Antimicrobial Resistance of 615 *Escherichia coli* Isolated from Complicated and Non-Complicated Urinary Tract Infections

Komplike ve Non-Komplike Üriner Sistem Enfeksiyonlarından İzole Edilen 615 *Escherichia coli* Suşunda Antimikrobiyal Direnç

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ABSTRACT Objective: *Escherichia coli* strains are the most common pathogens of urinary tract infections (UTI) and are capable of producing "extended spectrum beta-lactamases" (ESBL). Since high ciprofloxacin resistance has been emerging recently among *E.coli* strains, this study is aimed to investigate ESBL production and antibiotic resistance pattern including ciprofloxacin, in 615 *E.coli* strains isolated from complicated and uncomplicated UTIs and differences between two groups. **Material and Methods:** The antimicrobial susceptibility testing for ciprofloxacin, trimethoprim-sulfamethoxazole, amoxicilline-clavulanate, amikacin, piperacilline-tazobactam and imipenem/meropenem was performed using Kirby-Bauer disc diffusion method according to Clinical and Laboratory Standards Institute (CLSI) rules. ESBL presence was investigated with double disc diffusion method. Antibiotic susceptibilities of complicated and uncomplicated group with UTI were compared statistically using Fisher's chi square test. **Results:** *E.coli* strains were isolated from 333 of 2458 patients with uncomplicated UTI and 282 of 2098 patients with complicated UTI. ESBL presence was in 13% and 20%, and ciprofloxacin resistance was 38% and 46% in uncomplicated and complicated groups, respectively. ESBL presence in ciprofloxacin resistance strains was 25% in uncomplicated group and 40% in complicated group. ESBL ratio in ciprofloxacin-susceptible strains was 4% in both groups. Statistically, ESBL production in ciprofloxacin resistance strains was higher in the complicated group ($p< 0.05$). **Conclusion:** Antibiotic resistance in pathogens which are responsible from UTIs is emerging worldwide. We found that ESBL production in ciprofloxacin resistant *E.coli* strains was significantly higher in the complicated group. This may result from misuse and injudicious use of antimicrobials, especially ciprofloxacin. Nowadays, ESBL producing multidrug resistant *E.coli* strains are in community as a new challenge emerged for clinicians to overcome.

Key Words: Urinary tract infections; community-acquired infections; *Escherichia coli*; beta-lactamases; ciprofloxacin

ÖZET Amaç: *Escherichia coli* suşları üriner sistem enfeksiyonlarında (UTI) en sık gözlenen patojendir ve genişlemiş spektrumlu beta laktamaz (GSBL) üretme yeteneğine sahiptirler. Yakın zamanlarda *E.coli* suşlarında yüksek siprofloksasin direnci gözlenmeye başlandığından bu çalışma komplike ve non-komplike üriner sistem enfeksiyonlarından elde edilen 615 *E.coli* suşunun GSBL üretimi ve siprofloksasini de içeren antibiyotik direnç paternini ve iki grup arasındaki farklılıkları belirlemeyi amaçlamaktadır. **Gereç ve Yöntemler:** Kirby-Bauer disk difüzyon metoduyla siprofloksasin, trimetoprim-sulfametoksazol, amoksisilin-klavulanat, amikasin, piperasilin-tazobaktam ve imipenem/meropenem kullanılarak Klinik ve Laboratuarlar Standartları Enstitüsü (CLSI) kuralları çerçevesinde antimikrobiyal duyarlılık testi uygulandı. GSBL varlığı çift disk difüzyon metoduyla araştırıldı. Komplike ve komplike olmayan UTI grupları Fisher'in kesin ki-kare yöntemiyle karşılaştırıldı. **Bulgular:** Komplike olmayan UTI grubunda 2458 olgudan 333'ünde, komplike olan UTI grubunda 2098 olgudan 282'sinde *E. coli* suşları izole edildi. Non-komplike ve komplike grupta sırasıyla GSBL varlığı %13 ve %20; siprofloksasin direnci %38 ve 46 idi. Siprofloksasin direnci olanlarda ESBL sıklığı non-komplike grupta %25, komplike grupta ise %40 bulundu. Siprofloksasine duyarlı olan suşlarda GSBL oranı her iki grupta da %4 idi. Siprofloksasine dirençli suşlarda GSBL üretimi, komplike grupta istatistiksel olarak daha yüksek bulundu ($p< 0.05$). **Sonuçlar:** Üriner sistem enfeksiyonlarından sorumlu patojenlerde antibiyotik direnci dünya çapında artmaktadır. Çalışmamızdaki sonuçlara göre, komplike üriner sistem infeksiyonlarından izole edilen ve siprofloksasine dirençli *E.coli* suşlarında GSBL üretimi, non-komplike gruptan yüksektir. Bu durum, siprofloksasin başta olmak üzere antibiyotiklerin uygunsuz ve gereksiz kullanımından kaynaklanabilir. Günümüzde, toplumda klinisyenlerin çözmesi gereken yeni bir sorun olarak GSBL üreten çok ilaca dirençli *E.coli* suşları artmaktadır.

Anahtar Kelimeler: Üriner kanal enfeksiyonları; toplumdan-edinilmiş enfeksiyonlar; *Escherichia coli i*; beta-laktamazlar; siprofloksasin

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Urinary tract infections (UTIs) are the most common infections in both community and hospital settings, and about 150 million people are diagnosed with UTI costing billions of dollars each year.[1,2] UTIs treatment is usually initiated empirically with respect to age, gender, underlying co-morbidities, responsible agent and existence of lower or upper urinary tract involvement due to time consuming culture procedures.

E.coli is responsible for 80% of community-acquired UTIs and it is an important microorganism for complicated UTIs.[3] In the last 25 years, flouroquinolones are in use for treatment of both community and hospital-acquired UTIs largely, because of their favorable pharmacological profiles and high activities against most of the clinically important members of Enterobactericeace,[4] however, more recently resistance to ciprofloxacin and levofloxacin has been on increase.[5]

ESBL producers are the most difficult agents to overcome due to multiple drug resistance including beta lactams and flouroquinolones. Prior antibiotic exposure, especially ciprofloxacin, urinary catheter or previous hospitalization are well-known predisposing factors for production of ESBL. It is therefore important to follow-up antibiotic resistance profiles in both the local settings and community in order to compose an empiric approach to the management of UTIs. We aimed to investigate antibiotic susceptibility and ESBL presence of *E. coli* strains isolated from urine samples of the patients with complicated and uncomplicated UTI in our hospital.

MATERIAL AND METHODS

PATIENTS

Patients between 2-70 years of age and with symptoms of UTI were included in this study. Patients with at least one complicating factor as follows were assessed as having complicated UTI: Male gender, current bladder instrumentation, obstructive uropathy, urogenital surgery or a functional or anatomical urogenital tract abnormality.[6] Only a single positive culture per patient was included in the analysis.

DATA COLLECTION

Data were collected on 615 positive cultures of 4556 urine cultures from our hospital laboratory records for a period of 12 months, between 2007 and 2008, and were evaluated retrospectively.

LABORATORY METHODS

Clean-catch urine samples obtained from patients were inoculated onto chocolate agar and Mc Conkey agar with 0.01 ml calibrated loops by semi-quantitative technique in our laboratory. Culture plates were incubated at 35-37°C for 18-24 h. The isolated bacteria were identified by conventional methods. All isolates were classified according to whether they were isolated from a complicated or an uncomplicated UTI. The antimicrobial susceptibility testing for amoxicillin/clavulanate, gentamicin, trimethoprim-sulfamethoxazole (SXT), nitrofurantoin, cefuroxime, ceftriaxone, ciprofloxacin, cefoperazone-sulbactam and meropenem was performed on Mueller Hinton agar (Oxoid®, UK) with Oxoid® discs using Kirby-Bauer disc diffusion method according to Clinical and Laboratory Standards Institute (CLSI) rules.[7] Nitrofurantoin was also tested for uncomplicated UTI. ESBL presence was detected with double-disc synergy method using ceftazidime and amoxicilline-clavulanate discs. Discs were placed 25 mm (centre to centre of the discs) from the amoxicilline-clavulanate disc. After overnight incubation at 37°C, a clear extension of the edges of the inhibition zone of any of the antibiotics towards the disc containing clavulanic acid was regarded as a phenotypic confirmation of the presence of ESBL.[8] All antibiotic discs were obtained from Oxoid, UK. *E.coli* ATCC 25922 was used for growth control.

STATISTICAL METHODS

All data input and statistical analysis were made by using SPSS 17.0 Windows program (SPSS, Chicago, IL, USA) that is licensed to our institution. We investigated the difference between complicated and uncomplicated group in terms of ESBL presence in ciprofloxacin-resistant isolates by Chi-square test (Fisher's exact test), and a p value <0.05 was accepted as a significant difference.

RESULTS

A total of 4556 samples were delivered to our laboratory during the 12-months study period (2458 urine samples of patients with uncomplicated UTI, and 2098 urine samples of patients with invasive intervention to urinary tract, complicated UTI). A total of 615 *E.coli* strains were isolated from the samples (13.5%); 333 of *E.coli* isolates originated from uncomplicated and 282 from complicated UTI samples. Patients' ages ranged between 1-98 (median 36.07 ± 13.55) years. Female/male ratio was 3.2 (470/145) among all patients while it was 1.9 among patients with complicated UTI. Recurrent UTI (49%), functional or anatomical urogenital tract abnormalities (19%), obstructive uropathy (9%) and urogenital surgery (9%) were the most frequent underlying comorbidities in patients with complicated UTI. Previous ciprofloxacin and ceftriaxone use were found in 9% and 2% of complicated patients.

The antimicrobial susceptibilities and ESBL presence of 615 *E.coli* isolated from uncomplicated and complicated patients are shown in Table 1.

ESBL production was found in 56 complicated (20%) and in 42 uncomplicated (13%) patients with UTI. ESBL production was significantly higher in complicated group ($p< 0.05$). ESBL presence was compared between two groups according to ciprofloxacin susceptibilities. ESBL production prevalence was high among *E.coli* isolates resistant to ciprofloxacin that originated from complicated UTI samples (40%) while this rate was 25% in isolates from uncomplicated group. Figure 1 shows ESBL rates of both groups according to ciprofloxacin susceptibilities. On the other hand, ciprofloxacin resistance was 83% and 32% in ESBL producing and non-producing strains, respectively and it was significantly higher in former group ($p< 0.05$).

DISCUSSION

Antimicrobial resistance of bacteria has been emerging as a global problem especially in Gram negative microorganisms. Inappropriate antibiotic use results in antimicrobial resistance. It is known that pathogenic isolates of *E.coli* incline to be resistant against antimicrobials. The resistance rates in local settings should be considered, since empirical antibiotics are administered for UTI. Most of the patients with UTIs are treated empirically. Antimicrobial susceptibility testing of uropathogens aims to estimate the rates of resistance. However, antibiograms are usually performed when empirical treatment becomes ineffective or patients have underlying co-morbidities.[9] In developing countries, patients undergo a urine analysis only in case of repeated or complicated UTI. Empirical antibiotic policies should be formulated according to local surveillance data in order to prevent increasing resistance to drugs which are used for treatment of UTIs.[10,11] UTIs are classified as uncomplicated and complicated infections based on the host condition.[12] In our laboratory, urine samples from patients with uncomplicated and complicated UTIs are evaluated separately and uropathogenic *E.coli* isolates have been followed up for years in terms of antimicrobial resistance especially for common agents that are used for UTI treatment. This study revealed the susceptibility patterns of *E.coli* isolates to antimicrobial agents that are the most commonly used for empirical treatment of UTIs.

It is stated that UTIs are mostly seen in women due to anatomic factors such as short urethra and proximity of urethra to anus.[13,14] In this study, there

TABLE 1: Extended spectrum beta lactamase positivity and antimicrobial resistance rates of 615 *E.coli* isolates (%).

	AMC	CN	SXT	F	CXM	CRO	CIP	SCF	MEM	ESBL positivity
Uncomplicated	24	23	44	11	29	23	38	15	0	13
Complicated	26	28	57	13	39	31	46	11	0	20
Total	25	25	50	12	34	27	42	13	0	16

AMC: Amoxicillin-clavulonic acid, CN: Gentamicin, SXT: Trimethoprim- Sulfamethoxazole, F: Nitrofurantoin, CXM: Cefuroxime, CRO: Ceftriaxone, CIP: Ciprofloxacin, SCF: Cefoperazone-Sulbactam, MEM: Meropenem.

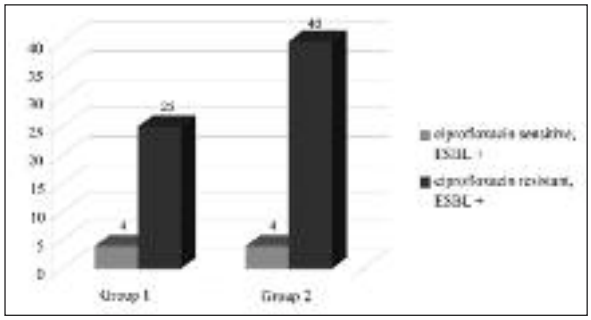

FIGURE 1: ESBL positivity in *E.coli* isolates originated from non-complicated (Group 1) and complicated (Group 2) groups according to ciprofloxacin susceptibilities.

was a female dominance in patients with both complicated and uncomplicated UTIs, similar to these previous reports (68% and 78%, respectively).

High resistance rates of *E.coli* strains to numerous antimicrobial agents were observed in the present study. Resistance rates were comparably higher in complicated UTI group compared the other group. In general, about half of all strains were resistant to SXT. There were also high resistances to some antibiotics such as ciprofloxacin (42%), cefuroxime (34%) and ceftriaxone (27%), which are the most frequently used agents for empirical treatment of UTI in Turkey. In 1999, the Infectious Diseases Society of America recommended alternative therapies for uncomplicated UTI in women due to SXT resistance rates ≥ 10-20% in urinary pathogens isolated from female outpatients in the United States, and these rules still remain valid.[15,16] This recommendation resulted in increased antimicrobial resistance rates against the other agents, such as amoxicillin/clavulanate, cephalosporins and quinolones, in urinary pathogens. There are many reports from Turkey and other countries that highlighted the high resistance rates to cephalosporins, SXT or quinolones, and the emergencence of multidrug resistant *E.coli* isolates.[13,17-20] However, in a recent report, resistance rate of ciprofloxacin (%19) in *E.coli* isolates that were obtained from patients with uncomplicated UTI was detected relatively lower than the other reports from Turkey.[20] Aboderin et al.[21] cited that except for nitrofurantoin, resistance of *E.coli* isolates against to amoxicillin, gentamicin, SXT, tetracycline and ciprofloxacin is increasing. Similar to these results, nitrofurantoin was the most active oral agent in our study. Boyd et al.[22] revealed that floroquinolone resistance has been increasing day by day and it is probably related with consumption of the agent. However recent studies have shown that the spread and increase of quinolone resistance is due to plasmid-mediated resistance mechanism. In 1998, Martinez-Martinez et al. reported the first plasmid mediated quinolone resistance determinant (qnrA) in a multiresistant *Klebsiella pneumoniae* in the world, and Nazik et al.[23] reported the first plasmid mediated quinolone resistance in our country in 2005. Poirel et al.* found a plasmid mediated quinolone resistance determinant (aac(6')-Ib-cr) in 78% of ESBL producing *E.coli* and *K.pneumoniae* isolates in Turkey. There for, plasmid mediated quinolone resistance in addition to existing high resistance rates may cause restriction of quinolone usage in most of infections.

According to antibiotic policy in Turkey, hospitalization of patients to administer parenteral drugs increases bed occupation rates, hospital infections and costs. Therefore, oral agents are preferred for empirical treatment of UTIs in Turkey, and this approach results in increasing resistance rates for these oral agents. In this study, with the exception of nitrofurantoin, resistance to agents commonly used as empirical oral treatments for UTIs was extremely high. Resistance rates of trimethoprim and ciprofloxacin render them unsuitable for empiric therapy. In a study reported from Turkey in 2007, 53% of hospital and 29% of community acquired *E.coli* isolates were resistant to SXT.* These reports suggest disutility of SXT for empirical treatment of UTI.[24,25]

Prior antibiotic exposure, especially ciprofloxacin, urinary catheterization or previous hospitalization are well-known predisposing factors for production of ESBL. Yilmaz et al.[26] compared two groups of patients with UTIs due to ESBL-positive and negative *E.coli* and *K.pneumoniae in our coun-*

* *Poirel L, Gür D, Minarini L, Arslan U, Nordmann P. Molecular epidemiology of plasmid mediated quinolone resistance determinants in extended spectrum beta-lactamase producing E.coli and K.pneumoniae isolates from Turkey. 18th European Congres of Cilinical Microbiology and Infectious Diseases. Barcelona, 2008. P1527.*

try. The presence of previous urological operation and quinolone or cephalosporin use for any infection during the last three months were found as independent risk factors in their study.[26] In addition to high rates of resistance to ciprofloxacin and SXT in this study, ESBL production was ascertained in 99 (16%) of all isolates. ESBL existence was 13% in uncomplicated patients while it was found as 20% in complicated patients. ESBL production was significantly higher in complicated group ($p<0.05$). In this study, this group was composed of patients with similar predisposing factors with the study of Yilmaz et al.[26] When ciprofloxacin susceptibility, was taken into consideration, ESBL production was extremely higher in ciprofloxacin resistant isolates originated from patients with complicated UTI (40%) compared to isolates originated from uncomplicated ones (25%). In ciprofloxacin susceptible strains, ESBL rate was 4% in both groups. These results may be related to frequent usage of ciprofloxacin due to recurrent UTIs or colonization of resistant and ESBL producing pathogens after urinary tract instrumentations in complicated group. In a recent study reported from Iran, ESBL production was found in 29% of uropathogenic *E.coli* isolates and 61% of them had ciprofloxacin resistance.[27] They concluded that relatively high frequency of ESBL production and multidrug resistance were seen in uropathogens, and it seems that this is likely to be due to misuse of antibiotics in this area. We believe that, similar reasons resulted in multidrug resistant *E.coli* isolates especially accompanying with high ciprofloxacin resistance in our country. In a previous multicenter report from Turkey, the most frequent risk factor for ciprofloxacin resistance among uropathogenic *E. coli* isolates was found as previous ciprofloxacin usage.[28] In addition, ESBL producing isolates are extremely high locally and this is an important problem in some regions of the world such as Turkey. Kadar and Angamathu[29] reported ESBL production as high as our results (40%) among *E. coli*, *K.pneumoniae* and other Gram negative microorganisms. Another study, which was carried out in Sudan, revealed that ESBL production was found in 53% of *E.coli* and *K.pneumoniae* isolates.[8]

In this study, all isolates that belong to complicated and uncomplicated groups were susceptible to carbapenems. We concluded that carbapenems are still the single choice for treatment of UTIs caused by both ciprofloxacin resistant and ESBL producing *E.coli* isolates, according to our results in our hospital. Since high prevalence of ESBL producing *E.coli* was found in ciprofloxacin resistant *E.coli* isolates in the present study, we suggested a relation between ciprofloxacin resistance and ESBL production in *E.coli* isolates. ESBL producing *E.coli* isolates were found more resistant to the other frequently used agents in UTI treatment in complicated group. Among ciprofloxacin susceptible isolates, ESBL production was extremely low in both complicated and uncomplicated groups (4%) whereas it was significantly high among ciprofloxacin resistant isolates (25% and 40%, respectively). Therefore, ciprofloxacin use is thought to be a major predisposing factor for ESBL production among *E.coli* isolates in our hospital.

In conclusion, antibiotic resistance in pathogens which are responsible for UTIs is emerging worldwide. Misuse of frequently used antimicrobials resulted in multidrug resistant strains that are responsible for hospital acquired UTIs, however injudicious use of rest of the antibiotics may result in an increase in ESBL producing multidrug resistant *E.coli* that causes to community-acquired UTIs, and may emerge a new challenge for clinician to overcome.

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