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INVESTIGATION OF ANTIBIOTIC RESISTANCE STATUS OF *ESCHERICHIA COLI* AND *KLEBSIELLA PNEUMONIAE* ISOLATES CAUSING URINARY TRACT INFECTIONS: 4-YEAR STUDY

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Abstract

Objective: The aim of the study is to guide clinicians regarding empirical treatment in our region and to contribute to the literature by determining antibiotic resistance frequency of *E. coli* and *Klebsiella pneumoniae* strains which cause urinary tract infections (UTIs).

Methods: In the study, a total of 27,443 mandatory cultures sent from various outpatient clinics and services between January 2016 and September 2019 were retrospectively evaluated. Bacterial identification and antibiotic susceptibilities were performed by conventional methods and automatic systems. SPSS 25 statistical package program was used in the evaluation of the study data, and the statistical significance level of the results was accepted as $p<0.05$.

Results: A total of 333 *Escherichia coli* and 373 *Klebsiella pneumoniae* isolates from which growth was detected in urine samples were included in the study. The antibiotic to which *E. coli* isolates were most resistant was ampicillin (48.4%), and no antibiotic resistance was detected against fosfomycin and was statistically significant. The least resistant antibiotic of *Klebsiella pneumoniae* strains was amikacin (4.27%), and the most resistant antibiotic was ceftazidime (58.73%). Renal failure was the most common comorbidity.

Conclusion: Increasing antibiotic resistance makes the treatment of UTIs more difficult. It is thought that the study data will guide clinicians in contributing to the success of treatment by selecting the appropriate antibiotic and in preventing unnecessary or incorrect antibiotic use. Fosfomycin is an important agent in the empirical treatment of ESBL positive *E. coli* and amikacin in *K. pneumoniae* isolates.

Keywords: *Urine culture, Escherichia coli; Klebsiella pneumoniae., antibiotic resistance.*

Introduction

Urinary tract infections (UTIs) are the most common bacterial infections in every age group, whether in hospital or out of hospital settings.[1] It is reported that an estimated 150 million people who apply to clinics each year are diagnosed with UTI.[2] Although many types of bacteria cause UTI, it is reported that *Escherichia coli* and *Klebsiella pneumoniae* cause approximately 90% of these infections.[3] A single bacterium is responsible for more than 95% of UTIs.[4] The Infectious Diseases Society of America has reported the importance of knowing the causative agents and antibiotic resistance rates in UTIs in a region.[5] Increases in resistance rates to antimicrobial agents initiated in empirical treatment of UTI have been reported.[1]

The fact that increasing rate of antibiotic resistance, the failure to develop new drugs makes it difficult to treat resistant bacterial infections. Following the discovery of broad-spectrum cephalosporins in the early 1980s, extended spectrum beta lactamase (ESBL) enzyme positivity was detected in *Klebsiella pneumoniae* (*K. pneumoniae*) strains, and the increased use of carbapenem class antibiotics in these microorganisms also brought about carbapenem resistance. The Centers for Disease Control and Prevention (CDC) reported that Enterobacterales, which have been found to be resistant to carbapenems, are one of the bacterial groups that pose a serious public health threat.[6]

If the necessary measures are not taken to control antibiotic resistance, it is estimated that 10 million people may develop antibiotic-resistant bacterial infections each year by 2050 due to the increase in drug-resistant infections in many countries.[7] The European urology guideline states that the use of antibiotics with antibiotic resistance rates above certain levels in empirical treatment is not appropriate.[8] Determining resistance rates in *E. coli* and *Klebsiella pneumoniae* isolated from UTIs is important in terms of contributing to empirical treatments. The drugs to be preferred in empirical treatment should be planned by taking into account regional antibiotic resistance. The aim of this study is to determine the frequency and antibiotic resistance profile of *E. coli* and *Klebsiella pneumoniae* isolates that cause UTI and sent to the microbiology laboratory from various clinics, and to guide clinicians regarding empirical treatment in our region and to contribute to the literature.

Methods

In this study, *E. coli* and *Klebsiella pneumoniae* isolates detected in urine cultures sent from various polyclinics, clinics and intensive care units (ICUs) to the Medical Microbiology Laboratory of a tertiary healthcare institution between January 2016 and September 2019 were included in the study. Antibiotic resistance statuses were examined retrospectively from the hospital's automation system. Patients' age, gender, unit information where the sample was sent, bacterial species grown, comorbidity status and antibiotic resistance rates were recorded.

Patients with multiple growths within a year and those with growths below 100,000 CFU/ml in urine culture were excluded from the study.

After appropriate cleaning and antisepsis, urine samples taken from patients under sterile mid-flow and aseptic conditions were inoculated into blood agar (Condolab, Spain) and eosin methylene blue (EMB) agar (Oxoid, England) media using loops capable of taking 0.01 ml urine samples using a quantitative method. The media were incubated at 37°C for 18–24 hours in an aerobic environment. Identification of gram-negative microorganisms that suggest infection, such as colony counts and the presence of leukocytes on microscopy, in samples with microorganism growth of 10^5 CFU/ml (colony-forming units) and above, was performed using conventional microbiological methods (colony morphology, gram staining characteristics, carbohydrate and citrate usage, urease production, etc.) and automated systems (Vitek-2, bioMérieux- France). Antibiotic susceptibility tests of microorganisms were performed using both conventional microbiological methods and automated systems. Antibiotic susceptibilities were evaluated in accordance with CLSI (Clinical and Laboratory Standards Institute)[9] guidelines between 2016-2017 and TMP-SXT susceptibility in accordance with EUCAST (European Committee on Antimicrobial Susceptibility Testing) guidelines between 2018–2019.[10] The presence of ESBL enzyme was determined by the combined disk test method.

Statistical Analysis

The number of samples in the study was shown as "n" and calculated as a percentage (%). SPSS 25 statistical package program was used in the evaluation of the study data, and the statistical significance level of the results was accepted as $p<0.05$. The chi-square test was used in the statistical evaluation of the comparison of annual differences, and the results with $p<0.05$ were accepted as statistically significant.

Table 1. Distribution percentages of samples according to the department they came from, comorbidity status, age, and gender according to bacterial type.

	E.coli **% (n)**	***K. pneumoniae*** **% (n)**	**Total % (n)**
Gender			
Female	82.9 (276)	56.3 (210)	68.8 (486)
Male	17.1(57)	43.7 (163)	31.2 (220)
Age			
<18 years	36 (120)	22.5 (84)	28.9 (204)
18–64 years	37.8 (126)	31.9 (119)	34.7 (245)
≥ 65 years	26.1 (87)	45.6 (170)	36.4 (257)
Clinic			
Outpatient	69.4 (231)	38.6 (144)	53.1 (375)
Service	24.3 (81)	34.6 (129)	29.7 (210)
Intensive care	6.3 (21)	26.5 (99)	17.2 (120)
Comorbidity status			
Malignancy	5.7 (19)	7.5 (28)	6.7 (47)
Renal colic	3.3 (11)	1.9 (7)	2.5 (18)
BND	3.3 (11)	1.6 (6)	2.4 (17)
Pregnancy	3 (10)	1.3 (4)	2 (14)
DM	2.4 (8)	0.8 (3)	1.6 (11)
UI	0.9 (3)	1.1 (4)	1 (7)
Renal failure	2.7 (9)	14.2 (53)	8.8 (62)
Trauma	0.3 (1)	2.1 (8)	1.3 (9)
NS	1.5 (5)	3.2 (12)	2.4 (17)
PH	0.6 (2)	1.1 (4)	0.8 (6)
HT	0.9 (3)	1.1 (4)	1 (7)
Heart failure	0.3 (1)	0.3 (1)	0.3 (2)

BND: Bladder neuromuscular dysfunction; UI: Urinary incontinence; NS: Neurological sequelae; PH: Prostatic hypertrophy; HT: Hypertension

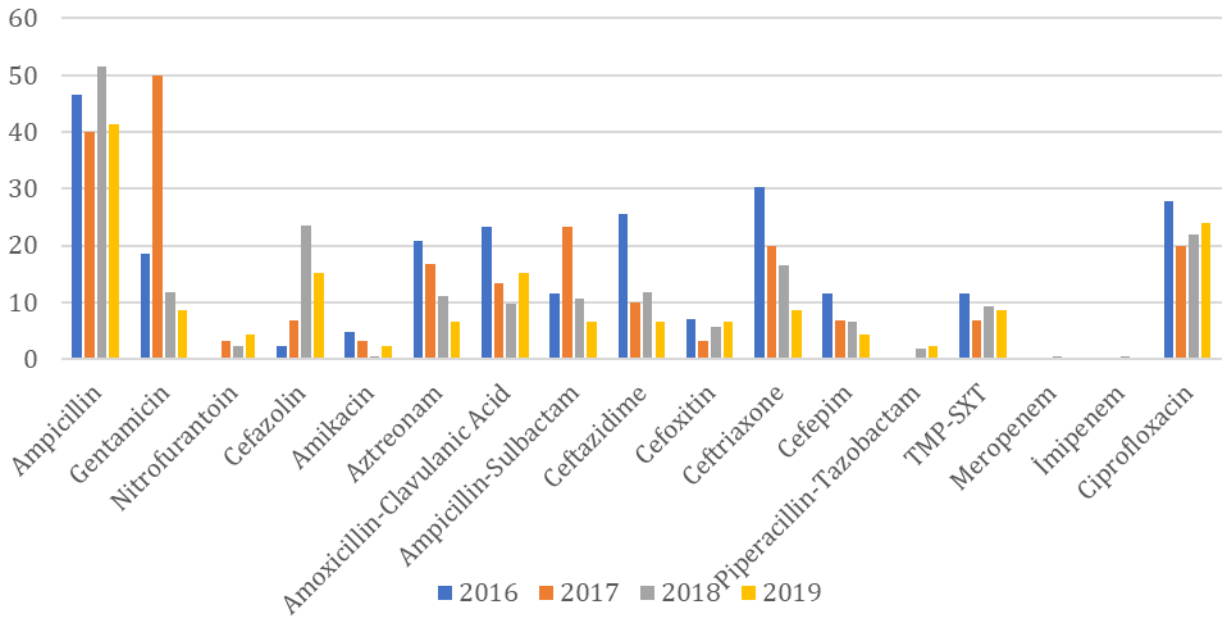

Figure 1. Resistance profile of *E.coli* strains isolated from urine culture to various antibiotics over the years.

Results

In the study data, it was observed that 68.8% of 333 *E. coli* and 373 *Klebsiella pneumoniae* samples belonged to female patients and 31.2% to male patients. 204 (28.9%) of the patients were under the age of 18, 245 (34.7%) were between the ages of 18–64, and 257 (36.4%) were over the age of 65. Of the studied cultures, 375 (53.1%) were sent from outpatients, 210 (29.7%) from ward patients, and 120 (17.2%) from ICU patients. The distribution of microorganisms detected in urine cultures according to the department they came from, gender, comorbidity status, and age groups is shown (Table 1). 6.3% of *E. coli* isolates and 26.5% of *Klebsiella pneumoniae* were isolated from patients hospitalized in the ICU.

The most commonly used antibiotics for empirical treatment were ampicillin, gentamicin, nitrofurantoin, cefazolin, amikacin, aztreonam, amoxicillin clavulanic acid, ampicillin/sulbactam, ceftazidime, cefoxitin, cefriaxon, cefepime, piperacillin tazobactam, trimethoprim-sulfamethoxazole (TMP-SXT), meropenem, imipenem, ciprofloxacin and were analyzed for resistance status (Table 2). The distribution of resistance rates of these antibiotics by year is shown (Figures 1 and 2).

The antibiotic with the highest resistance rate in the *E. coli* strains included in the study was ampicillin (48.4%), while no antibiotic resistance was detected in fosfomycin and was statistically significant ($p<0.05$ ($p=0.002$)). TMP-SXT (47.6%), ceftriaxone (42.64%) and ciprofloxacin (42.49%) are other antibiotics with high resistance (Figure 3).

Table 2. Antibiotic resistance and broad-spectrum β-lactamase positivity percentages of *Escherichia coli* and *K. pneumoniae* strains isolated from patients.

	E.coli				***K. pneumoniae***			
	Outpatient	**Service**	**Intensive Care**	***p***	**Outpatient**	**Service**	**Intensive Care**	***p***
Ampicillin	32.1	13.20	3.00	0.303	-	-	-	
Gentamicin	9.6	4.50	1.50	0.501	6.20	12.60	11.00	0.002
Nitrofurantoin	1.50	0.60	0.30	0.002	17.90	15.40	5.90	0.000
Cefazolin	11.70	5.40	0.90	0.612	32.40	16.80	1.20	0.001
Amikacin	1.60	1.09	0.00	0.233	1.40	1.40	1.40	0.001
Aztreonam	14.70	7.60	1.70	0.391	14.70	19.40	24.80	0.001
Amoxicillin-clavulanic acid	15.00	7.80	2.40	0.726	13.70	15.70	28.80	0.000
Ampicillin-sulbactam	14.20	7.79	2.59	0.616	17.00	13.00	14.00	0.250
Ceftazidim	16.3	7.5	2.5	0.688	16.40	21.50	20.30	0.000
Cefoxitin	7.5	3.75	0.6	0.600	9.50	12.30	8.90	0.000
Ceftriaxone	29.40	10.20	2.90	0.277	24.20	24.20	9.20	0.000
Cefepime	7.60	4.45	2.50	0.299	12.70	20.76	21.60	0.000
Piperacillin-tazobactam	1.20	1.20	0.60	0.174	8.05	14.10	15.50	0.000
Trimethoprim-sulfamethoxazole	35.30	7.60	4.61	0.686	13.40	19.60	13.70	0.005
Meropenem	0.00	0.57	0.00	0.025	1.60	4.70	8.60	0.000
Imipenem	0.00	0.50	0.00	0.072	0.85	3.10	1.90	0.000
Ciprofloxacin	25.20	12.30	5.05	0.131	9.60	13.60	15.05	0.000
Fosfomycin	0	0	0	0.002				
ESBL positivity*	6.00	3.60	0.90	0.252	9.70	9.70	4.80	0.348

*ESBL: Extended Spectrum β-lactamase

The antibiotics to which *Klebsiella pneumoniae* strains were least resistant were amikacin (4.27%) and imipenem (5.96%), while the most resistant antibiotic was ceftazidime (58.73%) (Figure 4). Ampicillin was not included in the study because it was intrinsically resistant in *K. pneumoniae* strains. Of the 125 bacteria with ESBL enzyme production detected by the combined disk test method, 35 (28%) were identified as *Escherichia coli* and 90 (72%) as *K. pneumoniae*.

Low antibiotic resistance was detected against imipenem and amikacin in *E. coli* strains with ESBL enzyme production (both p=0.000). Resistance to carbapenems and amikacin was 1.3% in *Klebsiella pneumoniae* strains with ESBL enzyme production. While low antibiotic resistance rate was detected for piperacillin-tazobactam in *E. coli* strains producing ESBL enzyme, this rate was 32% for *Klebsiella pneumoniae*.

Antibiotic resistance rates were higher in outpatient clinic patients for *E. coli* and in hospitalized patients for *Klebsiella pneumoniae*. The difference in resistance to nitrofurantoin in both bacterial groups was found to be statistically significant (*E. coli* p= 0.002; *Klebsiella pneumoniae* p=0.000).

In the evaluation of comorbidity status in the study group, renal failure was the most common (8.8%) found to be statistically significant (p=0.000). This was followed by malignancy (6.7%) and renal colic (2.5%).

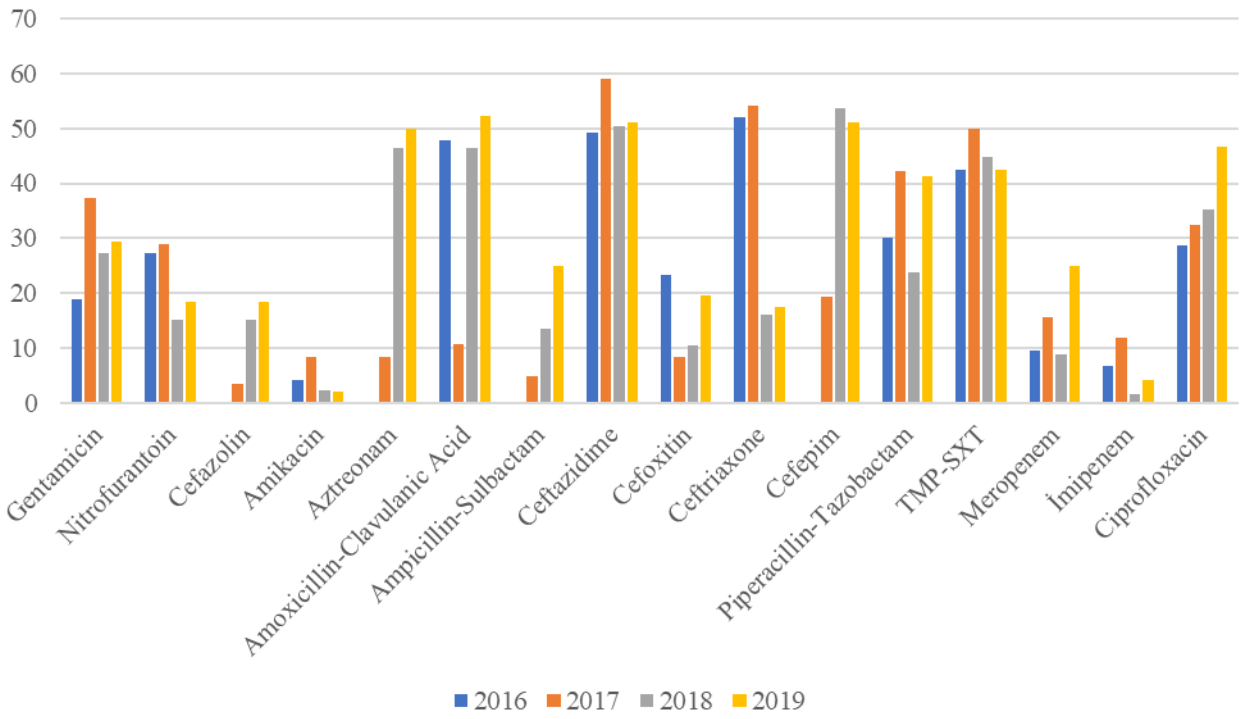

Figure 2. Resistance profile of *K. pneumoniae* strains isolated from urine culture to various antibiotics over the years.

Discussion

In bacterial infections, the distribution of agents and antibiotic resistance varies over the years, even from region to region, city to city, and hospital to hospital. Therefore, monitoring regional resistance is of great importance in empirical antimicrobial drug use in UTI. In our study conducted for this purpose, *E. coli* and *Klebsiella pneumoniae* strains grown in urine cultures were examined and ESBL positivity rates and antibiotic resistance rates were investigated.

In our study, the most frequently isolated agent in 706 urine samples was *Klebsiella pneumoniae* (52.9%), followed by *E. coli* with a rate of 47.1%. The most common agent in UTIs in Turkey and the World is *E. coli*.[11] In terms of Gram-negative bacteria, the most frequently detected pathogenic agent after *E. coli* is *K. pneumoniae*. In our study, *K. pneumoniae* took the first place.

According to the data of our study, the ESBL enzyme production rate was found to be 28% in *E. coli* isolates and 72% in *K. pneumoniae*. In a study conducted in Mexico, the ESBL enzyme production rate in *E. coli* was found to be 31.3%, similar to our study data.[12] In a multicenter study, the ESBL positivity rate in UTI was found to be 24.6% in *E. coli* strains.[13] In the study conducted by Şenol et al. in 2020, the ESBL production rate was reported to be 40% in *E. coli* strains isolated from community-acquired UTI and 47.4% in *K. pneumoniae* strain.[3] ESBL enzyme plays an important role in the development of resistance to penicillin, cephalosporin and monobactams.[14] The continuous increase in ESBL enzyme positivity in *E. coli* and *K. pneumoniae* strains makes treatment difficult. When the literature is examined, ESBL enzyme production in Klebsiella strains varies between 10% and 55%.[4,15-17]

In this study, carbapenems were determined to be antibiotics with low resistance rates in all *E. coli* and *K. pneumoniae* strains. While imipenem resistance is very low (0.5%) in ESBL positive *E. coli* strains, it is 5.96% in *K. pneumoniae*. In some studies investigating imipenem resistance in *E. coli* strains with positive ESBL enzyme production in Turkey, imipenem resistance was found to be similar to our study.[18,19] In the study of Vachvanichsanong et al., imipenem resistance was not detected in ESBL positive *K. pneumoniae* strains.[20]

Early diagnosis of ESBL production is important for appropriate treatment and effective infection control. In our study, ampicillin, ciprofloxacin, TMP-SXT and ceftriaxone were the antibiotics with the highest resistance rates for *E. coli*. Ceftazidime, ceftriaxone and aztroneam were the agents with the highest resistance rates in *K. pneumoniae*. Today, TMP-SXT, ciprofloxacin and beta-lactam group antibiotics are frequently used in the empirical treatment of UTI and sensitivity to these agents has varied over the years. The increased use of third generation cephalosporins has led to the emergence of resistant strains.[21]

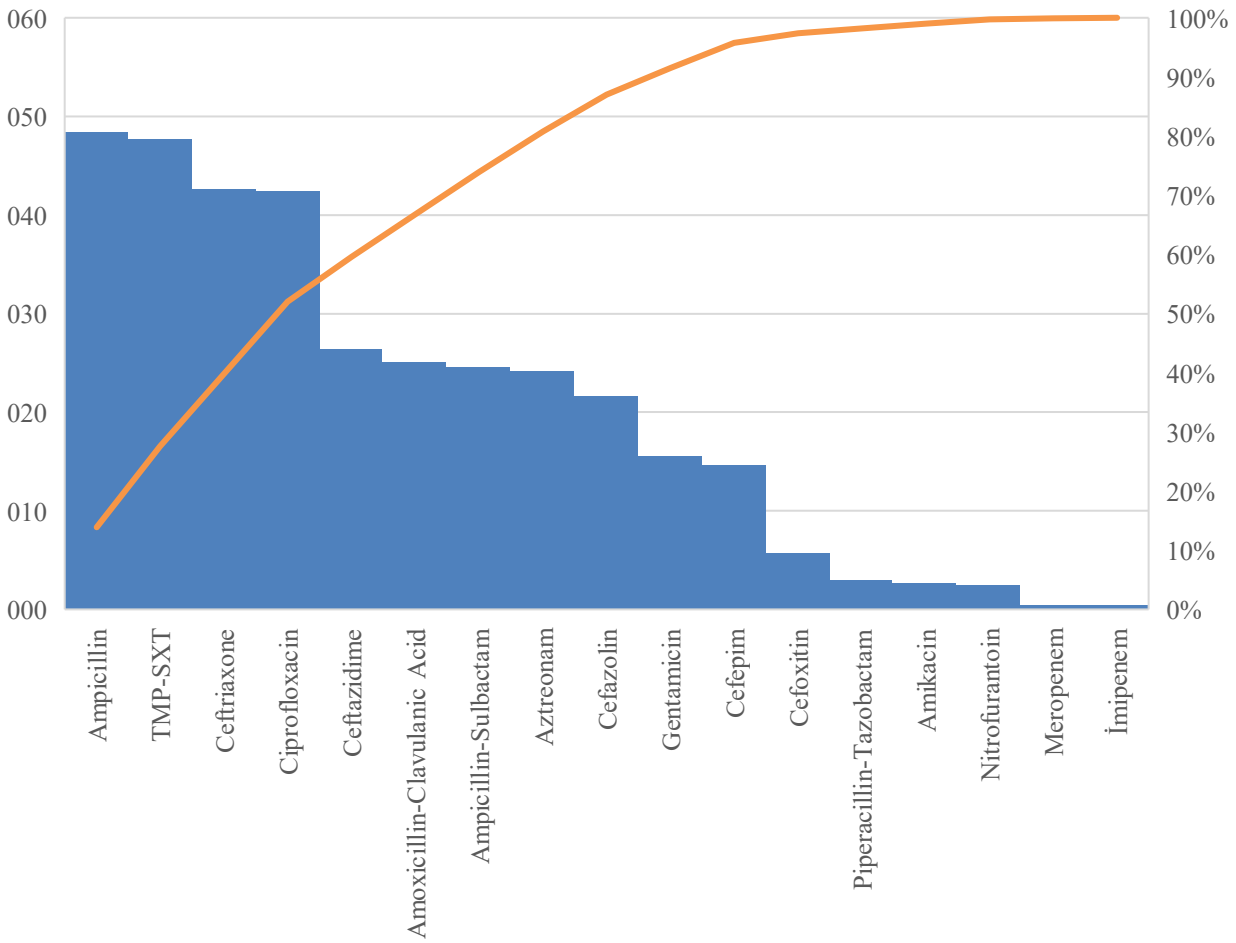

Figure 3. Antibiotic resistance percentages of *E. coli* strains.

The high resistance rates detected against ciprofloxacin, beta-lactam and TMP-SXT in UTI have brought the issue of using alternative antimicrobials to the agenda.[22] Nitrofurantoin and fosfomycin are among the antimicrobial agents that have gained importance for this reason.

According to our study data, fosfomycin resistance was not detected in all *E. coli* strains. Resistance to fosfomycin was detected at 0–19% worldwide and 0–11.5% in Turkey.[23-26]

In the context of empirical treatment for urinary tract infections caused by multidrug-resistant pathogens, fosfomycin has demonstrated considerable efficacy against *Escherichia coli*, including extended-spectrum beta-lactamase (ESBL)-producing strains. Its favorable pharmacokinetic profile, oral administration route, and retained activity make fosfomycin a valuable therapeutic option, particularly in uncomplicated lower urinary tract infections. Conversely, for *Klebsiella pneumoniae* isolates, aminoglycosides such as amikacin remain an important component of empirical therapy due to their potent bactericidal activity and sustained susceptibility observed in clinical isolates. While carbapenems continue to represent the mainstay for severe infections, the adjunctive use of amikacin can enhance treatment efficacy, especially in complicated cases or where carbapenem-sparing strategies are considered. These findings underscore the necessity of tailoring empirical regimens based on pathogen-specific susceptibility patterns and clinical presentation to optimize therapeutic outcomes. In studies examining the antibiotic susceptibility of bacteria isolated from urine cultures, similar antibiotics have been reported to exhibit comparable efficacy.[27-28]

In our study, nitrofurantoin resistance rates were found to be 2.5% and 34.6% in *E. coli* and *K. pneumoniae*, respectively. In a study by İgan and Hanlı in Turkey, 9.6% of *E. coli* isolates and 25% of Klebsiella isolates were found to have nitrofurantoin resistance.[29] In a study conducted in Switzerland in 2019, nitrofurantoin resistance was found to be below 5% for *E. coli* and >58% for Klebsiella.[30] We attribute the high rate of nitrofurantoin resistance to the increased use rate.

It is stated that in cases where the resistance rate in antibiotics exceeds 20%, it would not be appropriate to use that drug in empirical treatment.[31] In our study, ceftriaxone, trimethoprim-sulfamethoxazole, ciprofloxacin were found to be more than 20% in outpatients in *E. coli* strains; amoxicillin-clavulanate, aztreonam, cefepime resistance rates were found to be higher than 20% in intensive care patients from whom *K. pneumoniae* was isolated. We can recommend that these drugs should not be used in empirical treatment in these patients.

In our study, the distribution of antibiotic resistance rates by year shows a different course. It was observed that resistance in *E. coli* and *K. pneumoniae* increased significantly in some years, and then decreased again in the following years. This situation shows that there may be epidemics caused by resistant strains, that these epidemics can be prevented with infection control measures, effective cleaning and hygiene, and that the spread of resistance can be reduced. In *E. coli*, a decrease in the resistance of aztreonam, cefriaxone, cefepime antibiotics and an increase in piperacillin-tazobactam were observed by years. In *K. pneumoniae* an increase in the resistance of cefazolin, aztreonam, ampicillin-sulbactam and ciprofloxacin antibiotics was observed by years.

In our study, while the antibiotic susceptibility profiles of ESBL-producing *E. coli* and *Klebsiella pneumoniae* isolates were evaluated, a detailed clinical classification of the infections (e.g., complicated vs. uncomplicated urinary tract infections) based on anatomical localization could not be performed. This is considered a limitation of the study, primarily due to its retrospective design and the lack of access to complete clinical data for all cases.

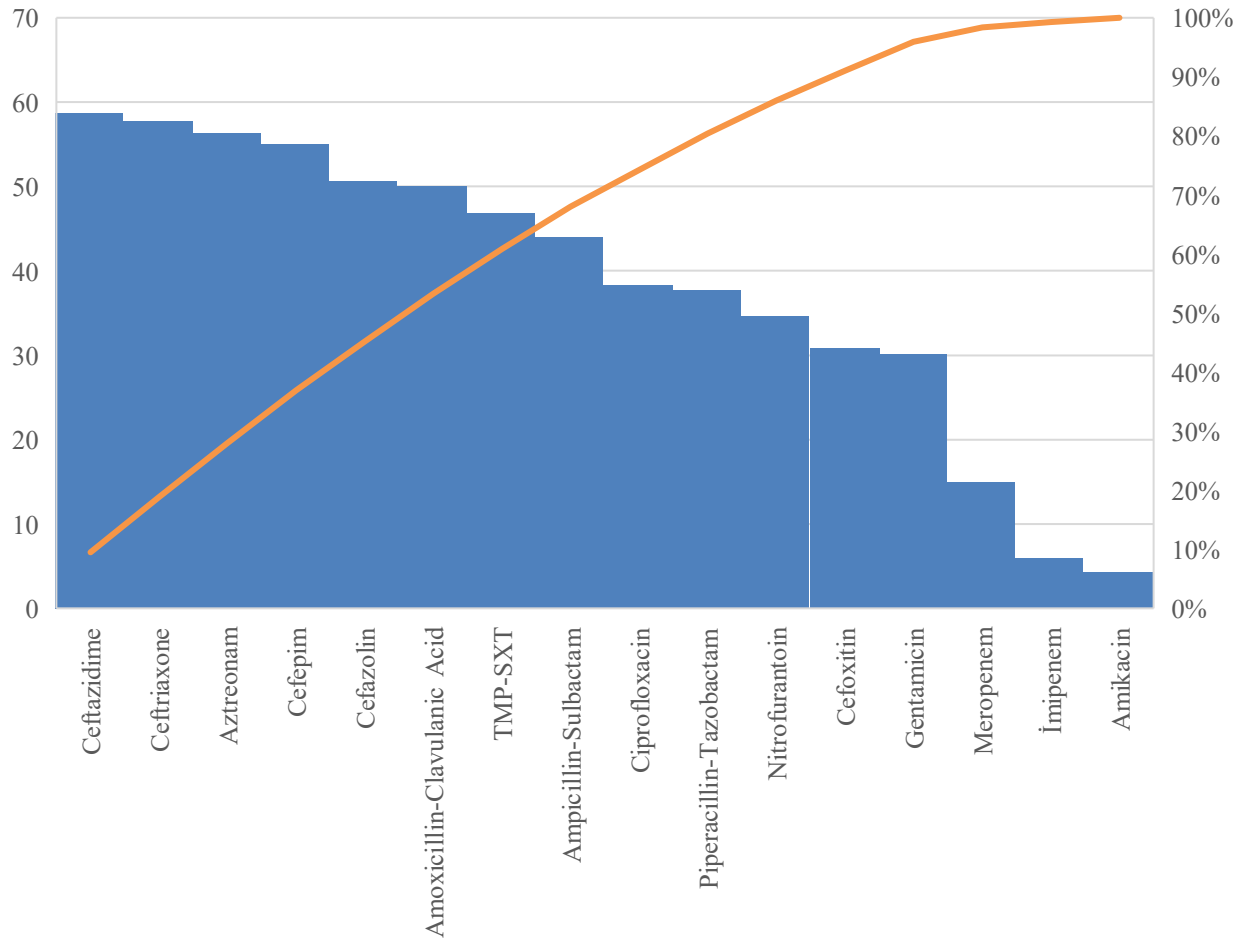

Figure 4. Antibiotic resistance percentages of *K. pneumoniae* strains.

As rightly pointed out, classifying urinary tract infections according to clinical criteria and analyzing only isolates obtained from confirmed UTI cases would allow for more targeted and reliable empirical treatment recommendations. Therefore, the empirical treatment suggestions provided in this study are based on overall susceptibility data and should be interpreted in conjunction with individual clinical assessments.

Future prospective studies that include precise clinical categorization of infections will enable the development of more specific and clinically applicable empirical treatment strategies.

The most common comorbidity in the study group was renal failure. These patients are frequently hospitalised, undergo invasive procedures such as haemodialysis and have weakened immunity. This increases the possibility of infection with pathogens with multiple antibiotic resistance. In addition, decreased urinary excretion, stasis and other concomitant chronic diseases explain the strong association of *Klebsiella pneumoniae* and *E. coli* infections with renal failure.

Antibiotic resistance analysis in outpatients, clinics, and intensive care patients constitutes a key focus of our study. We identified certain differences among pathogens in terms of resistance to commonly used antibiotics. *E. coli* isolates demonstrated higher resistance to most antibiotics in outpatient samples. For example, ampicillin resistance was determined to be 32.1%, 13.2% and 3%, respectively, while trimethoprim-sulfamethoxazole resistance was determined to be 35.3%, 7.6% and 4.61%, respectively. A study published in 2023 similarly found high resistance to the penicillin group and trimethoprim-sulfamethoxazole.[32]

In aminoglycoside and nitrofurantoin group antibiotics, resistance rates remained low in both patient groups (<10%). ESBL positivity was 6%, 3.6% and 0.90% in outpatient, ward and intensive care patient samples, respectively, showing no statistically significant difference (p=0.252). However, the resistance rates observed in our study for beta-lactams, including penicillins and cephalosporins, are concerning because ESBL-producing strains are resistant to other commonly used antibiotics in UTIs, rendering beta-lactam antibiotics unsuitable for the empirical treatment of UTIs. Studies have shown that ESBL-producing strains are no longer confined to hospital settings and are becoming increasingly common in outpatients with UTIs.[32-35]

These findings suggest that resistance rates to common antibiotics are higher in *E. coli* isolates from outpatients, and that inappropriate antibiotic use may play a role as a possible cause. In *K. pneumoniae* isolates, however, the antibiotic resistance profile followed a different course. Resistance rates for most antibiotics were higher in clinics samples than in outpatient samples. Resistance to broad-spectrum β-lactam antibiotics, particularly gentamicin (12.6% vs 6.2%), ceftazidime, cefepime, and piperacillin-tazobactam, was significantly higher in inpatient samples. However, cefazolin resistance was found to be higher in outpatient samples (32.4%); this may be due to local antibiotic usage patterns or specific patient profiles. Various studies published in 2024 and 2025 reported higher antibiotic resistance rates in strains isolated from ward and intensive care patients, similar to our study.[36,37] Similarly, a study conducted by Kalyoncu et al.[38] also reported significantly higher antibiotic resistance rates in inpatients.

The prevalence of ESBL was approximately 9.7% in both groups, showing no significant difference (p=0.348). These findings are consistent with factors contributing to the development of resistance in hospitalised patients, such as the intensity of antibiotic use, prolonged hospital stay, and frequency of invasive procedures.[39]

Conclusion

When our study and literature data are evaluated, it may be rational to start treatment with piperacillin-tazobactam, aminoglycoside, nitrofurantoin and fosfomycin according to the severity of the patient in UTIs and to determine the course of treatment according to the urine culture results. However, caution should be exercised in terms of carbapenem resistance in hospitalized patients in whom *K. pneumoniae* is isolated. Antibiotic resistance rates may differ in hospitalized and outpatient patients in whom *E. coli* and *K. pneumoniae* are isolated; this situation should be considered especially in empirical antimicrobial treatment management. In addition, regional differences are also seen in antibiotic susceptibility and resistance status of infectious agents. This situation reveals the importance of hospitals knowing the antimicrobial resistance status of their own regions. It is thought that the study data will guide clinicians in selecting the appropriate drug to ensure success in treatment and in preventing the use of incorrect or unnecessary antibiotics.

Limitations of the Study

Our study retrospectively analyzes the antibiotic resistance profiles of *Escherichia coli* and Klebsiella species that cause UTIs using data obtained between 2016 and 2019. The fact that our study covers a certain time period can be considered a limitation. However, our analyses supported by current literature provide important findings in terms of understanding resistance trends and providing a basic reference for future studies.

Due to the retrospective design of the study and incomplete clinical data, clinical classification of infections as complicated/uncomplicated in ESBL positive *E. coli* and *K. pneumoniae* isolates could not be made; this is the main limitation of the study.

Conflict of Interest

The authors have no conflicts of interest to disclose.

Compliance of Ethical Statement

The approval of this study in accordance with the ethical rules of the Declaration of Helsinki was approved by Tokat Gaziosmanpaşa University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee at the meeting on 2.3.2023 with decision number 23-KAEK-029.

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Author Contributions

M.S., U.S.Ş.C.: Study idea/Hypothesis; M.S., U.S.Ş.C.: Design; M.S., Y.D., U.S.Ş.C.: Data collection; M.S., Y.D., U.S.Ş.C.: M.S., Y.D., U.S.Ş.C.: Biological material collection; Literature review; M.S., Y.D.: Analysis; M.S., U.S.Ş.C.: Writing; M.S., U.S.Ş.C.: Critical review.

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