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Fosfomycin and nitrofurantoin susceptibilities of *Escherichia coli* and *Klebsiella pneumoniae* isolates producing extanded spectrum Beta-lactamase causing urinary tract infections

Üriner sistem enfeksiyonlarına neden olan genişlemiş spektrumlu Beta-laktamaz üreten *Escherichia coli* ve *Klebsiella pneumoniae* izolatlarının fosfomisin ve nitrofurantoine duyarlılıkları

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Abstract

Introduction: *Escherichia coli* and *Klebsiella pneumoniae* are the most common pathogens causing urinary tract infection. Increasing numbers of extended spectrum β-lactamase producing *Esherichia coli* and *Klebsiella pneumoniae* isolates in urinary tract infection, limits to treatment options. The aim of this study was to determine the susceptibility of fosfomycin and nitrofurantoin to extended spectrum beta-lactamase producing *Esherichia coli* and *Klebsiella pneumoniae* isolates in hospitalized patients, contribute to the planning of empirical treatment of urinary tract infection.

Methods: A total of 14.383 midstream urine samples sent to Tokat Gaziosmanpasa University Hospital Microbiology Laboratory between January 2016 and December 2017 were evaluated retrospectively in this study. Isolates were identified by conventional methods (Gram stain, motility, biochemical tests etc) and VITEK 2 (bioMérieux, France) automated system. Antibiotic susceptibilities were detected by VITEK 2 automated system.

Results: Extended spectrum β-lactamase producing 85 *Esherichia coli* and 23 *Klebsiella pneumoniae* isolates, sent from hospitalized patients were included in the study. The strains were most frequently isolated in the intensive care units (46.3%). The most effective antibiotics against to *Esherichia coli* and *Klebsiella pneumoniae* were carbapanems and susceptibility rates were %100 and %87, followed by fosfomycin 98 % and 83 %, nitrofurantoin 94 % and 30.4% respectively.

Discussion and Conclusion: Fosfomycin was found effective treatment option against extended spectrum β-lactamase producing

Özet

Amaç: *Escherichia coli* ve *Klebsiella pneumoniae*, idrar yolu enfeksiyonuna neden olan en yaygın patojenlerdir. İdrar yolu enfeksiyonlarına neden olan genişletilmiş spektrumlu β-laktamaz üreten *Esherichia coli* ve *Klebsiella pneumoniae* izolatlarının sayılarının artması, tedavi seçeneklerinde azalmaya yol açmaktadır. Bu çalışmanın amacı, hastanede yatan hastalarda genişletilmiş spektrumlu β-laktamaz üreten *Esherichia coli* ve *Klebsiella pneumoniae* izolatlarının fosfomisin ve nitrofurantoine duyarlılıklarını saptayarak idrar yolu enfeksiyonunun ampirik tedavisinin planlanmasına katkıda bulunmaktadır.

Gereç ve Yöntem: Bu çalışmada, Ocak 2016-Aralık 2017 tarihleri arasında Tokat Gaziosmanpaşa Üniversitesi Hastanesi Mikrobiyoloji Laboratuvarı'na gönderilen toplam 14.383 adet orta akım idrar örneği retrospektif olarak değerlendirildi. İzolatlar konvansiyonel yöntemler (Gram boyama, motilite, biyokimyasal testler vb.) ve VITEK 2 (bioMérieux, Fransa) otomatik sistem ile tanımlandı. Antibiyotik duyarlılıkları VITEK 2 otomatik sistem ile tespit edildi.

Bulgular: Hastanede yatan hastalardan gönderilen örneklerden tanımlanan genişlemiş spektrumlu β-laktamaz üreten 85 *Esherichia coli* ve 23 *Klebsiella pneumoniae* izolatları çalışmaya dahil edildi. İzolatların en sık yoğun bakım ünitelerinden (%46.3) gönderildiği tespit edildi. *Esherichia coli* ve *Klebsiella pneumoniae* için en duyarlı antibiyotikler %100 ve %87 duyarlılık oranları ile karbapanemler olup, bunu sırasıyla %98 ve %83 oranı ile fosfomisin, %94 ve% 30.4 oranı ile nitrofurantoin izlemekteydi.

Sonuç: Hastanemizde yatan hastalarda genişlemiş spektrumlu β-laktamaz üreten *Esherichia coli* ve *Klebsiella pneumoniae* izolatlarının neden olduğu üriner sistem enfeksiyonlarında fosfomisinin ampirik

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Escherichia coli and *Klebsiella pneumoniae* in urinary tract infections. However, nitrofurantoin is thought to be more suitable for use in urinary tract infections caused by *Escherichia coli* isolates producing expanded spectrum β-lactamase.

Keywords: *Escherichia coli*; extended spectrum β-lactamase; fosfomycin; *Klebsiella pneumoniae*; nitrofurantoin.

tedavide iyi bir alternatif ajan olarak kullanılabileceği görülmüştür. Ancak nitrofurantinin genişlemiş spektrumlu β-laktamaz üreten *Escherichia coli* izolatlarının neden olduğu üriner sistem enfeksiyonlarında kullanılmasının daha uygun olacağı düşünülmüştür.

Anahtar Sözcükler: *Escherichia coli*; genişlemiş spektrumlu β-laktamaz; fosfomisin; *Klebsiella pneumoniae*; nitrofurantoin.

Urinary tract infection (UTI) is the most common infection after respiratory and gastrointestinal infections, and also the most common cause of both community-acquired and nosocomial infections for patients admitted to hospitals.[1] If UTIs are not diagnosed early and properly treated, chronic infection can lead to kidney damage in the long term.[2] *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) are the most common pathogens causing UTI both in adults and children.[3–6]

Extended spectrum β-lactamase (ESBL) is one of the antibiotic resistance mechanisms. While ESBL is produced, causes resistance to oxyimino-cephalosporins such as cefotaxime, ceftazidime, ceftriaxone and monobactams like aztreonam. Cephamycins and carbapenems can be used in the treatment of ESBL producing isolates.[7] ESBL production was mostly detected in uropathogens such as *E. coli* and *K. pneumoniae*.[8] ESBL produced by *E. coli* and *K. pneumoniae* reduces the number of therapeutic options for the infection caused by these pathogens.[4,9] Increasing numbers of ESBL producing *E. coli* and *K. pneumoniae* isolates and multiple drug resistant isolates are leading to a reduction in treatment options. The use of fosfomycin and nitrofurantoin, which are broad-spectrum cell wall inhibitors, is important in the treatment of these isolates.[10] Delay detection and report of ESBL production leads to prolongation of hospital stay, increased morbidity, mortality and health-care costs.[11] Knowing the resistance patterns is an important parameter for the determination of treatment in the selection of antibiotics.[12]

The aim of this study was to determine the sensitivity of fosfomycin and nitrofurantoin to ESBL producing *E. coli* and *K. pneumoniae* isolates in hospitalize patients, contribute to the planning of empirical treatment in our hospital.

Materials and Method

A total of 14.383 midstream urine samples sent to Tokat Gaziosmanpasa University Hospital Microbiology Laboratory between January 2016 and December 2017 were evaluated retrospectively in this study. Urine samples were inoculated onto 5% sheep blood agar (ORBAK, Turkey) and eosin methylene blue agar (ORBAK, Turkey), using a 0.001-ml calibrated loop. Cultures were incubated at 37°C for 24-48 hours and those microorganisms isolated in the range of 10^5 colony forming units (CFU) per milliliter (ml) were identified. Samples containing three or more isolates in counts of 10^4 CFU/ml and with no single isolate in the 10^5 range were reported as "contaminated," and a repeat specimen was requested. Isolates were identified by conventional methods (Gram stain, motility, biochemical tests etc) and VITEK 2 (bioMérieux, France) automated system. Antibiotic susceptibilities were detected by VITEK 2 (bioMérieux, France) automated system and interpreted according to the Clinical and Laboratory Standards Institute in January 2016 – March 2017(CLSI)[13] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[14] in April 2017 - December 2017. The following antibiotics were tested by VITEK 2 (bioMérieux, France) automated system: gentamicin, ciprofloxacin, trimethoprim/sulfamethoxazole, piperacillin-tazobactam, ertapenem, meropenem, imipenem, fosfomycin, nitrofurantoin. Child patients samples are excluded from the study. Only one strain from a patient was taken to the study. Intermediate susceptibility isolates were considered resistant. Reference isolate of *E. coli* ATCC 25922 was used for quality control for antimicrobial susceptibility tests.

Ethical approval was obtained from Tokat Gaziosmanpasa University of Medicine Clinical Research Ethics Committee (Project number: 18-KAEK-013).

Results

ESBL positive 85 *E. coli* and 23 *K. pneumoniae* isolates, sent from hospitalized patients were included in the study. The isolates were most frequently obtained from the intensive care units (46.3%). The units to which the samples were sent shown in Table 1. The most effective antibiotics for *E. coli* and *K. pneumoniae* are carbapanems with susceptibility rates 100% and 87%, followed by fosfomycin 98% and 83%, nitrofurantoin 94% and 30.4% respectively. Susceptibility rates of all isolates against all antibiotics were shown in Table 2.

Discussion

Urinary tract infection is one of the most common infectious diseases worldwide. Antimicrobial resistance is increasing and antimicrobial resistance patterns vary over time and in different geographical regions, antibiotic treatment of infections should be based on the local sensitivity and resistance patterns.[15] Urinary tract infections in critically ill adult patients is associated with considerable morbidity and prolonged hospitalization. Within the hospital environment, the intensive care unit (ICU) has the highest prevalence of nosocomial UTIs.[16,17] In this study, 50 isolates (38 *E. coli*, 12 *K. pneumoniae*) (46.3%) were isolated from intensive care unit samples in accordance with the literature.

Early identification of ESBL production is becoming increasingly important in terms of appropriate treatment and effective infection control in hospitals. Patients with infections

Table 1. Clinical distribution of ESBL positive *Escherichia coli* and *Klebsiella pneumoniae* isolates

	Escherichia coli	*Klebsiella pneumoniae*	Total
İntensive care unit	38	12	50
Oncology service	11	1	12
İnfection disease service	9	1	10
Brain surgery service	1	-	1
Neurology service	3	1	4
Oncological surgery	2	1	3
Urology service	4	1	5
Orthopedic service	1	-	1
Plastic surgery service	1	-	1
Physical therapy service	4	2	6
Internal Medicine service	7	1	8
General surgery service	2	-	2
Thoracic surgery service		1	1
Cardiovascular surgery service	1	2	3
Gastroenterology service	1	-	1
Total	85	23	108

ESBL: Extended spectrum β-lactamase

Table 2. Antibiotic susceptibility rates of ESBL positive *Escherichia coli* and *Klebsiella pneumoniae* isolates

	Escherichia coli		*Klebsiella pneumoniae*	
	n	%	n	%
Gentamycin	53	62.3	12	52.2
Ciprofloxacin	25	29.4	9	39.1
TPM/SMX*	26	30.6	7	30.4
PTZ*	40	47	6	26.1
Ertapenem	85	100	20	87
Meropenem	85	100	20	87
İmipenem	85	100	20	87
Fosfomycin	83	98	19	83
Nitrofurantoin	80	94	7	30.4

ESBL: Extended spectrum β-lactamase; TPM/SMX*: Trimethoprim/sulfamethoxazole; PTZ*: Piperacillin-tazobactam

caused by ESBL producers may experience delay in the initiation of appropriate therapy compared with patients with non-ESBL infections.[15] The studies which evaluated the ESBL rates of *E. coli* and *K. pneumoniae* in UTI were 13.1–28.17%[18–21] ve 12–35%[18,21] respectively.

ESBL producing bacteria, make treatment difficult UTI's both hospital and community-acquired infections and lead to increased use of expensive broad-spectrum antibiotics like carbapenems. Carbapenems used for the treatment of multiple antibiotic resistant and ESBL producing isolates infections.[22]

Patel et al. found that antibiotic susceptibilities in enteric bacteria including *E. coli* and *K. pneumoniae* caused by UTI, the sensitivity of fosfomycin were 92% in ESBL producing isolates and 72.4% in carbapenem-resistant isolates in 2017. They indicated fosfomycin was effective both in ESBL producing isolates and in carbapenem-resistant strains.[23]

Alpay et al. observed the most effective antimicrobial agents were fosfomycin (96%) and nitrofurantoin (84%) in 152 ESBL positive *E. coli* isolated from suspicion UTI samples. It has been emphasized the use of fosfomycin and nitrofurantoin as an alternative to the carbapenems in the treatment of community-acquired urinary tract infections with ESBL positive *E. coli* isolates.[24] Sonmezer et al. determined the sensitivity of fosfomycin was 91.4% in ESBL producers, 100% in non-ESBL *E. coli* in outpatients, and indicated that the most effective antibiotic is fosfomycin in 2016.[25]

The use of fosfomycin and nitrofurantoin in treatment is also important for UTI, in the hospitalized patients, caused by ESBL producing *E. coli* and *K. pneumoniae*. Fosfomycin sensitivity in the study conducted in 2017 by Fajfr et al. was 95.8% in ESBL positive *E. coli* isolates and 85.3% in ESBL positive *K. pneumoniae* isolates. Fosfomycin was found to be more effective in the complicated UTI in hospitalized patients than other antibiotics.[26] Coskun et al. evaluated 71 ESBL producing *E. coli* and 27 *K. pneumoniae* isolates which isolated from urine samples of hospitalized patients between 2014 and 2016. In the study, the rate of susceptibility to fosfomycin was 90.1% and 66.6%, and the rate of nitrofurantoin sensitivity was 91.5% and 70.4%, respectively. Fosfomycin and nitrofurantoin have been reported to be significantly more effective in isolates producing ESBL than ampicillin-sulbactam, trimethoprim-sulfamethoxazole and ciprofloxacin.[27]

In 2018 Tulara et al. indicated fosfomycin remains the most effective antibiotic while nitrofurantoin still preserves the good activity against ESBL-producing *E. coli* and *K. pneumoniae* and found to be an only oral effective antibiotic.[28]

In this study, the antibiotic susceptibility of *E. coli* and *K. pneumoniae* are 98% and 83% for fosfomycin, 94% and 30.4% for nitrofurantoin respectively. Compared with the previous studies susceptibility rates of fosfomycin are quite similar. However, the susceptibility rate to nitrofurantoin was lower in *K. pneumoniae* isolates. The fact that including of patients hospitalized in intensive care units (46.3%) may be the reason for the low susceptibility rate of nitrofurantoin.

This study evaluated ESBL producing *E. coli* and *K. pneumoniae* isolates that cause UTI in hospitalized patients. The inability to determine whether or not infections are complicated or noncomplicated infections the limitation of this study. Carbapenems are the most effective antibiotics against the isolates. As in other studies, fosfomycin is a good alternative to carbapenems because ESBL producing *E. coli* and *K. pneumoniae* isolates are highly susceptible to fosfomycin. Nitrofurantoin was found to be more susceptible in *E. coli* isolates than *K. pneumoniae* isolates. The susceptibility rate to nitrofurantoin

in *K. pneumoniae* isolates is low compared to previous study. As a result, fosfomycin seen as a good alternative agent in UTIs caused by ESBL producing *E. coli* and *K. pneumoniae*, however nitrofurantoin should use in ESBL producing *E. coli* isolates for empirical treatment in our hospital.

Conflict of interest: There are no relevant conflicts of interest to disclose.

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