Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1240882

Anatolian Curr Med J 2023; 5(2); 97-101

Determination of antibiotic resistance rates of *Escherichia coli* and *Klebsiella pneumoniae* isolates, which are the causative agents of urinary tract infection in pregnant women

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Cite this article as: Aydoğmuş S, Kaya Kılıç E. Determination of antibiotic resistance rates of *Escherichia coli* and *Klebsiella pneumoniae* isolates, which are the causative agents of urinary tract infection in pregnant women. Anatolian Curr Med J 2023; 5(2); 97-101.

ABSTRACT

Aim: Urinary tract infections are common infections during pregnancy. Infections seen during pregnancy have a spectrum ranging from asymptomatic bacteriuria to cystitis, pyelonephritis and, urosepsis. In this study, it was aimed to determine the antibiotic resistance rates of *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) isolates isolated from urinary cultures of pregnant women who applied to the Ankara Training and Research Hospital.

Material and Method: The identification and antibiotic susceptibility of *E. coli* and *K. pneumoniae* isolates isolated from urinary samples of pregnant women who applied to the Ankara Training and Research Hospital between January 2021 and December 2022 were investigated with VITEK-2 (Biomerioux, France) fully automated system, and the presence of extended-spectrum beta-lactamase (ESBL) was investigated by combined disc diffusion method. The obtained data were analysed retrospectively.

Results: Bacterial growth was detected in 1090 (1.2%) out of a total of 8923 urine samples over a two-year period. 480 (4.4%) of the microbial agents reproducing in urine culture were *E. coli* and 105 (0.96%) were *K. pneumoniae*. The rate of extended-spectrum beta-lactamase (ESBL) in *E. coli* strains was 16.04% (77/480), and the rate of ESBL in *K. pneumoniae* strains was 20.9% (22/105). Resistance rates of amoxicillin-clavulanic acid, ceftriaxone, phosphomycin, ciprofloxacin, piperacillin-tazobactam, nitrofurantoin, imipenem, meropenem, ertapenem in ESBL negative *E. coli* strains were 15.9%, 8.82%, 20%, 11.1%, 5.88%, 0%, 0%, 0% and 0%, respectively. Resistance rates of amoxicillin-clavulanic acid, ceftriaxone, phosphomycin, ciprofloxacin, piperacillin-tazobactam, nitrofurantoin, imipenem, meropenem, ertapenem in ESBL positive *E. coli* strains were determined as 66.5%, 100%, 2.2%, 33.8%, 11.5%, 0%, 0%, 0% and, 0%, respectively. Resistance rates of amoxicillin-clavulanic acid, ceftriaxone, phosphomycin, ciprofloxacin, piperacillin-tazobactam, nitrofurantoin, imipenem, meropenem, ertapenem in ESBL negative *K. pneumoniae* strains were 53%, 100%, 12.5%, 28.5%, 2.2%, 3.5%, 0%, 0% and, 4.5%, respectively. Resistance rates of amoxicillin-clavulanic acid, ceftriaxone, phosphomycin, nitrofurantoin, ciprofloxacin, piperacillin-tazobactam, imipenem, meropenem, ertapenem in ESBL positive *K. pneumoniae* strains were 62.5%, 100%, 12.5%, 35%, 28.5%, 22.7%, 0%, 0% and, 4.5%, respectively.

Conclusion: According to the antibiotic susceptibility data in our hospital, phosphomycin or carbapenems may be preferred due to the low resistance rate in the empirical treatment of *E. coli*-related urinary tract infections in pregnant women. In the treatment of urinary tract infections due to *K. pneumoniae*, phosphomycin, piperacillin-tazobactam or carbapenems may be preferred due to low resistance rates.

Keywords: Pregnancy, urinary tract infection, *Escherichia coli*, *Klebsiella pneumoniae*, extended-spectrum beta-lactamase, antibiotic susceptibility

INTRODUCTION

Urinary tract infections are more common in women than men. Most urinary tract infections in women are asymptomatic urinary tract infections. While more than 60% of women have urinary tract infections throughout their lives, 10% of women may have urinary tract infections every year (1).

Anatomical and physiological changes during pregnancy are predisposing factors for urinary tract infections. The increase in uterine dimensions with pregnancy, facilitates urinary tract infections by causing stasis in the dilatation of urinary flow in the ureter and bladder with the effect of progesterone. Glucosuria, urine osmolality and changes in urine pH during pregnancy are also factors that predispose to urinary tract infections (2,3).

Escherichia coli (*E. coli*) is the most common cause of urinary tract infections in society and hospitals (4-6). Antibiotic resistance rates in *E. coli* strains may differ between countries, geographical regions and hospitals (2,4-7).

The main urinary tract infections seen in pregnant women are asymptomatic bacteriuria, cystitis, pyelonephritis. The most common cause of urinary tract infection in pregnant women is *E. coli* (2,3,8,9). While

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Received: 23.01.2023 **Accepted:** 07.02.2023

asymptomatic bacteriuria seen during pregnancy should be treated, asymptomatic bacteriuria that can be seen in non-pregnant women does not need to be treated (10).

In this study, it was aimed to determine the antibiotic resistance rates of *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*) bacteria isolated from the urine cultures of pregnant women who applied to Ankara Training and Research Hospital and to determine the appropriate empirical antibiotic treatment options.

MATERIAL AND METHOD

No human or animal material was used. It is the study of antibiotic resistance in bacteria. It does not require an ethics committee decision. Institutional approval has been obtained.

Urine samples of pregnant women who applied to Ankara Training and Research Hospital between January 2021 and December 2022 were incubated in 5% sheep-blooded agar and eosin methylene blue (EMB) agar medium with quantitative culture method at 37 ° C for 18-24 hours under aerobic conditions. Samples with single species and 105 colony forming units (CFU) reproduction in urine culture were evaluated. Only *E. coli* and *K. pneumoniae* isolates were included in the study. Identification and antibiotic susceptibility of *E. coli* and *K. pneumoniae* isolates isolated from urine samples were investigated with VITEK-2 (Biomerioux, France) fully automated system, and the presence of extended-spectrum beta-lactamase (ESBL) was investigated by the double-disc synergy method.

Double-Disc Synergy Test

For the test, bacterial suspension was prepared from colonies in fresh bacterial culture equal to 0.5 McFarland turbidity and transplanted into Mueller-Hinton Agar plaque. Three antibiotic discs [aztreonam (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg)] were placed 20 mm away from the center of the amoxicillin-clavulanic acid (20/10 µg) disc and incubated at 37°C for 24 hours (11,12). Antibiotic susceptibilities of isolated *E. coli* and K. pneumonia strains were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria (13). The obtained data were analysed retrospectively. Antibiotic resistance rates were calculated as %.

RESULTS

Results: Bacteria grew in 1090 (1.2%) of a total of 8923 urine samples over a two-year period. 480 (4.4%) of the factors reproducing in urine culture were *E. coli* and 105 (0.96%) were *K. pneumoniae*. The rate of extended-spectrum beta-lactamase (ESBL) in *E. coli* strains was 16.04% (77/480), and the rate of ESBL in *K. pneumoniae* strains was 20.9% (22/105).

In our study, phosphomycin, ceftriaxone and piperacillin-tazobactam resistance rates were found to be high in ESBL negative *E. coli* strains in pregnant women, while amoxicillin-clavunate, ciprofloxacin and piperacillin-tazobactam resistance rates were found to be high in ESBL positive *E. coli* strains, respectively. High resistance to ceftriaxone, amoxicillin-clavulanate, ciprofloxacin, and ertapenem were detected in ESBL negative *K. pneumoniae* strains, respectively, while high resistance to amoxicillin-clavulanate, nitrofurantoin, ciprofloxacin, and piperacillin-tazobactam was detected in ESBL positive *K. pneumoniae* strains, respectively.

ESBL rate and resistance rates to various antibiotics in *E. coli* and *K. pneumoniae* strains isolated from pregnant patients are shown in **Table**.

DISCUSSION

Urinary tract infections such as cystitis and pyelonephritis, especially asymptomatic bacteriuria, are the most common infections during pregnancy (1-3).

The Infectious Diseases Society of America (IDSA), the UK National Screening Committee and numerous international associations recommend urine culture screening during pregnancy and treatment of urinary tract infections, including asymptomatic bacteriuria (2,10,14).

Studies have reported that bacterial colonization of the urinary system during pregnancy may cause undesirable conditions due to renal infection, intrauterine growth retardation and preterm birth risks (10,15). In approximately 25% of the patients, asymptomatic bacteriuria may progress to symptomatic urinary tract infection (16).

Table. ESBL rate and resistance rates to various antibiotics in *E. coli* and *K. pneumoniae* strains isolated from pregnant patients (%)

Bacteria/antibiotic resistance rate	AMC	CRO	CIP	FF	NT	TZP	IMP	MEM.	ETP
ESBL negative *E. coli*, n:403	15.9	8.82	11.1	20	0	5.88	0	0	0
ESBL positive *E. coli*, n:77	66.5	100	33.8	2.2	0	11.5	0	0	0
ESBL negative *K. pneumoniae*, n:83	53	100	28.5	12.5	3.5	2.2	0	0	4.5
ESBL positive *K. pneumoniae*, n:22	62.5	100	28.5	12.5	35	22.7	0	0	4.5

(*) AMC: Amoxicillin/clavulanic acid, CRO: ceftriaxone, CIP: ciprofloxacin. NT: Nitrofurantoin, FF: Phosphomycin, TZP: Piperacillin-tazobactam, IMP: Imipenem, MEM: Meropenem, ETP: Ertapenem

Treatment of asymptomatic bacteria during pregnancy reduces the risk of pyelonephritis, hypertension and preterm birth in the mother. Second and third-generation cephalosporins, fosfomycin, nitrofurantoin, and sulfonamides at term in the treatment of urinary system infections during pregnancy, and piperacillin-tazobactam and carbapenems can be used in the treatment of infections caused by resistant Gram-negative bacteria (1). Increased antibiotic resistance in *E. coli* and *K. pneumoniae* isolates, which cause urinary tract infections, is an important problem in recent years (4-7).

E. coli is the most common cause of urinary tract infection in society, hospitals, pregnant women, and adults (1-9). In recent years, the increase in antibiotic resistance rates in *E. coli* and *K. pneumoniae* strains, the causative agent of urinary tract infection, has been an important problem (4,5). The increase in antibiotic resistance rates makes it difficult to choose in empirical antibiotic treatment and causes the failure of treatment (1,2,5,11). In international guidelines, it has been recommended to determine local antibiotic resistance rates in the selection of empirical antibiotic treatment and not to use antibiotics with a resistance rate of more than 20% in empirical treatment (1,2,17).

In a meta-analysis study, the resistance rate of trimethoprim-sulfamethoxazole (TMP-SMZ) in *E. coli* strains was reported to be approximately 30% in China and South Korea, and above 15% in Europe and Mediterranean regions. It has been reported that the reason for the low TMP-SMZ resistance rate in Europe may be due to the low prescription of this drug (7).

Rosana et al. (9) In a study conducted on pregnant women in Indonesia, asymptomatic bacteriuria was detected in 10.5% of 715 pregnant women. The most common causes of urinary tract infection were determined as *E. coli* (26.7%), *K. pneumoniae* (20%) and Streptococcus agalactiae (9.3%), respectively. In the study, no phosphomycin resistance was detected in ESBL positive *E. coli* isolates, while resistance to trimethoprim/sulfamethoxazole was reported at 40% and piperacillin-tazobactam at 20%. In the study, no side effects were observed in pregnant women and new-borns who started phosphomycin with the diagnosis of urinary tract infection, and it was reported that phosphomycin was an appropriate option in the treatment of pregnant women.

In our study, 25% resistance was detected in ESBL-negative *E. coli* isolates and 2.2% resistance was detected in ESBL-positive *E. coli* isolates, while 11.1% resistance was detected in ESBL-negative *E. coli* isolates for piperacillin-tazobactam, and no resistance was detected in ESBL-positive *E. coli* isolates.

Lee et al. (8) reported urinary tract infection in 8.9% (4.4% symptomatic urinary tract infection, 4.5% asymptomatic bacteriuria) of pregnant women in a study conducted in Bangladesh. In the study, the frequency of urinary tract infection factors were reported as *E. coli* (38%), staphylococci (23%), *Klebsiella* species (spp.) (12%) and Group B streptococci (5.3%), respectively. In the study, ceftriaxone resistance was reported as 21.1%, trimethoprim/sulfamethoxazole (TMP/SMZ) resistance as 37.3% and nitrofurantoin resistance as 0.8% in *E. coli* strains. In the same study, ceftriaxone resistance was reported as 11.4% nitrofurantoin resistance as 25.7% and TMP/SMZ resistance as 2.8% in *Klebsiella* spp.

The bacteria that secrete the extended-spectrum beta-lactamase enzyme (ESBL) the most are *E. coli* and *K. pneumoniae*. Turkey is one of the countries where infections due to ESBL-producing *E. coli* and *K. pneumoniae* isolates are common all over the world.

In the Hitit University's multi-center study conducted by Gür et al. (18), ESBL rates in *E. coli* and *Klebsiella pneumoniae* isolates were reported as 42% and 41.4%, respectively. In our study, the ESBL rates we found in *E. coli* and *Klebsiella pneumoniae* isolates were 16.04% and 20.9%, respectively, and were lower than the rates reported by Gür et al. In the study of Gür et al., no imipenem resistance was detected in *E. coli* strains, while ciprofloxacin resistance was reported to be 58%. In the same study, imipenem resistance was reported as 3.1% and ciprofloxacin resistance as 17.8% in *K. pneumoniae* isolates.

In our study, no resistance to imipenem, meropenem and ertapenem was detected in *E. coli* isolates, and the resistance rate to ciprofloxacin was determined as 11.1% in ESBL negative *E. coli* isolates and 33.8% in ESBL positive *E. coli* isolates. In our study, ESBL positive and ESBL negative *K. pneumoniae* isolates showed 4.5% resistance to carbapenem group, while no resistance to imipenem and meropenem was detected. In ESBL positive and ESBL negative *K. pneumoniae* isolates, ciprofloxacin resistance was determined as 28.5%.

In studies conducted in our country, ciprofloxacin resistance rates in *E. coli* strains have been reported between 36.5% and 43%, and phosphomycin resistance rates have been reported between 4-15% (19-23).

Avcıoğlu et al. (21) In their retrospective study on 1466 *E. coli* isolates, they reported resistance to amoxicillin/clavulanic acid by 42%, nitrofurantoin and phosphomycin by 4%, ciprofloxacin by 41%, and imipenem by 2%. In our study, unlike this study, no imipenem resistance was detected in *E. coli* strains, while our quinolone resistance rate was lower than the rate reported in this study.

Bayram et al. (22) found ESBL positivity in 30% of the strains in their study on 375 *E. coli* strains. In the study, no imipenem and meropenem resistance was detected in ESBL-positive and ESBL-negative *E. coli* strains; ESBL-positive and ESBL-negative *E. coli* strains reported resistance to phosphomycin at 15% and 5%, respectively; and nitrofurantoine at 18% and 10%. In our study, no nitrofurantoin resistance was detected in ESBL positive and ESBL negative *E. coli* strains, while resistance to phosphomycin was found in ESBL positive and ESBL negative *E. coli* strains by 2.2% and 20%, respectively.

Tekin et al. (23) In their in vitro study on 3279 *E. coli* strains, they detected phosphomycin resistance in ESBL positive *E. coli* strains by 5.7%, while they did not report resistance in ESBL negative *E. coli* strains. In the same study, the ciprofloxacin resistance rate in *E. coli* strains was reported as 58.9%.

In our study, the ciprofloxacin resistance rates we found in ESBL positive and ESBL negative *E. coli* isolates were 33.8% and 11.1%, respectively, and were lower than the resistance rates in the studies conducted in our country. This may be due to the fact that quinolone group antibiotics cannot be used in pregnant women because they are contraindicated.

Asgın et al. (2) In their study on pregnant women diagnosed with urinary tract infection in Karabuk province, they reported that the most frequently isolated bacteria from urine culture were *E. coli* (567), Streptococcus agalactiae (11%) and *K. pneumoniae* (9%), respectively. In the study, ESBL rate in *E. coli* and *K. pneumoniae* strains was reported as 8% and 13%, respectively. In this study, the ESBL rate reported in *E. coli* and *K. pneumoniae* strains was lower than the rates reported by Gür et al. (18).

Aşgın et al. (2) reported phosphomycin resistance in *E. coli* and *K. pneumoniae* strains as 3% and 17%, nitrofurantoin resistance as 3% and 8%, ciprofloxacin resistance as 5% and 0%, amoxicillin/clavulanic acid resistance as 53% and 92%, respectively. In the study, it was reported that phosphomycin and nitrofurantoin were appropriate options due to the low resistance rates in the treatment of urinary tract infections in pregnant women in Karabük province.

In our study, ceftriaxone, phosphomycin and carbapenems may be preferred due to the low resistance rate in the empirical treatment of urinary tract infections due to ESBL negative *E. coli*n pregnant women in our hospital. In the treatment of infections due to ESBL positive *E. coli*, phosphomycin may be preferred due to low resistance rates, and phosphomycin and carbapenems may be preferred due to lack of resistance. Piperacillin-tazobactam, nitrofurantoin and ertapenem may be preferred in the treatment of urinary tract infections due to ESBL negative *K. pneumoniae* due to low resistance rates, and imipenem and meropenem may be preferred due to the absence of resistance. In the treatment of urinary tract infections due to ESBL positive *K. pneumoniae*; ertapenem and phosphomycin can be used due to low resistance rates, and imipenem and meropenem can be used due to lack of resistance.

One limitation of our study was that it was not known whether *E. coli* and K.pneumoniae strains were community- acquired or nosocomial.

CONCLUSION

As a result, determining the distribution of urinary tract infection factors and antibiotic susceptibility in pregnant women will guide clinicians in the initiation of appropriate empirical treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: No human or animal material was used. It is the study of antibiotic resistance in bacteria. It does not require an ethics committee decision. Institutional approval has been obtained.

Informed Consent: No human or animal material was used. It is the study of antibiotic resistance in bacteria. It does not require an informed consent.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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