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Which antibiotics should we prefer empirical treatment of urinary tract infections in elderly patients?

Yaşlı hastalarda üriner sistem infeksiyonlarının ampirik tedavisinde hangi antibiyotikleri tercih etmeliyiz?

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Abstract

Aim: Urinary tract infection (UTI) is a major cause of mortality and morbidity in elderly patients. In this cross-sectional study, we aimed to determine the frequency and antibiotic resistance profile of the bacteria causing UTI and contribute to the empirical treatment options in elderly patients.

Methods: This study included urine culture results from 347 elderly outpatients who were referred to Karabuk Training and Research Hospital between January 2018 and June 2019. The identification and antibiotic susceptibilities of microorganisms were determined using the BD-Phoenix 100 fully automated system, and the extended-spectrum beta-lactamase (ESBL) positivity was analyzed using the combined disk diffusion method. The results were retrospectively analyzed.

Results: The most common pathogens were *Escherichia coli* (58%), *Enterococcus* spp. (18%) and *Klebsiella pneumoniae* (11%). The rate of resistance to ampicillin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole (TMP-SMX), cefixime, and ciprofloxacin, which are oral antibiotics used in the treatment of UTI, was between 30% and 70%. The rate of resistance to nitrofurantoin was 3%. The gentamicin and piperacillin-tazobactam resistance were 12% and 9%, respectively. The ESBL positivity for *E. coli* and *K. pneumoniae* were 29% and 49%, respectively (P=0.03).

Conclusion: The rates of resistance to oral antibiotics such as ampicillin, amoxicillin-clavulanic acid, TMP-SMX, cefixime, and ciprofloxacin, which are used treatment of UTI, were more than 20%. Therefore, these antibiotics should not be used in the empirical treatment of UTI. Instead, nitrofurantoin may be preferred in the empirical treatment of uncomplicated UTI, or gentamicin and piperacillin-tazobactam, which are parenteral antibiotics that may be used depending on the patient's clinical condition.

Keywords: Antibiotics, *Enterococcus* species, *Escherichia coli*, Nitrofurantoin, Ciprofloxacin, Urinary tract infection

Öz

Amaç: Üriner sistem infeksiyonları (ÜSİ) yaşlı hastalarda önemli bir mortalite ve morbidite nedenidir. Bu kesitsel çalışmada yaşlı hastalarda toplum kaynaklı ÜSİ etkenlerinin sıklığını ve antibiyotik direnç profilini belirleyerek ampirik tedavi seçimine katkıda bulunmayı amaçladık.

Yöntemler: Ocak 2018 - Haziran 2019 tarihleri arasında Karabük Eğitim ve Araştırma Hastanesi'ne ayaktan başvuran 347 yaşlı hastanın idrar kültür sonuçları çalışmaya dahil edilmiştir. Mikroorganizmaların identifikasyonu ve antibiyotik duyarlılıkları BD-Phoenix (Becton-Dickinson, MD,USA) tam otomatize sistem ile, genişlemiş spektrumlu beta-laktamaz varlığı (GSBL) ise kombine disk difüzyon yöntemi ile araştırılmıştır. Sonuçlar retrospektif olarak incelenmiştir.

Bulgular: En sık izole edilen patojenler *Escherichia coli* (%58), *Enterococcus* spp (%18) ve *Klebsiella pneumoniae* (%11) idi. Üriner infeksiyon tedavisinde kullanılan oral antibiyotiklerden ampisilin, amoksisilin-klavulanik asit, trimethoprim-sulfametoksazol (TMP-SMX), sefiksim ve siprofloksasine direnç %30-70 arasında idi. Nitrofurantoin direnci ise %3 idi. Gentamisine %12 ve piperasilin-tazobaktama ise %9 oranında direnç saptandı. GSBL pozitifliği ise *E.coli*'de % 29 iken, *K. pneumoniae* suşlarında %49 idi (P=0.03).

Sonuç: Üriner sistem infeksiyonlarının tedavisinde kullanılan oral antibiyotiklerden ampisilin, amoksisilin-klavulanik asit, TMP-SMX, sefiksim ve siprofloksasine %20'nin üzerinde direnç saptanmıştır. Bu nedenle ÜSİ' nın ampirik tedavisinde bu antibiyotikler kullanılmamalıdır. Onun yerine komplike olmayan ÜSİ' da nitrofurantoin, parenteral antibiyotiklerden ise gentamisin ve piperasilin-tazobaktam hastanın klinik durumuna göre tercih edilebilir.

Anahtar kelimeler: Antibiyotik, *Enteroccus türleri, Escherichia coli,* Nitrofurantoin, Siprofloksasin, Üriner sistem infeksiyonları

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Introduction

The elderly population has increased due to the rise in life expectancy worldwide. People over 65 years of age are considered to be elderly. Elderly people constitute one-sixth of the world's population. However, this rate increases to one-third in outpatient visits [1]. The elderly population in Turkey has been on the rise over the years. The rate of the elderly population was 4.3% in 1990, whereas this rate increased to 8.8% in 2018 [2].

Elderly people are more susceptible to infections due to comorbid conditions as well as anatomical and physiological changes associated with aging. In the literature, approximately one-third of the infections observed in elderly patients have been reported as urinary tract infections (UTIs) [1,3,4]. It has been estimated that UTIs cause 100,000 hospitalizations, 1 million emergency room visits, and 7 million outpatient admissions in the USA [3,5]. On the other hand, increasing drug resistance has been a major public health threat worldwide. Infections associated with multi-drug resistant bacteria occur more frequently in elderly patients who reside in nursing homes. UTIs have been reported to account for 15.5% of hospitalizations and 2% of mortalities in elderly patients [3]. Advanced age is a major risk factor for UTIs. Comorbid conditions such as increased urinary incontinence, urinary retention, increased urinary catheterization, and diabetes mellitus (DM) associated with aging lead up to the development of UTI [4,6]. In addition, decreased cognitive functions, along with decreased personal hygiene, dementia, immunodeficiency, and malnutrition can also facilitate the development of the infection [3,4,6]. The fact that elderly patients are more sensitive to the side effects of drugs and chronic comorbidities (chronic liver and renal failure, DM) can limit treatment options [4,5]. In the treatment of UTI in elderly patients (where urine culture test is not available), the empirical treatment is recommended to be chosen based on local antibiotic resistance data [3,7].

In this study, we aimed to determine the prevalence and antibiotic resistance pattern of bacterial causes of community-acquired UTI and contribute to the choice of empirical treatment in elderly patients who were admitted to our hospital's outpatient clinic.

Materials and methods

This cross-sectional study included urine culture results obtained from patients aged over 65 years who were referred to Karabuk Training and Research Hospital between January 2018 and June 2019. The results of the inpatients, patients younger than 65 years, and repetitive patients were excluded. The distribution of uropathogens causing UTIs and their antibiotic susceptibilities were retrospectively examined. The ethics approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Karabuk University. (Date: 7 October 2019, no: 6/18).

The urine samples sent to the microbiology laboratory were cultured on Columbia agar with 5% sheep blood (RTA laboratories, Kocaeli, Turkey), eosin-methylene blue agar (RTA laboratories, Kocaeli, Turkey) and using a sterile plastic ring loop with a urine sample capacity of 0.01 mL, and then incubated for 18–24 hours at 35°C under aerobic conditions. The culture samples were evaluated in accordance with the Society of Clinical Microbiology guidelines [8]. The identification and antibiotic susceptibility of bacteria were determined using the BD-Phoenix 100 (Becton-Dickinson, Sparks, MD, USA) fully automated microbiology system. Antibiotic susceptibility results were evaluated based on the European Committee on Antimicrobial Susceptibility Testing guidelines [9]. The presence of the extended-spectrum beta-lactamase (ESBL) enzyme was analyzed using the combined disk diffusion method [9]. *Escherichia coli* ATCC 25922 and *S. aureus* ATCC 29213 strains were used as quality control strains.

Statistical analysis

The data were statistically analyzed using SPSS software version 22.0 (IBM Corporation, Chicago, IL, USA). The descriptive statistics were expressed as number, percentage and median value. Pearson's chi-squared test was used for comparison of descriptive data between groups. The *P*-value ≤0.05 was considered statistically significant within a 95% confidence interval.

Results

Among 347 patients, 157 (45%) were male, and 190 (55%) were female. The median age of the patients was 74 (65–94) years. *Escherichia coli* was isolated in 58% (n= 202) of the urine cultures, and the distribution of the isolated bacteria is shown in Table 1. The most common pathogen was *E. coli* (58%), followed by *Enterococcus* spp. (18 %) and *K. pneumoniae* (11 %). The antibiotic resistance profiles of *E. coli* and *K. pneumoniae* (the most frequently isolated gram-negative pathogens) strains are shown in Table 2.

Table 1: Distribution of microorganisms isolated from urine cultures of elderly patients

Microorganisms	n (%)
Gram-negative bacteria	
Escherichia coli	202(58)
Klebsiella pneumoniae	37(11)
Enterobacter spp.	9(3)
Proteus mirabilis	7(2)
Pseudomonas aeruginosa	7(2)
Gram-positive bacteria	
Enterococcus spp.	62(18)
Streptococcus agalactiae	13(4)
Staphylococcus spp.	5(1)
Other	
Candida spp.	5(1)
TOTAL	347(100)

Table 2: Antibiotic susceptibilities of E. coli and K. pneumoniae isolates

Antibiotics	*E. coli* (n=202)	*K. pneumoniae* (n=37)	*P*-value
	n (%)	n (%)	
Ampicillin	125(62)	*	NA
Amoxicillin-clavulanic acid	104 (52)	26(70)	0.05
Trimethoprim-sulfamethoxazole	70 (35)	11(30)	0.69
Ciprofloxacin	85(42)	18(49)	0.57
Cefixime	75(37)	20(54)	0.08
Nitrofurantoin	6(3)	**	NA
Ceftriaxone	59(29)	18(49)	0.03
Ceftazidime	56(28)	18(49)	0.02
Gentamicin	25(12)	6(16)	0.72
Piperacillin-tazobactam	18(9)	7(19)	0.12
ESBL	59(29)	18(49)	0.03

* Intrinsic resistant, ** no EUCAST recommendation, NA: not applicable, ESBL: Extended spectrum beta-lactamase

K. pneumoniae strains were found to be more resistant compared with the *E. coli* strains in all the antibiotic groups. The rates of resistance to amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole (TMP-SMX), cefixime, and ciprofloxacin, which are oral antibiotics, ranged between 30% and 70% in both groups. The rates of resistance to the third-generation cephalosporins ranged between 28% and 49%, whereas the rate of resistance to nitrofurantoin was 3% in *E. coli* strains. The rates

of resistance to gentamicin in *E. coli* and *K. pneumoniae* strains were 12% and 16%, respectively (P=0.72).

The production of ESBL in *K. pneumoniae* strains was significantly higher than *E. coli* strains (P=0.03). The antibiotic resistance was relatively high in ESBL-positive *E. coli* strains. The rates of resistance to ciprofloxacin, TMP-SMX, gentamicin, and piperacillin-tazobactam were 92%, 59%, 30%, and 25%, respectively. The lowest rate of resistance was seen to nitrofurantoin with 7%.

Among 62 *Enterococcus* spp. strains, 48 (77%) were isolated from the male patients; 95% of the strains (n=59) were *E. faecalis*, and 5% were *E. faecium*. The rate of resistance to ciprofloxacin in the *E. faecalis* strains was 55%. The rates of resistance to ampicillin, amoxicillin-clavulanic acid, and nitrofurantoin were found to be at low levels of 8%, 5%, and 10%, respectively. The high level of gentamicin resistance (HLGR) rate was 48%. All the strains were found to be susceptible to vancomycin, linezolid, and teicoplanin.

Discussion

Due to the increased elderly population worldwide, the diagnosis and treatment of diseases in this age group have become more significant. UTI is a significant cause of mortality and morbidity in elderly patients. UTI is one of the most significant causes of sepsis in elderly patients, and the rate of mortality associated with urosepsis has been reported as 33% [1]. The elderly population's visits to the outpatient clinic due to UTI have been reported to be three times more than in the young population [3]. This has been commonly associated with age-related bladder dysfunction, urethral catheterization, and bladder obstruction due to benign prostatic hyperplasia, particularly in men [1,4]. In addition, antibiotic resistance is higher in elderly patients compared with young patients due to repetitive antibiotic treatments and urinary interventions [4].

In the literature, *E. coli* has been reported as the most common pathogen for UTI in both the elderly and other groups such as children, adults, and pregnant women [3,4,6,11]. In this study, the most frequently isolated pathogen was *E. coli* (58 %). Similarly, Ulug et al. [6] reported the rate of *E. coli* isolated as a causative agent of UTI was 64% in 401 elderly patients. This rate was 32% in elderly patients admitted to the emergency room and diagnosed with UTI in the study by Ginde et al. [12], 69% in elderly patients who resided in nursing homes in the study by Sundwall et al. [11], and 54% in the study by Das et al. [13].

There is no agreement in the literature regarding the choice or duration of antibiotics in the treatment of UTI in elderly patients. Therefore, empirical treatment protocols should be established based on local antibiotic resistance profiles. As the Infectious Diseases Society of America has identified *E. coli* as the most common causative agent of UTI, it recommends that the local antibiotic resistance pattern of *E. coli* be monitored by active surveillance and that antibiotics with a rate of resistance below 20% are to be preferred for empirical treatment [3,7]. Due to the limited number of studies on the antibiotic resistance profile of uropathogens in elderly patients in Turkey, the results of the studies consisting of adult age groups have also been included in the discussion.

In our study, the rate of resistance to ampicillin in *E. coli* strains was 62%. This rate is between 52% and 77% in the other studies conducted in Turkey [14-16], whereas it has been reported to be 32% in the study by Fagan et al. (Norway) [17] and 46% in the study by Sanchez et al. (USA) [8]. Due to its high rates of resistance, ampicillin is no longer an empirical treatment option in UTI in Turkey and worldwide.

In this study, the rate of resistance to amoxicillin-clavulanic acid in *E. coli* strains was 52%. This rate has been reported to be 33% in elderly patients in the study by Ulug et al. [6] and between 6.5% and 32% in the studies consisting of various groups in Turkey [14,15,19,20]. Sanchez et al. [18] have found a rate of resistance of 7% against amoxicillin-clavulanic acid in *E. coli* strains in elderly patients.

In the present study, the rates of resistance to cefixime in *E. coli* and *K. pneumoniae* strains were 37% and 54%, respectively. The data on the resistance to cefixime, which is a third-generation oral cephalosporin, is limited. A rate of resistance of 8%–26% [10,21-23] and 10% [20] has been reported in pediatric patients and pregnant women in Turkey, respectively. Kacmaz et al. [24] have found a rate of resistance of 6% against cefixime in community-acquired *E. coli* strains. In our study, high resistance to cefixime may be due to the fact that our study group consisted of elderly patients. Generally, it is considered that antibiotic resistance is higher in the elderly population compared with that in young people. This may be associated with repetitive antibiotic treatments and urinary interventions [4].

In this study, the rate of resistance to TMP-SMX in *E. coli* and *K. pneumoniae* strains was 35% and 49%, respectively. This rate has been reported to vary between 19-58% in the other studies conducted in Turkey [6,14,16,19]. Similarly, high rates of resistance have been reported in the studies from Brazil (35%) [5] and the USA (60%) [13]. On the contrary, the study by Fagan et al. [17] (Norway) has found rates of resistance of 24% and 19%, respectively.

Although TMP-SMX has previously been used in prophylaxis and maintenance treatment in patients with UTI, it is no longer a treatment option for UTI.

In the present study, the rate of resistance to ciprofloxacin in *E. coli* and *K. pneumoniae* strains were 42% and 49%, respectively. Rates of resistance between 10%-41% have been reported in the other studies conducted in Turkey [6,15,16,19]. We believe that the overuse of fluoroquinolones in the treatment of infections other than UTI in our hospital resulted in high fluoroquinolone resistance. In a multi-center study conducted on elderly patients, the rates of resistance to ciprofloxacin in *E. coli* strains have been reported to be 30% in Canada and 44% in the USA [25]. Sanchez et al. [18] have found rates of resistance of 11% in adults and 30% in elderly patients. Fagan et al. [17] have reported relatively low rates of resistance in *E. coli* and *K. pneumoniae* strains, which were 8% and 3%, respectively.

A study conducted in Spain has found that the prevalence of fluoroquinolone-resistant *E. coli* increased with age over 60 years [4]. A history of hospitalization and quinolone use have also been reported as independent risk factors [13,26]. Marquez et al. [5] have reported that the rate of resistance to

fluoroquinolone is 21% in *E. coli* strains isolated from elderly women residing in nursing homes, and the history of UTI, vaginitis, and DM are risk factors for UTI.

In our study, the prevalence of ESBL in *K. pneumoniae* was significantly higher than *E. coli* and were 49% and 29%, respectively (P=0.03). These rates were 27% and 2% in the study by Caliskan et al. [15] and 29% and 24% in the study by Gulcan et al. [27]. In community-acquired *E. coli* isolates, Tasbakan et al. [19] have found ESBL prevalence to be 13%, whereas Uyanik et al. [28] have found it to be 26%. Lob et al. [25] have reported the prevalence of ESBL in elderly patients diagnosed with UTI to be 13% in Canada and 23% in the USA. The prevalence of ESBL is also increasing in community-acquired infections. Rodriguez et al. [29] have reported that advanced age, being male, the presence of DM, and the use of fluoroquinolones in the past two months are risk factors in community-acquired ESBL-producing *E. coli* infections. In addition, in May 2016, the United States Food and Drug Administration reported severe adverse reactions such as fluoroquinolone-induced QT prolongation, delirium, and seizures [1]. Therefore, the use of fluoroquinolone in patients at risk should be limited. In this study, the presence of ESBL was higher than in other studies [14-16]. This may be due to our patient group consisting of elderly patients and fluoroquinolone being excessively prescribed.

The use of nitrofurantoin is prominent in the treatment of UTI associated with ESBL-positive isolates. However, nitrofurantoin is only recommended in uncomplicated UTI [3,4]. In the current study, the rate of resistance to nitrofurantoin in *E. coli* strains was 3%. However, this rate was higher in ESBL-positive *E. coli* strains (8%). The other studies in Turkey have reported rates of resistance to nitrofurantoin between 14%-40% in ESBL-positive *E. coli* strains [15,27,30]. The rates of resistance to nitrofurantoin have been reported to be 2% in the study by Fagan et al. (Norway) [17] and 7% in the study by Das et al. (USA) [13].

In the present study, the second most common pathogen was *E. faecalis*. The majority of strains were isolated from male patients. Gulcan et al. [27] found that *Enterococcus* spp. was significantly high in male patients aged over 65 years in the study group. In this study, the rate of resistance to ampicillin was low (8%), and the HLGR rate was relatively high (48%). Similarly, Gulcan et al. [27] reported resistance to ampicillin to be 7% and the HLGR rate to be 37%. Also, Kutlu et al. [31] reported the rate of resistance to ampicillin and HLGR rate to be 5.6% and 44.7%, respectively. In our study, the rate of resistance to nitrofurantoin was 10%, whereas no resistance to vancomycin, linezolid, and teicoplanin was found. Kutlu et al. [31] reported resistance to nitrofurantoin 4.8% and vancomycin to be 1.5%. On the basis of our results, nitrofurantoin may be preferred in the treatment of UTI caused by enterococci.

Limitations

There are some limitations to this study; since it is a retrospective study based on laboratory data, the data on the clinical characteristics and treatments of patients were not available. In addition, as the reference method, the agar dilution test could not be performed, the susceptibility of fosfomycin to *Enterobacterales* spp. was excluded.

Conclusion

In the present study, the rates of resistance to ampicillin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, cefixime, and ciprofloxacin, which are oral antibiotics used in the treatment of UTI in elderly patients, were found to be >20%. Therefore, these antibiotics should not be used in the empirical treatment of UTI. Instead, nitrofurantoin may be preferred in the empirical treatment of uncomplicated UTI. Gentamicin and piperacillin-tazobactam, which are parenteral antibiotics, may also be used depending on the clinical condition of the patient. Since the antibiotic resistance profile of each region is different, the empirical treatment protocols should be established on the basis of the antibiotic resistance data, and the resistance profiles should be monitored through active surveillance.

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