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İdrar Örneklerinden İzole Edilen Escherichia Coli Suşlarının Çeşitli Antimikrobiyallere Direnç Oranı

Resistance Rates Against Various Antimicrobials in Escherichia Coli Strains Isolated from Urine Samples

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ÖZ

GİRİŞ ve AMAÇ*: Çalışmamızda üriner sistem infeksiyonlarından izole edilen genişlemiş spektrumlu beta laktamaz GSBL pozitif ve negatif Escherichia coli infeksiyonlarındaki antibiyotiklere direnç sıklığının belirlenmesi amaçlanmıştır.*

YÖNTEM ve GEREÇLER*: 2013-2014 yıllarında kliniklerde yatan ve polikliniklere başvuran hastalardan laboratuvara gelen idrar örneklerinden, anlamlı üreme olan 1392 adet GSBL pozitif ve negatif E.coli suşu değerlendirilmştir. Üreyen mikroorganizmalar VITEK®2 Compact (bioMerieux, MarcyI'Etoile, France) cihazında, CLSI (Clinical and Laboratory Standards Institute) standartlarına göre değerlendirilmiştir. Sayısal ve oransal (n, %) hesaplamalar için tanımlayıcı testler, karşılaştırmalar için Z testi kullanılmıştır. p < 0,05 değerler istatistiksel olarak anlamlı kabul edilmiştir.*

BULGULAR*: GSBL pozitif E.coli suşlarında en yüksek direnç ampisiline %99.6, en düşük direnç %3.4 ile meropeneme, %2.8 ile fosfomisine, %2.1 ile imipeneme, %1.8 ile amikasine karşı bulunmuştur. GSBL negatif suşlarda en yüksek direnç %51.4 ile ampisiline, en düşük direnç %1.7 ile fosfomisine, %0.6 ile meropeneme, %0.6 ile amikasine, %0.3 ile imipeneme karşı bulunmuştur. Direnç durumları arasındaki fark p < 0.05 olarak bulunmuş, istatistiksel olarak anlamlı kabul edilmiştir.*

TARTIŞMA ve SONUÇ*: İnfeksiyonlardaki tedavi başarısızlıklarını önlemek ve dirençli patojenlerin yayılımının engellenmesi için hastaneler direnç oranlarını düzenli aralıklarla izlemelidir. Bu çalışmaların ampirik tedaviye yol gösterici olacağı sonucuna varılmıştır.*

Anahtar Kelimeler: *Antibiyotik direnci, GSBL, üriner sistem infeksiyonu.*

ABSTRACT

INTRODUCTION*: We aimed to determine the antimicrobial resistance rates of extended-spectrum beta-lactamase (ESBL) positive and negative Escherichia coli strains isolated from the urine samples of patients with urinary system infections.*

METHODS*: Among the urine samples from the patients in the clinics or outpatient clinics between 2013 and 2014, 1392 ESBL-positive and ESBL-negative E.coli strains with significant growth were evaluated. The VITEK® 2 Compact (bioMerieux, MarcyI'Etoile, France) automated device was used for bacterial identification and antibiotic susceptibility testing and results were evaluated with CLSI (Clinical and Laboratory Standards Institute) standards.*

Z Test We used for comparisons and descriptive tests for numerical calculations p <0.05 was considered statistically significant.

RESULTS*: The ESBL-positive E.coli strains showed the highest resistance to ampicillin (99.6%) and the lowest resistance, to meropenem (3.4%), fosfomycin (2.8%), imipenem (2.1%) and amikacin (1.8%). The ESBL-negative strains showed the highest resistance to ampicillin (51.4%) and the lowest resistance, to fosfomycin (1.7%), meropenem (0.6%), amikacin (0.6%) and imipenem (0.3%). The difference among these rates was p < 0.05 and statistically significant.*

DISCUSSION and CONCLUSION*: Hospitals should regularly evaluate level of resistance to urinary system infections to prevent spread of resistant pathogens. Our study shows a new path for empirical treatment, indicating that fosfomycin can be given priority for the treatment of urinary tract system infections caused by E.coli.*

Keywords: *Antibiotic resistance, ESBL, urinary system infection.*

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INTRODUCTION

More than 95% of the urinary tract infections are caused by a single pathogen. Also the studies from Turkey report E.coli as the leading bacteria isolated from community-acquired infections, with other agents isolated less commonly (1).

The incidence of infections with Gram-negative bacilli such as Klebsiella pneumoniae and E.coli has begun to increase gradually since the mid-1980s, and these agents have become resistant to many antibiotics owing to either chromosomally- or plasmid-mediated beta lactamase enzyme they produce (2). The history of beta lactamases begins in 1940 with the introduction of a penicillinase that was able to destroy beta-lactam in an E.coli strain by Abraham and Chain. In 1944, Kirby identified an enzyme with similar nature in Staphylococcus aureus strains. The number and variety of beta lactamases have remained quite limited over the 20-25 years after the penicillin has been put into clinical use. Over this period, it is seen that most of the Gram-negative bacteria produce TEM-1, K. pneumoniae strains produce SHV-1, and S. aureus strains produce a penicillinase. However, it is observed that the types of beta-lactamases have rapidly increased in 1978-80s with the introduction of new beta-lactam agents produced by soil bacteria (cephamycin, carbapenems, sulphones and monobactams) into the clinical treatment (2). Beta lactamases are the leading causes of bacterial resistance against beta-lactam antibiotics. The genes responsible for beta lactamase production might have been localized in the chromosomes, transposons or plasmids; however, the genetic information in the plasmids poses the greatest threat. The fact that plasmids are able to transfer the resistant genes easily via conjugation among the organisms means that resistance genes can be transferred rapidly to many different species, thus propagation of beta-lactamase-mediated resistance among pathogen strains becomes easy (3). Extended-spectrum beta lactamases are the enzymes that inactivate all cephalosporin excluding cephamycin, as well as penicillin and aztreonam.

Beta lactamases are the enzymes that destroy the cyclic amide bond in beta lactam ring and accordingly inhibit the efficacy of beta lactam agents. Penicillin, cephalosporin, monobactams and carbapenems can be inactivated by one or several enzymes in beta lactamase family. Beta lactamase production is the most critical mechanism in beta lactam resistance of Gram-negative bacteria, primarily the members of Enterobacteriaceae. Beta-lactamase genes can be found in bacterial chromosome, as well as in motile genetic elements such as plasmid, transposon or integron. These enzymes are directly released into the outer media in Gram-positive species, whereas they are found in the periplasmic space in Gram-negative species.

Therefore, mechanisms of drug permeation as well play a role in beta-lactamase-associated resistant among Gram-negative bacterial species (2). In the present study, we aimed to make contribution to the regional resistance rates by retrospectively detecting antibiotic resistance of ESBL-positive and negative E.coli strains isolated from the urine samples sent to the Central Microbiology laboratory.

METHODS

In the present study, 1,392 ESBL-positive and negative E.coli strains with significant growth, which were isolated from the urine samples sent between January 2013 and December 2014 to the Health Sciences University, Gazi Yaşargil Training and Research Hospital, Microbiology Laboratory from the policlinics and clinics, were retrospectively evaluated. Only one of the repeated specimens was included in the study. For quantitative examination, the midstream urine collected from the patients under sterile conditions was inoculated onto 5% sheep blood agar and Eosin Methylene Blue (EMB) agar using 0.01 ml loop and then incubated in an incubator at 36.5-37°C for 16-24 hours. In order to identify the strains with ≥ 105 cfu/ml growth at the end of this time, as well as to determine their antibiotic susceptibility, automated VITEK®2 Compact device (bioMerieux, MarcyI'Etoile, France) was used, and the evaluation was made in accordance with 2013 CLSI standards (4).

Mechanism of ESBL resistance is studied by automated VITEK® 2 Compact device (bioMerieux, MarcyI'Etoile, France) on the basis of CLSI standards as six-well using cefotaxime, ceftazidime, cefepime, cefotaxime-clavulanic acid,

ceftazidime-clavulanic acid, and cefepime-clavulanic acid. It gives the result in a mean of 6.6 hours by assessing as positive or negative.

In the present study, identification of ESBL-positive and ESBL-negative E.coli strains and their antibacterial susceptibility were studied by automated VITEK®2 Compact (bioMerieux, MarcyI'Etoile, France) system using GN and AST-N327 cards.

Statistical analysis of the study data was done using IBM SPSS statistics 20.0 (SPSS, Inc., Chicago, IL, US). Descriptive statistics was used for numerical (n) and proportional (%) calculation of the antibiotic resistance of different strains. The difference between the antibiotic resistances of bacterial strains was statistically assessed by comparison of proportions using Z test. p value smaller than 0.05 within 95% confidence interval was considered statistically significant.

RESULTS

Resistance rates to various antibiotics were evaluated in a total of 1,392 (696 ESBL-positive and 696 ESBL-negative) E.coli strains isolated from the urine samples with ≥105 cfu/ml growth detected in the microbiology laboratory. ESBL-positive E.coli strains were associated with high resistance rates to ampicillin, cefuroxime, ceftriaxone and cefixime among beta-lactam antibiotics. Both ESBL-positive and ESBL-negative strains showed lower resistance rates to ceftazidime, amoxicillin/clavulanic acid, piperacillin/tazobactamand cefoperazone/sulbactam as compared to the other beta-lactam antibiotics.

Resistance rates to meropenem and imipenem among carbapenems were higher in ESBL-positive vs. ESBL-negative strains. Likewise, resistance rate to non-beta-lactam antibiotics trimethoprim-sulfamethoxazole, ciprofloxacin, gentamycin, nitrofurantoin, fosfomycin and amikacin were higher in ESBL-positive strains as compared to ESBL-negative strains. However, resistance rates to fosfomycin and amikacin among these antibiotics were found low both in ESBL-positive and ESBL-negative strains. Resistance rates of ESBL-positive and ESBL-negative E.coli strains are illustrated in Table 1.

Statistical difference between the antibiotic resistance rates of bacterial strains was determined comparing by Z test. In the present study, $p < 0.05$ within 95% confidence interval was considered statistically significant.

Table 1. Resistance rates among *E.coli* strains (%)

	ESBL (+)			ESBL (-)			
	%	n^1	N^1	%	n^2	N^2	p
Antibiotic							
Ampicillin	99.6	526	528	51.4	280	544	0.003
Cefuroxime	98.6	517	524	20	107	535	<0.001
Ceftriaxone	97.3	515	529	16.7	91	544	<0.001
Cefixime	97.1	503	518	17.8	94	528	<0.001
Ceftazidime	69.8	450	644	7.1	49	687	<0.001
SXT	64	415	648	34	237	696	<0.001
Ciprofloxacin	61.5	399	648	23.9	167	696	<0.001
AMC	41.4	219	528	14.7	80	543	<0.001
Gentamycin	33.3	217	651	8	56	696	<0.001
TZP	26.6	172	646	13.9	96	688	<0.001
Cefoxitin	22.5	118	523	8.2	44	536	<0.001
CES	12.3	79	640	4.4	30	677	<0.001
Nitrofurantoin	10.1	53	524	4.6	25	535	<0.001
Meropenem	3.4	24	695	0.6	4	648	<0.001
Fosfomycin	2.8	15	528	1.7	9	518	<0.001
Imipenem	2.1	15	696	0.3	2	646	<0.001
Amikacin	1.8	13	696	0.6	4	647	<0.001

%: Antibiotic resistance rate, ESBL (+) *E.coli* ;
N_1: total number of specimens; n_1 : number of resistant strains
ESBL(-) *E.coli* ; N_2 : total number of specimens;
n_2 : number of resistant strains,
SXT : Trimethoprim/sulfamethoxazole
AMC : Amoxicillin/clavulanic acid
TZP : Piperacillin/tazobactam,
CES : Cefoperazone/sulbactam

DISCUSSION

Ampicillin is the first penicillin with good activity against Gram-negative bacteria, primarily against E.coli. E.coli strains that are resistant to this antibiotic by producing a plasmid-borne beta-lactamase called TEM have been identified few years after ampicillin has been put into clinical use. Extended spectrum cephalosporin cefotaxime, ceftizoxime, ceftriaxone and ceftazidime are strong antibiotics resistant to the original TEM enzyme. Unfortunately, increased clinical usage of these drugs, particularly of ceftazidime, has led to the

generation of resistant Gram-negative bacteria, primarily K. pneumoniae. Molecular analysis of these resistant strains revealed that resistance develops due to beta lactamases and that majority of these beta lactamases originate from one or more point mutations in bla TEM gene and from the original TEM enzyme (5). In the present study, antibiotic resistance was evaluated using automated system. Being laborsaving, reproducibility, data management by expert system analyses, and opportunity of faster outcomes are among the advantages of automated systems. Barenfanger et al. as well demonstrated that automated system provides faster reporting of the antibiotic susceptibility test results, which enable earlier modification of antimicrobial therapy, thus shortens the duration of hospital stay and reduces cost.

Equipment and consumables with higher cost than the manual methods, premeditation of antibiotic panels, lack of potential for testing all of the clinically isolated organisms, and problems in detecting some resistance phenotypes are among the disadvantages of automated systems (5). Reviewing the studies published between 2006 and 2014, no significant difference was determined between the resistance rates to ampicillin and ceftriaxone, members of the beta-lactam antibiotics, in ESBL-positive E.coli strains isolated from the urinary tract infections.

Deveci et al. (6) conducted a study in 2009 with ESBL-positive E.coli strains isolated from the urine samples sent from various policlinics and clinics and found the resistance rate to be 72.2% for cefuroxime. In the present study, however, it was higher as 98.6% in ESBL-positive strains.

Coşkun et al. (7) conducted a study between 2011 and 2013 with outpatients and found the resistance rate of ESBL-positive E.coli strains isolated from urinary tract infections to be 95.3% for ceftazidime, which was found to be 69.8% in the present study. In the same study, resistance rate against amoxicillin/clavulanic acid was 42.1% vs. 41.4% in the present study, which is considered closer. In the other studies, resistance rate against amoxicillin/clavulanic acid was higher in ESBL-positive strains (6,8,9,13).

Deveci et al. (6) found the resistance rate against piperacillin/tazobactam to be 44.4% in ESBL-positive E.coli strains; in their study conducted in 2010, Bayram et al. (8) found the resistance rate to be 41% in ESBL-positive E.coli strains isolated from the urine samples sent from policlinics and clinics, whereas it was found to be 26% in ESBL-positive strains in the present study.

Gündem et al. (9) found the resistance rate against cefoxitin to be 92.2% in ESBL-positive E.coli strains isolated from the urine samples of patients admitted to the policlinics and clinics between 2011 and 2012; it was found to be 22.5% in ESBL-positive strains in the present study.

In their study conducted in 2007, Kaşkatepe et al. (10) found the resistance rate against cefoperazone/sulbactam to be 8% in ESBL-positive E.coli strains in the urine samples of patients visited microbiology laboratory, which was found to be 7.8 by Coşkun et al. (7); in the present study, it was found to be higher as 12.3% in ESBL-positive strains.

Bayram et al. (8) and Coşkun et al. (7) found the resistance rate against imipenem to be 0% in ESBL-positive E.coli strains, whereas it was found to be 2.1% in the present study.

The resistance rate against imipenem was found to be 11.1% by Deveci et al. (6) and 4.7% by Gündem et al. (9) in ESBL-positive E.coli strains; it was to be 2.1% in ESBL-positive strains in the present study.

With regard to the resistance against non-beta-lactam antibiotics, no significant difference was determined between the present study and the other studies for trimethoprim-sulfamethoxazole. Resistance rate against ciprofloxacin was found to be 96% by Kaşkatepe et al. (10) in ESBL-positive E.coli strains, to be 85.6% by Yaşar et al. (11) in ESBL-positive E.coli strains isolated from hospitalized and ambulatory patients with complicated urinary system infections in 2010, and it was found to be 61.5% in ESBL-positive strains in the present study. In our gentamycin resistance study, the resistance rate was found to be 33.3% in ESBL-positive strains, which was found to be 59% by Kaşkatepe et al. (10), to be 53% by Uyanık et al. (12), and to be 70% by Inci et al. (13). In the

present study, resistance rate against nitrofurantoin in ESBL-positive strains was found to be 10.1%,

whereas it was found to be 23.2% by Pullukçu et al. (14), and 38.9% by Deveci et al.(6). While Bayram

et al. (8) and Coşkun et al. (7) determined no resistance against Meropenem in ESBL-positive strains, it was found to be 3.4% in the present study. Beta-lactam antibiotics are the leading antibacterial agents used for the treatment of both community-acquired and hospital-acquired infections. It is seen that the bacteria have developed new mechanisms of resistance in line with this extensive usage resulting in increased resistance. Resistance against fosfomycin in ESBL-positive strains, which was found to be 2.8% in the present study, was found to be 15% by Bayram et al. (8), 9.3% by Coşkun et al. (7), and 13.9% by Kurt et al. (15). Resistance against imipenem in ESBL-positive strains was found to be 2.1% in the present study, whereas it was found to be 11.1% by Deveci et al. (6) and 4.7% by Gündem et al. (9). The present study found the resistance against amikacin in ESBL-positive strains to be 1.8%, which was found to be 11.1% by Deveci et al. (6) and 7.8% by Gündem et al. (9).

In the present study, the lowest resistance rate in ESBL-positive and ESBL-negative strains was observed against amikacin, imipenem, fosfomycin and meropenem. In the recent years, increased resistance rates were observed also against carbapenem, which is considered as the last resort particularly in multidrug-resistant Gram-negative bacterial infections owing to its activity spectrum and resistance to beta-lactamases (2).

Table 2 and Table 3 illustrate the comparison between the resistance rates determined in the present study vs. earlier studies. Resistance rate against carbapenems was higher in the present study as compared to the earlier studies. Since carbapenem is quite resistant to ESBL enzymes, they are considered as the first line medications in the treatment of infections. However, selection of carbapenemase-producing bacteria may be in question in case of wide and uncontrolled usage. As ESBL-producing Enterobacteriaceae family produces also carbapenemase, it appears as the resistance issue in Gram-negative bacteria.

In conclusion, development of resistance in gram-negative bacteria particularly in hospital environment remains as an increasing problem.

Table 2. Resistance rates in ESBL-positive *E.coli* strains in Turkey (%).

Trial	AMP	CXM	CRO	CFM	CAZ	SXT	CIP	AMC	GM
Pullukçu et al.	-	-	-	-	-	-	-	-	-
Kaşkatepe et al.	-	-	96	-	-	59	96	-	59
Uyanık et al.	100	-	100	-	-	72	69	-	53
Deveci et al.	-	72.2	-	-	77.8	50	55.6	94.4	27.8
Yaşar et al.	-	-	-	-	-	-	85.6	-	-
Bayram et al.	89	-	-	-	-	78	63	89	-
Gündem et al.	-	100	95.3	-	-	84.4	64.1	75	40.6
Şay et al.	100	100	-	-	95.3	53.1	68.8	42.1	21.8
İnci et al.	100	-	93.3	-	70	80	75	61.7	70
Kurt et al.	-	-	-	-	-	-	85.3	-	-
Current study	99.6	98.6	97.3	97.1	69.8	64	61.5	41.4	33.3

AMP: Ampicillin. CXM: Cefuroxime. CRO: Ceftriaxone. CFM: Cefixime. C: Ceftazidime. SXT: Trimethoprim- sulfamethoxazole. CIP: Ciprofloxacin. AMC: Amoxicillin Clavulanic acid. GM: Gentamycin

Table 3. Resistance rates in ESBL-negative *E.coli* strains in Turkey (%)

Trial	TZP	FOX	CES	FT	MEM	FOS	IMP	AN
Pullukçu et al.	-	-	-	23.2	-	-	-	-
Kaşkatepe et al.	19	-	8	-	-	-	-	0
Uyanık et al.	-	-	-	-	-	0	0	3
Deveci et al.	44.4	33.3	-	38.9	-	-	11.1	11.1
Yaşar et al.	-	-	-	-	-	4.8	-	-
Bayram et al.	41	-	-	18	0	15	0	0
Gündem et al.	17.2	92.2	-	-	-	-	4.7	7.8
Şay et al.	6.2	0	7.8	4.6	0	9.3	0	-
İnci et al.	-	-	-	10	-	6.7	-	-
Kurt et al.	-	-	-	12.6	-	13.9	-	-
Current study	26.6	22.5	12.3	10.1	3.4	2.8	2.1	1.8

TZP: Piperacillin tazobactam. FOX: Cefoxitin. CES: Cefoperazone sulbactam. FT: Nitrofurantoin. MEM: Meropenem. FOS: Fosfomycin. IMP: Imipenem. AN: Amikacin

Therefore, in order to prevent development of resistance during treatment of the patients with urinary system infections, treatment needs to be chosen based on the results of culture and antibiotic susceptibility testing, and regional resistance rates need to be identified to prevent treatment failure in

ESBL-positive bacteria as well as the propagation of resistant pathogens. It should be noted that infection control measures and the policies for rational antibiotic use are of considerable importance since today any recently available antibiotic has almost become dysfunctional in a short time due to development of resistance. In addition to the precise management of actions for surveillance and feedback regarding these bacteria, education about rational antibiotic use and infection control, collaboration among health care professionals and administrative departments is also very important to take the problem under control.

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