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Resistance patterns of gram negative bacteria in urinary tract infections and efficacy of empirical treatment in noncomplicated cases: Retrospective cohort study of 2180 women

Üriner sistem enfeksiyonlarında gram negatif bakterilerin direnç paternleri ve komplike olmayan hastalarda ampirik tedavinin uygunluğu: 2180 kadın hastada retrospektif kohort çalışma

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Abstract

Aim: Community and hospital acquired urinary tract infections (UTI) are the most common bacterial infections in all age groups. In this study, the women diagnosed UTI, which complicated and uncomplicated, were referred to outpatient clinics between 2011 and 2015 were selected. The suitability of empirical antimicrobial therapy prescribed with resistance patterns of Gram negative bacteria isolated from these patients was investigated.

Methods: UTI complaining and urine culture $\geq 10^5$ cfu / ml of bacteria that women aged 18-65 were comprised the study group. HIS (Hospital Information System Software) was scanned for these patients and uncomplicated and complicated UTI distinction was made according to the criteria set by Infectious Diseases Society of America (IDSA, 2016). Of the 2180 patients studied, 836 were complicated and 896 were noncomplicated. Identification of Gram negative isolates in urine culture; Conventional methods and Matrix-Assisted Laser Desorption and Ionization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS), (Biotyper, Bruker, Germany) systems were used. The antimicrobial susceptibilities of the isolated strains from 2011 to 2014 were determined according to the Clinical Laboratory Standards Institute (CLSI) and the isolated strains in 2015 were determined according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Results: The distribution of 2180 female patients (18 to 65 years old) was urology polyclinic (68%), family medicine, infectious disease and physical medicine and rehabilitation polyclinics (19.1%), and emergency medicine polyclinic (12.6%). E. coli (84%), K. pneumonia / oxytoca (7%) and Enterobacter spp (2.6%) were the most frequently detected agents in the uncomplicated UTIs, while complicated UTI E. coli (91%), K. pneumonia / oxytoca (5.7%) and P. aeruginosa (1%) were found to be the first, second and third in the patients. Quinolones were prescribed 18.2%, phosphomycin 16.7%, nitrofurantoin 15.6%, nitrofurantoin and phosphomycin combined 16.3%, second generation oral cephalosporins 9.6% and third generation oral cephalosporins 10.7%. Resistance to quinolones, the most commonly prescribed antibiotic, was found in 19% of E. coli, 21% of Klebsiella spp., 13% of Enterobacter spp. and 9% of Proteus spp.

Conclusion: When these prescriptions were compared with the results of antimicrobial susceptibility, it was observed that 38 (14%) were incompatible with the sensitivity results. It was found that 42% of cefuroxime prescriptions, 28% of quinolone prescriptions and 17% of ceftriaxone prescriptions were incompatible with the antibiogram results.

Keywords: Urinary tract infections, Antimicrobial resistance, Empirical therapy, Escherichia coli, Klebsiella spp

Öz

Amaç: Toplum ve hastane kaynaklı üriner sistem enfeksiyonları (ÜSE), tüm yaş gruplarında en sık karşılaşılan bakteriyel enfeksiyonlardır. Bu çalışmada 2011-2015 yılları arasında polikliniklere ÜSE şikayetiyle başvuran hastalardan izole edilen Gram negatif bakterilerin direnç paternleri ile bu hastalara reçetelenen ampirik antimikrobiyal tedavinin uygunluğunun araştırıldı.

Yöntemler: ÜSE şikayetiyle başvuran ve idrar kültüründe $\geq 10^5$ kob/ml bakteri üremesi olan 18-65 yaş arası kadın hastalar çalışma grubunu oluşturdu. HBYS (Hastane Bilgi Yazılım Sistemi)'nden bu hastaların dosyası taranarak Infectious Diseases Society of America (IDSA, 2016) tarafından belirlenen kriterler doğrultusunda komplike olmayan ve komplike ÜSE ayrımları yapıldı. Buna göre 2180 hastanın 836'sı komplike ÜSE tanısı alırken, 896'sının nonkomplike ÜSE tanısı aldığı tespit edildi. İdrar kültüründe izole edilen Gram negatif izolatların identifikasyonu; konvansiyonel yöntemler ve Matrix-Assisted Laser Desorption and İonization Time-Of-Flight Mass Spectrometry (MALDI-TOF MS), (Biotyper, Bruker, Almanya) sistemleri ile yapıldı. İzole edilen suşların antimikrobiyal duyarlılıkları 2011-2014 yılları için Clinical Laboratory Standards Institute (CLSI), 2015 yılı için ise The European Committee on Antimicrobial Susceptibility Testing (EUCAST) önerilerine göre belirlendi.

Bulgular: ÜSE şikayetiyle çalışmaya alınan 18-65 yaş arası 2180 kadın hastanın poliklinik dağılımı; %68 Üroloji, %19,1 Aile Hekimliği pol., Enfeksiyon pol ve Fizik Tedavi ve Rehabilitasyon pol. ve %12,6 Acil pol. idi. Komplike olmayan ÜSE'lerde 1., 2. ve 3. sırada en çok tespit edilen etken sırasıyla E. coli (%84), K. pneumoni/oxytoca (%7) ve Enterobacter spp (%2,6) iken, komplike ÜSE'li hastalarda 1., 2. ve 3. sırada E. coli (%91), K. pneumoni/oxytoca (%5,7) ve P. aeruginosa (%1) tespit edildi. Hastalara reçete edilen antimikrobiyallere bakıldığında; kinolonların %18,2 oranında, fosfomisin %16,7, nitrofurantoin %15,6, nitrofurantoin ve fosfomisin kombine olarak %16,3 oranında, 2. kuşak oral sefalosporinlerin %9,6 ve 3. kuşak oral sefalosporinlerin ise %10,7 oranında reçetelendiği saptandı. Ayaktan tedavi edilen hastalara en sık reçete edilen antibiyotik olan kinolonlara direnç, E.coli'de %19, Klebsiella spp.'de %21, Enterobacter spp.'de %13, Proteus spp.'de %9 olarak bulundu.

Sonuç: Bu reçetelerin antimikrobiyal duyarlılık sonuçları ile uyumuna bakıldığında ise, 38 (%14)'inin duyarlılık sonuçları ile uyumsuz olduğu gözlendi. Sefuroksim reçetelerinin %42, kinolon reçetelerinin %28, seftriakson reçetelerinin ise %17 oranında antibiyogram sonucu ile uyumsuz olduğu saptandı.

Anahtar kelimeler: Üriner sistem enfeksiyonu, Antimikrobiyal direnç, Ampirik tedavi, Escherichia coli, Klebsiella spp

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Introduction

Urinary tract infections are the most common bacterial infections in our country as well as all over the world [1]. It has been reported that every year, eight million people visit emergency services or outpatient clinics with the symptoms of urinary tract infection (UTI) in the United States, and that 100,000 of them have been hospitalized [2]. In our country also about 5 million cystitis cases have been reported every year [3]. Uncomplicated UTIs are the most important reason for the use of antibiotics under outpatient conditions. The use of unnecessary and inappropriate antibiotics is gradually increasing the prevalence of antibiotic-resistant uropathogens. Therefore, it is very important to choose an appropriate antibiotic in the empirical treatment of UTIs. Determining an effective treatment with systematic follow-up of the antibiotic resistance status according to regions is important in terms of preventing the development of bacterial resistance and time loss [4,5]. During the selection of empirical treatment, patient's antibiotic use and/or hospitalization history within the last 6 months should also be taken into consideration by questioning.

The aim of this study was to investigate the resistance patterns of Gram negative bacteria isolated from patients by analyzing the patients, who were admitted to policlinics with the complaints of UTI and received the pre-diagnosis of complicated and uncomplicated UTI, and to investigate the suitability of the empirical antimicrobial therapy prescribed for patients with uncomplicated UTI.

Materials and methods

Acute uncomplicated UTI is often categorized in women by Infectious Diseases Society of America (IDSA, 2016) and European Society for Microbiology and Infectious Diseases (ESCMID) as they are frequently seen in women. Therefore this study group included women between the ages of 18-65 who were admitted to polyclinics of our hospital between 2011 and 2015 and diagnosed with UTI. The files of these patients were scanned retrospectively from HBYS (Hospital Information Software System). The distinction between complicated and uncomplicated UTI was carried out according to the criteria set by the Infectious Diseases Society of America (IDSA, 2016). According to that, symptoms as frequent urination without fever, dysuria, and sensation of urinary urgency were defined as uncomplicated UTI. Fever, history of hospital visit with the complaints of UTI, functional or structural urinary system anomalies, catheterization, kidney and ureter stones, malignancy, transplantation, chronic renal disease, benign prostatic hypertrophy, hydronephrosis, neurogenic bladder, presence of double J catheter, chronic heart failure, diabetes, immunosuppression status, use of antibiotics in the last three months, and hospitalization history due to any cause in the last year were considered as the criteria of complicated UTI. Demographic information, risk factors, the polyclinic admitted, the cause of infection identified as a result of urinary culture, antibiotic susceptibility results of causative microorganism, and empirically initiated antibiotics of patients were recorded.

In Microbiology Laboratory of our hospital, the urine samples are incubated with 10 µl volumes in sheep blood and EMB agar media for 18-24 hours at 37 °C; all isolates that grow by counts of ≥105 cfu/ml at the end of this time are considered to be significant bacteriuria. Urine cultures identified to have a Gram negative growth of ≥105 cfu/ml were included in the study. Identification of isolates was carried out using conventional techniques and MALDI-TOF MS (Biotyper, Bruker, Germany) system.

Antimicrobial susceptibilities of isolated Gram negative bacteria were studied using the disc diffusion technique according to the recommendations of the Clinical Laboratory Standards Institute (CLSI) for 2011-2014 and according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for 2015; identification of ESBL was studied using combined disc synergy technique.

Statistical analysis

SPSS 23 (SPSS Inc. Chicago, IL, USA) program was used to analyze the data. The chi-square test was used to investigate the relationship between the changes in antimicrobial resistance over years and patient groups.

Results

It was found that there were 2180 female patients between the ages of 18-65 years who received a pre-diagnosis of UTI after admitting to polyclinics of our hospital between 2011 and 2015. Sixty-eight percent of the patients were admitted to Urology and 12.6% to Emergency Polyclinic, whereas 19% of them were admitted to different policlinics such as Family Medicine, Infectious Diseases and Clinical Microbiology and Physical Therapy and Rehabilitation. It was found that 836 of 2180 patients, who were included in the study according to the determined criteria, received the diagnosis of complicated UTI and 896 of them received the diagnosis of uncomplicated UTI.

The most common complicating factor was found to be a history of kidney/ureter stones (n:261, 31%), hydronephrosis and malignancy (n:188, 22%) in the case of complicated UTI . These were followed by a history of diabetes and hypertension (n: 96, 11%), neuromuscular dysfunction of bladder (n: 71, 9%) and a history of pregnancy (n: 51, 6%), respectively. There was a history of antibiotic use and hospitalization in 21% of patients (n:169).

The determinants of UTI in uncomplicated cases were E. coli (84%), K. pneumonia/oxytoca (7%), Enterobacter spp (2.6%), Proteus spp (2.4%), P. aeuginosa (2.2%), C. freundii (0.8%) and Salmonella spp (0.2%). In complicated UTI, the determinants were isolated to be E. coli (91%), K. pneumonia/oxytoca (5.7%), Enterobacter spp (0.5%), Proteus spp. (0.3%), P. aeuginosa (1%) and C. freundi (0.1%).

During this period, E. coli has been found to have ranked first as a determinant of complicated and uncomplicated UTI with n (%) values of 768 (91%) and 756 (84%), respectively. While K. pneumonia/oxytoca found to have ranked second in both groups with n values of 47 (5.7%) and 62 (7%), respectively, Enterobacter spp. ranked third in uncomplicated patients with n value of 24 (2.6%), and P. aeruginosa ranked third in complicated patients with n value of 8 (1%).

Considering the most common 5 microorganisms, ampicillin (AMP) (55%) was observed to have the highest resistance rate in both groups of patients in the case of E. coli,

whereas Trimetoprim-Sulfomethoxazole resistance (SXT) was 44%, ciprofloxacin (CIP) resistance was 27%, ceftriaxone (CRO) resistance was 20%, Extended Spectrum Betalactamase (ESBL) resistance was 9%, Nitrofurantoine (NT) resistance was 5% and Piperacillin Tazobactam (TPZ) resistance was 6%. Imipenem (IMP) 0%, phosfomycin (FF) 1% and amikacin (AK) 2% were found to have the lowest resistance rates (Table 1).

Table 1: Changes in the antimicrobial resistance of *E. coli* strains isolated from complicated and uncomplicated UTI's over the years

	2011 UC-C n(%)-n(%)	2012 UC-C n(%)-n(%)	2013 UC-C n(%)-n(%)	2014 UC-C n(%)-n(%)	2015 UC-C n(%)-n(%)
AMP	61(46)-84(61)	80(44)-187(65)	118(50)- 100(58)	28 (49)-25(51)	89 (58)-73(60)
SAM	15(11)-40(29)	24(13)-57(20)	46 (26)-53(30)	13 (23)-17(32)	32(21)-39(33)
AMC	8(6)-33(24)	19(11)-69(24)	39(7)-43(25)	11(19)-12(25)	31(20)-36(30)
GN	15(11)-26(18)	10(6)-47(16)	17(8)-31(28)	5(9)-9(18)	21(13)-22(18)
LEV	26(19)-38(28)	29(16)-99(34)	36(16)-58(34)	10(18)-18(36)	29(18)-42(35)
CIP	28(21)-42(30)	33(18)-107(37)	40(17)-61(36)	11(19)-19(38)	30(20)-40(34)
NOR	30(23)-41(31)	33(18)-110(38)	41(18)-63(37)	12(21)- 19(38)	28(18)-3(36)
AK	3(2)-5(4)	3(2)-10(4)	3(1)-6(4)	0-1(2)	0-4(3)
FF	0-4(3)	1(0.5)-0	1(0.4)-3(2)	0-1(2)	0-6(6)
NT	20(2)-10(7)	8(3)-8(3)	5(2)-11(6)	0-4(8)	4(2)-10(8)
CRO	24(18)-29(21)	27(16)-60(20)	44(19)-32(19)	12(21)-12(24)	27(18)-35(29)
SXT	50(38)-65(47)	67(37)-171(58)	93(40)-84(49)	20(35)-22(45)	46(30)-48(40)
TPZ	2(2)-13(10)	3(2)-21(7)	16(7)-13(8)	3(5)-3(6)	10(7)
IMP	0	0	0	0	0-0
ESBL	8(6)-8(7)	10(6)-19(7)	23(10)-17(10)	6(11)-6(12)	17(11)-18(15)

UC: Uncomplicated, C: Complicated, AMP: Ampicillin, SAM: Ampicillin-Sulbactam, AMC: Amoxicillin clavulanic acid, GN: Gentamicin, LEV: Levofloxacin, CIP: Ciprofloxacin, NOR: Norfloxacin, AK: Amikacin, FF: Phosphomycin, NT: nitrofurantoine, CRO: Ceftriaxone, SXT: Trimetoprim-Sulfomethoxazole TPZ: Piperacillin-Tazobactam, IMP: Imipenem ESBL: Extended Spectrum Betalactamase *The figures after the conviction are rounded

In the case of Klebsiella spp., AMP resistance was 92%, SXT resistance was 43%, CIP resistance was 19%, NT resistance was 21%, CRO resistance was 22%, TPZ resistance was 15% and AK resistance was 4% (Table 2). 21% of the strains were found to have ESBL.

Table 2: The antimicrobial resistance of K. pneumonia / oxytoca strains isolated from complicated and noncomplicated UTI's over the years

	2011 UC-C n(%)-n(%)	2012 UC-C n(%)-n(%)	2013 UC-C n(%)-n(%)	2014 UC-C n(%)-n(%)	2015 UC-C n(%)-n(%)
AMP	7 (87)-4(80)	9 (80)-12(100)	16 (80)-15(100)	5(100)-7(100)	13 (72)-12(100)
SAM	1 (13)-2(40)	3 (27)-3(33)	5 (25)-5(33)	1 (20)-2(28)	3 (17)-5(41)
AMC	1 (13)-2(40)	2 (18)-4(44)	5 (25)-4(26)	1 (20)-3(42)	6 (33)- 5(41)
GN	0 -0	1 (9) -1(11)	3 (15)-2(13)	0 -1(14)	2 (11)-2(16)
CIP	2 (25)-1(20)	2 (18)- 1(11)	4 (20)-2(13)	1 (20)	4 (22)- 2(16)
AK	0 -0	0-0	1 (5)-1(6.6)	0 -0	1 (5.5)-1(8)
NT	0 - 3(60)	1 (9)- 4(44)	2 (10)-5(33)	0 (0)- 1(14)	2 (11)-5(41)
CRO	1 (13)-1(20)	2 (18)-2(22)	4 (20)-3(20)	1 (20)-2(28)	4 (22)-4(33)
SXT	3 (37)-2(40)	5 (45)-5(55)	9 (45)-9(60)	2 (40)-4(57)	4 (22)-4(33)
TPZ	1 (13)-1(20)	2 (18)- 2(22)	1 (20)- 2(13)	1 (20)-2(28)	1 (5.5)-3(25)
ESBL	1 (12)- 1(20)	2 (18)- 2(22)	4 (20)-3(20)	1 (20)-2(28)	4 (22)- 3(25)

UC: Uncomplicated, C: Complicated, AMP: Ampicillin, SAM: Ampicillin-Sulbactam, AMC: Amoxicillin clavulanic acid, GN: Gentamicin, CIP: Ciprofloxacin, AK: Amikacin, NT: Nitrofurantoine, CRO: Ceftriaxone , SXT: Trimetoprim-Sulfomethoxazole TPZ: Piperacillin-Tazobactam, ESBL: Extended Spectrum Betalactamase, *The figures after the conviction are rounded

In the cases of Enterobacter spp. and P. aeruginosa, the resistance rates were found to be 14% and 25 % of CIP resistance, 21% and 25 % of Gentamycin (GN) resistance, 0% and 13% of AK resistance, 10% and 13% of TPZ resistance, respectively.

While an increase has been observed in STX and AK resistance of E.coli, which is a determinant of complicated and uncomplicated UTI, a partial increase has been observed in NT, CRO, TPZ resistance and ESBL rates (Table 1). A statistically significant correlation was found between the resistance increases of TPZ, AMC and NT antibiotics when the resistance correlation between the same antibiotics was investigated in E. coli strains isolated from uncomplicated UTIs according to years ($p<0.05$). When the correlation between antibiotic resistances of E. coli strains isolated from complicated UTI was investigated according to years, a statistically significant increase was identified in Sulbactam-ampicillin (SAM), FF and ESBL resistance, whereas a statistically significant decrease in SXT resistance ($p<0.05$).

While the prevalence of quinolone (LEV, CIP and NOR) resistance in patients with uncomplicated UTI decreased between 2011 and 2013, it displayed an increase between 2014 and 2015. While in patients with complicated UTIs, it increased between 2011 and 2014, a decrease was observed in 2015. The antimicrobial resistance rates of patients with complicated UTI were significantly higher than those with uncomplicated UTI ($p<0.05$).

Over the years, an increase was observed in NT, CRO, TPZ and GSBL resistance rates in the case of uncomplicated UTI with K. pneumonia/oxytoca determinant, and in AK, GN, CRO, TPZ, CIP and ESBL resistance rates in the case of complicated UTI. However, no statistically significant difference was found ($p>0.05$). The antibiotics to which Enterobacter spp was most resistant were found to be AMP (100%) and SAM (100%), whereas the antibiotics to which it is most susceptible were found to be AK, FF and NT in both groups. While no carbapenem resistance was observed in Pseudomonas spp, the highest resistance was observed in GN (25%), CIP (25%) and TIM (25%).

The prescriptions of 269 patients, for whom an empirical treatment was initiated, were reached. It was found that quinolones (18.2%), phosphomicine (16.7%), nitrofurantoin (15.6%), the combined use of nitrofurantane and phosphomycin (16.3%), 2nd generation oral cephalosporins (9.6%) and 3rd generation oral cephalosporins (10.7%) have been prescribed before urine culture (Figure 1). It was observed that 38 (14%) of these prescriptions were incompatible with the susceptibility results (Table 3). Forty-two percent of cefuroxime prescriptions, 28% of fluoroquinolone prescriptions and 17% of ceftriaxone prescriptions were resistant according to antibiogram results. When these prescriptions were analyzed, it was observed that only 4 (10%) of them were changed according to the antimicrobial susceptibility result, and that most of the prescription changes were made in FF and NT patients.

Table 3: Resistance rates according to culture results of empirically given antimicrobials in patients with uncomplicated UTI between 2011 and 2015

Empirical Prescription Antimicrobials	n(%)
Quinolone	14(28)
Phosphomycine	1(2.2)
Nitrofurantoine	2(6.6)
Cefuroxime	11(42)
Ceftriaxone	5(17.2)
Nitrofurantoine and Phoshomycine	0(0)
Ampicillin-Sulbactam and Amoxicillin clavulanic acid	5(15)

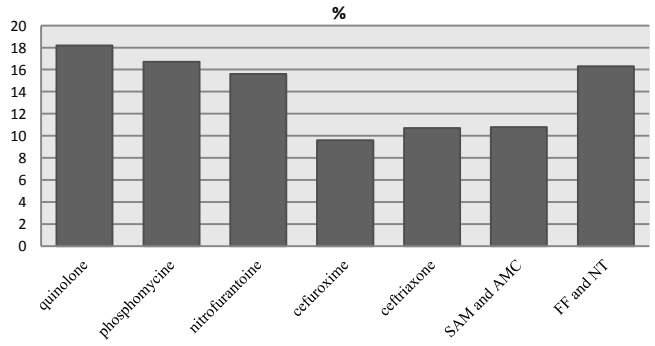

Figure 1: Percent distribution of empirically prescribed antimicrobials in patients with uncomplicated UTI

Discussion

It is mostly recommended that empirical treatment of uncomplicated UTI should be initiated because the diagnosis of UTI can usually be made based on the patient's symptoms and complete urinalysis [6]. First recommended medications according to various guidelines in the empirical treatment of uncomplicated UTI include nitrofurantoin and phosphomycin, alternatively quinolone and in cases where the resistance rate is below 20% trimethoprim/sulfamethoxazole (TMP-SXT) [6,7]. As in many studies conducted in our country, E. coli ranked first and Klebsiella spp. ranked second in the cases of complicated and uncomplicated UTIs [8,9].

When studies on antimicrobials prescribed in empirical treatments of UTIs were analyzed, it seemed that 77% quinolones, 10% TMP-SXT, 2% NT and 9% FF have been prescribed [10]. TMP-SXT (25.8%) is the most commonly prescribed medication for the empirical treatment of UTIs in Israel, followed by quinolones (22.8%) and nitrofurantoin (14.7%) [11]. In Germany, TMP-SXT (60%) and quinolones (21%) are the most commonly prescribed medications. Due to their high resistance rates, ampicillin is no longer found in empirical prescriptions.

Despite the resistance problem, perhaps because of the ease of oral use, TMP-SXT and quinolones still appear to be at the top on empirical prescriptions in several countries [12]. In our country, TMP-SXT resistance varies from 20% to 60% for E. coli strains isolated from community-acquired urinary tract infections (Table 4) [8,9,13-16]. Because of the high TMP-SXT resistance, it seems that TMP-SXT has not been included in the prescriptions arranged by our polyclinics in accordance with the recommendations of guidelines. In our study, TMP-SXT resistance was also found to be quite high in E. coli. However, there was a significant decrease in the resistance of TMP-SXT over the years in both groups, especially more evidently in patients with complicated UTI ($p<0.05$). This can be explained by the fact that TMP-SXT is not included in prescriptions arranged empirically.

Table 4: Antibiotic resistance rates of *E. coli* strains detected in uncomplicated UTI in studies conducted in Turkey (%).

	Province	Year	AMC	CRO	GN	AMP	AK	FEP	CIP	SXT	NT
Gözüküçük et al [13]	Istanbul	2012	36.6	19.2	10.2	63.7	1.1	6.4	19.8	40	12.4
Gül et al [8]	Kırıkkale	2014	182	3	-	-	-	-	18.2	21.2	-
DurmuşG et al [14]	Edirne	2009	11.1	10	0	60	0	-	30	60	0
Zengin et al [9]	Van	2014	42	18	10	55	5	-	33	45	-
Duman Y et al [15]	Maraş	2014	35	18	11	62	0	16	20	36	5
Yılmaz N et al [16]	Izmir	2016	37	28	24	67	0.3	12	50	20	0.9

AMC: Amoxicillin-Clavulanic acid, CRO: Ceftriaxone, GN: Gentamicin, AMP: Ampicillin, AK: Amikacin, FEP: Cefepime, CIP: Ciprofloxasin, SXT: Trimethoprime-Sulfametoxazole, NT: Nitrofurantoine

Ciprofloxacin (CIP) resistance rates of E.coli range from 3.2% to 22% in the world [17]. When we look at the studies on quinolone resistance in UTI conducted in our country, it seems that the (CIP) resistance rate was between 18.2% and 50% in uncomplicated urinary tract infections, showing an increase over the years (Table 4). According to a multi-centered study included 6 different geographical regions of Turkey, CIP resistance of patients with community-acquired complicated and uncomplicated UTI were found to be lowest in the Marmara Region (23%) [18]. In our study, CIP resistance was found to be higher in ESBL (+) E. coli strains isolated from patients with complicated urinary tract infections ($p<0.05$). Our study data is consistent with the studies conducted in our country, and quinolone resistance is higher in patients with complicated UTI and since CIP is a commonly preferred antimicrobial agent in the empirical treatment, care should be exercised while arranging prescriptions in polyclinics, especially for patients with complicated risk factors.

It was observed that the microorganism grew in 28% of the patients for whom empirical quinolone was prescribed for the treatment of uncomplicated UTI in our polyclinics was quinolone-resistant, and that prescription modification according to the antibiogram result was performed only in 4% of the cases.

Ceftriaxone (CRO) resistance in E. coli strains that are the determining factors for UTI ranges from 3% to 28% in Turkey (Table 4). CRO resistance in hospital-acquired E. coli strains is significantly higher than in community-acquired strains [19]. We also found a similarly high resistance in patients with complicated UTI.

NT resistance of E. coli ranges between 0% and 12.5% in studies conducted in our country (Table-4). A meta-analysis including the period between 1996 and 2012 reported that NT resistance has declined from 24% to 8.5%. The researchers argue that this is due to the fact that NT is less preferred in the treatment and accordingly not reported in antibiogram results because of its reduced use in recent years [20]. In our study, NT resistance of E. coli was also found to be below 10% in both complicated and uncomplicated cases, suggesting that NT may still be a preferred agent in the empirical treatment of patients with UTI. However, the increase in resistance of E.coli observed in uncomplicated cases over the years is significant ($p<0.05$). Therefore, the compatibility of initiated treatments should absolutely be confirmed by antibiogram results.

Phosphomycin is a preferred antibiotic in the empirical treatment because of its ease of use, which can be effective even in ESBL (+) cases. FF resistance is low in studies conducted in our country and FF resistance of E. coli strains isolated from community-acquired urinary system infections was found to be 4.3% in İzmir between the years of 2008-2014 [21,22]. In another study, resistance rates were reported to be 10% in ESBL (+) E. coli strains and 5% in ESBL (-) E. coli strains [18,23]. However, as drug use increases, resistance rates are also gradually increasing, as we have observed.

The prevalence of ESBL in E. coli strains ranges between 6%-25% in our country [24,25]. Over the years, ESBL positivity has increased in E.coli, which was a determinant of complicated and uncomplicated UTI in our study, and was found to be significant in patients with uncomplicated UTI ($p<0.05$). This demonstrates that resistant strains have also increased in our hospital, similar to the studies conducted, suggesting that phosphomicine may still be a suitable option in empirical treatment.

TMP-SXT resistance has been reported to be 14.3-30.2% in Klebsiella spp. strains isolated from patients with UTI in our country [8,18,26,27]. However, this rate was found to be even higher (22-60%) in our study (Table-2). The identified

resistance rates suggest that this antibiotic should be prescribed according to TMP-SXT culture antibiogram result in Klebsiella spp. When empirical prescriptions were analyzed, this antibiotic was found not to have been preferred empirically at all since TMP-SXT resistance was found to be greater than 20%.

Quinolone resistance of Klebsiella spp. is also increasing throughout the world (19-27%) [28,29]. Quinolone resistance rates range between 10-50% in Turkey. [8,18,26,27]. Our results are also parallel to this data, and antimicrobial resistance has increased significantly over the years ($p<0.05$). ESBL production in Klebsiella spp. is also increasing over the years, particularly more significantly in complicated UTI cases. It is also natural to see an increase in cephalosporin resistance rate in connection with that (24). CRO resistance rate in Klebsiella spp. strains isolated from patients with UTI in our country was found to be between 14.3-27%. [8,18,26,27]. Over the years, a linear increase was observed in CRO resistance rates (13-33%) of patients with uncomplicated UTI in our study, but this increase was not found to be statistically significant ($p>0.05$).

Our study found that third generation oral cephalosporins have been empirically prescribed at a rate of 10.7% and second generation oral cephalosporins have been empirically prescribed at a rate of 9,6%, and that 42% of cefuroxime prescriptions and 17% of cefixime prescriptions were incompatible with antibiogram results. The results suggest that these antimicrobials should be prescribed according to the antibiotic susceptibility result. On the other hand, NT resistance was found to be low, especially in uncomplicated cases. It may be a suitable option in the empirical treatment.

Similar resistance problems also exist in other microorganisms. However, since the number of these microorganisms was small in our study, these results were not included in the discussion.

Conclusion

Consequently, the problem of resistance is gradually increasing in UTI. As seen in other countries in which inappropriate use of antibiotic is high, other antibiotics that may be prescribed to outpatients in the cases of uncomplicated UTI also have a high resistance. Therefore, empirically initiated treatments are often ineffective. Considering all the prescriptions in our study, 38 (14%) of these empirically initiated prescriptions were found to be incompatible with antimicrobial susceptibility results. When these prescriptions were analyzed, it was found that only 4 (10%) of them were changed according to the antimicrobial susceptibility result, and that that most of the prescription changes were made in FF and NT patients because the susceptibility was found to be high in patients to whom FF and NT were prescribed. These results support the usability of FF and NT, which have good efficacy in uncomplicated UTIs, in the empirical treatment. However, it is considered that antimicrobials other than NT should be prescribed according to culture/antibiogram results in the case of complicated UTIs.

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