine samples ($p<0.001$). Furthermore, when compared to other Enterobacteriaceae strains, Escherichia coli strains exhibited lower resistance to amoxicillin/clavulanic acid, cefixime, amikacin, ciprofloxacin, nitrofurantoin, fosfomycin, and TMX-SXT (Table 3).

A multivariate analysis was performed using gender, age, and year to confirm their associations with ampicillin, ciprofloxacin, amikacin, nitrofurantoin, fosfomycin, and TMX-SXT resistance (Table 4). Amikacin and ciprofloxacin resistance were found to be affected by gender, age, and year, while fosfomycin and TMX-SXT resistance were affected by gender and age. Nitrofurantoin, cefixime, and amoxicillin/clavulanic acid resistance were found to be affected only by gender.

DISCUSSION

This study evaluates the prevalence of antibiotic resistance and risk factors of urine cultures due to Enterobacteriaceae isolates in local populations. This study also demonstrates that screening for UTIs in clinics is a reflexive practice without clear clinical indications, so it is valuable as it addresses the need for local studies that demonstrate the distribution and resistance profile of bacteria identified in urine samples from patients

Table 2. Resistance rates to antimicrobial agents in Enterobacteriaceae isolates

	AM	CP	SAM		AMC		PIP		TZP		CZ		FOX		FUR		CAZ	
S	378 (20.5)	22.08	90 (4.89)	45	257 (14)	14.0	11 (0.6)	44	1147 (62.3)	73.90	74 (4)	18.36	299 (16.2)	71.0	143 (7.8)	35.3	845 (45.8)	
I	0		13 (0.7)	6.5	632 (34)	34.3	1 (0.05)	4	123 (6.7)	7.93	118 (6.4)	29.28	17 (0.9)	4.0	33 (1.8)	8.1	103 (5.6)	
R	1334 (77.9)	**77.92**	97 (5.3)	**48.5**	14 (1)	0.8	13 (0.7)	**52**	282 (15.3)	**18.17**	211 (11.5)	**52.36**	105 (5.7)	**24.9**	229 (12.4)	**56.5**	669 (36.3)	
X					785 (43)	42.6											225 (12.3)	
Tot.	1712 (92.9)		200 (10.9)		154 (8.4)	8.4	25 (1.4)		1552 (84.3)		403 (21.9)		421 (22.9)		405 (22.0)		1842 (100)	
Mis.	130 (7.05)		1642 (89.14)		1842 (100)		1817 (98.6)		290 (15.7)		1439 (78.1)		1421 (77.1)		1437 (78.0)	0		
	CXM		CFM		AK		GM		NET		NN		LVX		CIP		NOR	
S	71 (3.9)	39.4	542 (29.4)	47.6	1642 (89.1)	92.4	1405 (76.3)	77.7	109 (5.9)	74.7	319 (17.3)	70.3	348 (18.9)	49.3	896 (48.6)	49.5	408 (22.1)	45.9
I					85 (4.6)	4.8	13 (0.7)	0.7	11 (0.6)	7.5			26 (1.4)	3.7	82 (4.5)	4.5	71 (3.9)	8
R	109 (5.9)	**60.6**	597 (32.4)	**52.4**	50 (2.7)	**2.8**	390 (21.1)	**21.6**	26 (1.4)	**17.8**	135 (7.3)	**29.7**	332 (18.0)	**47**	833 (45.2)	**44.0**	409 (22.2)	**46.1**
X																		
Tot.	180 (9.8)		1139 (61.8)		1777 (96.5)		1808 (98.2)		146 (7.9)		454 (24.6)		706 (38.3)		1811 (98.3)		888 (48.2)	
Mis.	1661 (90.2)		703 (38.2)		65 (3.5)		34 (1.8)		1696 (92.1)		1388 (75.4)		1136 (61.7)		31 (1.7)		954 (51.8)	
	ETP		IMP		MEM		ATM		NIT		FF		TXM-STX		CTX		FEB	
S	1531 (83.1)	90.4	1631 (88.5)	93.9	1696 (92.1)	95.1	495 (26.9)	58.2	1087 (59.0)	88.4	1222 (66.3)	88.6	986 (53.5)	54.6	38 (2.1)	38	628 (34.1)	56.8
I	18 (1.0)	1.1	54 (2.9)	3.1	38 (2.1)	2.1	34 (1.8)	4.0	2 (0.1)	0.2	3 (0.2)	0.2	5 (0.3)	0.3	2 (0.1)	2	57 (3.1)	5.2
R	145 (7.9)	**8.6**	52 (2.8)	**3.0**	50 (2.7)	**2.8**	322 (17.5)	**37.8**	140 (7.6)	**11.4**	155 (8.4)	**11.2**	816 (44.3)	**45.2**	60 (3.3)	**60**	420 (22.8)	**38.0**
X																		
Tot.	1694 (92.0)		1737 (94.7)		1784 (96.9)		851 (46.2)		1229 (66.7)		1380 (74.9)		1807 (98.1)		100 (5.4)		1105 (40)	
Mis.	148 (8.0)		19-05 (5.7)		58 (3.1)		991 (53.8)		613 (33.3)		462 (25.1)		35 (1.9)		1742 (94.6)		737 (40)	

Results were presented as count (n) and percentages. CP: Current percentage; Tot: Total; Mis: Missing; AM: Ampicilin; AK: Amikacin; CTM: Cefotiam; ZOX: Ceftizoxime; GM: Gentamisin; SAM: Ampicillin/sulbactam; CAZ: Ceftazidime; LEV: Levofloxacin; TXM-STX: Trimethoprim/sulphamethoxazole; AMC: Amoxicillin/clavulanic acid; FUR: Ceftiofur; NOR: Norfloxacin; CZ: Cefazolin; IMC: Cilastatin/imipenem; FEB: Cefepime; CFM: Cefixime; CXM: Cefuroxime; NIT: Nitrofurantoin; FOX: Cefoxitin; NET: Netilmisin; FF: Fosfomycin; PIP: Piperacillin; TZP: Piperacillin/tazobactam; NN: CIP: Ciprofloxacin; ETP: Ertapenem; MEM: Meropenem; ATM: Aztreonam; CTX: Cefotaxi-meS: Sensitive, I: Intermediate, R: Resistance, X: Unknown.

TABLE 3. Comparison of antibiotic resistance patterns of samples to year and gender of outpatient *Enterobacteriaceae* urinary isolates

	Escherichia coli n (%)	Other *Enterobacteriaceae* Species n (%)	p	2019 and before n (%)	2020 and after n (%)	p	Female n (%)	Male n (%)	p
SAM	65 (51.2)	45 (61.6)	0.152	99 (54.7)	11 (57.9)	0.98	69 (53.08)	41 (58.57)	0.456
AMC	520 (51.4)	279 (66.4)	<0.001	666 (56.25)	133 (53.85)	0.489	504 (48.89)	295 (73.75)	<0.001
CFM	417 (49.3)	180 (61.4)	<0.001	498 (51.98)	99 (54.70)	0.503	382 (45.80)	215 (70.49)	<0.001
AK	78 (6.1)	57 (11.5)	<0.001	65 (4.96)	70 (14.98)	<0.001	72 (5.7)	63 (12.28)	<0.001
CIP	643 (49.1)	272 (54.3)	0.047	664 (49.59)	251 (53.18)	0.180	559 (43.26)	356 (68.59)	<0.001
NIT	64 (6.1)	78 (44.8)	<0.001	105 (9.96)	37 (21.14)	<0.001	60 (6.76)	82 (23.98)	<0.001
FF	47 (4.6)	111 (31.5)	<0.001	119 (10.77)	39 (14.18)	0.112	96 (9.29)	62 (17.87)	<0.001
TXM-STX	570 (43.7)	251 (49.9)	0.018	610 (45.56)	211 (45.09)	0.860	526 (64.1)	295 (35.9)	<0.001

SAM: Ampicillin/sulbactam; AMC: Amoxicillin/clavulanic acid; CFM: Cefixime; AK: Amikacin; CIP: Ciprofloxacin; NIT: Nitrofurantoin; FF: Fosfomycin; TXM-STX: Trimethoprim/sulphamethoxazole. Results were presented as count (n) and percentages (%). For categorical variables, Chi-square test (or Fisher's exact) was performed. P<0.05, results were statistically significant.

TABLE 4. Logistic regression analysis of antimicrobial resistance and related risk factors

	Multivariate				Analysis			
	SAM		AK		CFM		NIT	
	OR (%95 CI)	p	OR (%95 CI)	p	OR (%95 CI)	p	OR (%95 CI)	p
Gender (male)	1.284 (0.684–2.411)	0.437	2.022 (1.395–2.932)	<0.001	2.716 (2.035–3.626)	<0.001	4.212 (2.881–6.156)	<0.001
Age	0.999 (0.983–1.014)	0.863	1.012 (1.001–1.024)	0.031	1.005 (0.998–1.011)	0.196219	1.003 (0.993–1.014)	0.55
Year	0.977 (0.854–1.118)	0.736	1.349 (1.238–1.47)	<0.001	0.994 (0.915–1.079)	0.88267	0.987 (0.886–1.1)	0.815
	FF		TXM-STX		AMC		CIP	
	OR (%95CI)	p	OR (%95CI)	p	OR (%95CI)	p	OR (%95CI)	p
Gender (male)	1.934 (1.354–2.764)	<0.001	1.766 (1.426–2.187)	<0.001	2.953 (2.271–3.839)	<0.001	2.464 (1.973–3.076)	<0.001
Age	1.01 (1–1.021)	0.043	1.01 (1.005–1.016)	<0.001	1 (0.994–1.007)	0.91	1.016 (1.01–1.021)	<0.001
Year	1.007 (0.931–1.09)	0.86	0.985 (0.942–1.03)	0.52	0.964 (0.916–1.014)	0.16	1.073 (1.025–1.123)	<0.001

AK: Amikacin; SAM: Ampicillin/sulbactam; TXM-STX: Trimethoprim/sulphamethoxazole; AMC: Amoxicillin/clavulanic acid; CFM: Cefixime; NIT: Nitrofurantoin; FF: Fosfomycin; CIP: Ciprofloxacin; OR: Odds ratio; CI: Confidence interval; p<0.05, results were statistically significant.

seeking treatment at a community clinic. It guides outpatient treatment recommendations for individuals diagnosed with urinary tract infections acquired within the community. Furthermore, being a local study adds to its significance. Typically, uncomplicated urinary tract infections acquired in the community are treated empirically without conducting a urine culture or antibiogram, unless there are frequent recurrences. However, our study highlights the significance of monitoring the initial usage of antimicrobial agents in the population, as suggested by the Infectious Diseases Society of America, to ensure the selection of appropriate empirical treatment [10]. Ensuring the appropriate use of empirical antibiotics raises concerns regarding antibiotic resistance patterns, safety, compliance, and cost. Thus, the ability to predict the risk of resistance to empirical antibiotics becomes crucial.

Traditionally, a resistance rate of 20% has been deemed as an acceptable threshold for an antibiotic to be considered suitable for empirical therapy. In the latest evaluation of antimicrobial susceptibility trends in urinary pathogens, it was found that around 20% of the tested isolates showed resistance to both trimethoprim-sulfamethoxazole and ciprofloxacin. Nitrofurantoin resistance, a treatment method increasingly used for uncomplicated UTIs, has been observed at rates of up to 10% [10, 11].

Our findings demonstrate that 55.3% of the urine culture results were deemed as contamination. A similar study conducted in our country also revealed a contamination rate of 60.7% [12]. The significant prevalence of contamination underscores the importance of thorough evaluation and patient education when requesting urine cultures, aiming to reduce wastage of time, money and prevent loss of workforce. It also can lead to delays in diagnosing and treating the underlying illness of the actual illness, resulting in potential complications or antibiotic resistance due to incorrect treatment. The results demonstrate that Escherichia coli was the most commonly isolated strain in urine samples, accounting for 57.8% of all isolates similar to the French study [13]. However, its prevalence was comparatively lower than in Europe and Canada where it ranges from 61.0% to 87.5% [6, 14–21]. The majority of the cultures were from female participants (71.5%), which was higher compared to previous studies [8, 15].

The resistance rates to first-line antimicrobials range from 3% to 80%. The highest resistance rates were observed for ampicillin at 77.92%, slightly lower than those reported in previous studies [21, 22]. The resistance rates for ciprofloxacin and TMX-SXT were 44.0% and 45.2%, respectively. A cohort study at 15 institutions in the United States involving more than 5,000 patients revealed notable in vitro resistance to commonly used antibiotics for community urinary tract infections, with quinolones, TMX-SXT, and b-lactams exhibiting a resistance rate below 20% and resistance rates over 20% in various studies [23]. Escalating ciprofloxacin- and TMX-SXT-resistant strains indicate inappropriate usage of these antibiotics for empiric treatment in outpatients. However, recent studies noted that nitrofurantoin and fosfomycin demonstrated relatively low resistance, indicating it could be a viable and effective treatment option for community-acquired UTIs [22, 24–26]. The resistance rates were observed against fosfomycin (11.2%) and nitrofurantoin (11.4%) in our study. In vitro, nitrofurantoin and fosfomycin demonstrate the highest antimicrobial activity against E. coli, including multi-drug-resistant strains, isolated from outpatients with acute cystitis. Moreover, resistance rates to these antibiotics remain comparatively constant over time [4, 14, 24, 25, 27]. The fosfomycin resistance was similar to a previous study from Turkiye [15, 28]. Because of its high effectiveness regarding E. coli, its safety profile, and its minimal effect on the gut microbiota, nitrofurantoin is the primary suggested antibiotic treatment for uncomplicated cystitis [27, 29]. A systematic review and meta-analysis determined that for female patients with uncomplicated UTIs, a single dose (3-gram) of oral fosfomycin treatment was as effective and safe as various regimens of nitrofurantoin [30]. Regarding aminoglycosides, despite being not widely utilized due to toxicity concerns, they still present a vital therapeutic choice for the therapy of infections resulting from antimicrobial-resistant (AMR) organisms in situations with limited treatment alternatives [31, 32].

In our study, when comparing urine samples and antibiotic resistance patterns before and after 2019 (n=1719 vs. n=592), we observed a substantial rise in the resistance levels against amikacin (4.96% vs. 14.98%, $p\leq0.001$) and nitrofurantoin (9.96% vs. 21.14%, $p\leq0.001$) and found no significant differences in resistance rates to other antibiotics. It is also assumed that the decrease in the number of urine cultures in 2020 and beyond is a result of reduced healthcare utilization due to the COVID-19 pandemic. Over the past decade, while the resistance rates to amoxicillin, cotrimoxazole, and amikacin remained unchanged, there has been a notable escalation in resistance to ciprofloxacin, mirroring trends observed in other nations [14, 33–35]. Between 2012 and 2020, a study emphasized that there was a statistically significant rise in the resistance rates to the antibiotic fosfomycin. Another study from Turkiye reported increased resistance to ciprofloxacin, nitrofurantoin, ampicillin, fosfomycin, and cefepime. Meanwhile, a study from Asia showed a consistent rise in resistance to all antibiotics examined. This study indicated a significant escalation in resistance to various classes of antibiotics over time in the patients studied, particularly in the carbapenem and aminoglycoside groups. A similar trend was observed for amikacin, gentamicin, amoxicillin/clavulanic acid, and nitrofurantoin [15, 36, 37]. Moreover, a meta-analysis of five studies conducted on UTIs treated in primary care identified a heightened risk of antibiotic resistance that lingered for up to a year, with the risk being even higher when multiple courses of antibiotics were involved [1].

Antibiotic resistance is related to morbidity, mortality, or healthcare expenses [4]. The identification of risk factors is crucial for the development of effective treatment strategies, which could potentially mitigate the spread of these infections and enhance the appropriate use of antibiotics. A multivariate analysis was performed using gender, age, and year to confirm their associations with resistance to ampicillin, ciprofloxacin, amikacin, nitrofurantoin, fosfomycin, and trimethoprim/sulfamethoxazole. Amikacin and ciprofloxacin resistance were found to have increased by male gender, age, and year, while fosfomycin and TMX-SXT resistance have been found to increase by male gender and age. Nitrofurantoin, cefixime, and amoxicillin/clavulanic acid resistance were found to be affected only by the male gender. In our study, we observed higher antibiotic resistance rates in male urine samples, a finding that aligns with a similar study conducted in Israel [25]. Meanwhile, Dash et al. [22] conducted a study on urinary tract infections acquired in the community setting, highlighting the prevalence in the female population. Milano et al. [38] reported a notable rise in resistance levels to ciprofloxacin, gentamicin, TMX-SXT, or third-generation cephalosporins with advancing age. This finding is consistent with other studies that have also underscored the correlation between increased age and escalating antibiotic resistance [21, 22, 24].

There are certain limitations to our study; given the study's retrospective nature, some data points were either unavailable or not incorporated into the analysis. These include information regarding the patient's clinical status, history of antibiotic usage, contributing factors for contracting bacteria resistant to treatment, and the patient's condition, whether it involved asymptomatic bacteriuria or uncomplicated or complicated UTIs. There is also missing data on antimicrobial resistance rates. Since the study was carried out in a single-center setting the generalizability of our conclusions is limited.

Conclusion

The outcomes of our study concluded that Escherichia coli and Klebsiella pneumoniae have become major etiological pathogens of UTI in Turkiye. The high rate of negative urine cultures and results consistent with contamination highlight the importance of careful evaluation and patient education when requesting urine cultures. Older age, male sex, and years were significant risk factors for AMR. The high rates of AMR can limit outpatient treatment options for UTIs and increase hospitalization rates. Our study is important because it demonstrates that nitrofurantoin and fosfomycin could be good options to use, and ampicillin and cotrimoxazole should be avoided in the outpatient and empirical treatment of UTIs.

Ethics Committee Approval: The Ankara Etlik City Hospital Clinical Research Ethics Committee granted approval for this study (date: 05.04.2023, number: AESH-EK1-2023-061).

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