URINARY INFECTION
Original Article

The resistance rates of urinary tract infections: Our data from year 2010

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ABSTRACT

Objective: More than 95% of all urinary tract infections are caused by a single bacterium. Although *E. coli* is the most common bacterium causing community-acquired infections, *Klebsiella* spp., enteric gram-negative bacteria and *S. saprophyticus* have been also identified. This study evaluated the microorganisms isolated from the urine cultures of patients admitted to our outpatient clinics in 2010 and assessed *E. coli* resistance and the frequency of extended-spectrum beta lactamase (ESBL)-producing bacteria.

Material and methods: In total, 7145 urine cultures were obtained from patients admitted to all clinics between 1 January 2010 and 31 December 2010. The double-disk synergy test was used to identify the presence of ESBL producers.

Results: The most frequently isolated microorganisms were *E. coli* (60.6%), *Enterococcus spp.* (10.3%), *Klebsiella spp.* (7.3%), *Pseudomonas spp.* (4.8%), and *Streptococcus spp.* (3.3%). *E. coli* strains were more resistant to ciprofloxacin (45.12%), trimethoprim-sulfamethoxazole (44.8%) and amoxicillin-clavulanate (31.6%), but they were less likely to be resistant to meropenem (0%), imipenem (0.2%), and amikacin (0.7%). The frequency of ESBL-producing *E. coli* strains was 14%.

Conclusion: The choice of antibiotic treatment influences the overall success of treatment and the development of resistance, and it is also closely related to the cost of the treatment. As a result, there is a need to review the current treatment protocols. As resistance rates show regional differences, it is necessary to regularly examine regional resistance rates to determine the appropriate empiric antibiotic treatment and reduce costs.

Key words: *E. coli*; extended-spectrum beta lactamase; urine culture.

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Introduction

Urinary tract infections (UTIs) take the place near the top among nosocomial, and community-acquired infections.[1,2] More than 95% of UTIs are usually caused by a single etiological agent.[2,3] UTIs are among the most frequently seen infectious diseases in the elderly, children, and especially in young women.[4] In the development of UTI, bacterial virulence is an important factor, however patient-related etiologies as old age, pregnancy, gender, presence of vesicoureteral reflux, status of the immune system, and urinary catheterization are also significant.[5] In community-acquired UTIs, *E.coli* is the most frequently encountered pathogen, however *Klebsiella spp.* other enteric bacteria, and *S. saprophyticus* are also seen.[2,3,6,7] As a pathogenic agent of UTI, gram-negative bacteria belonging to the *Enterobacteriacea spp.* are responsible for more than 70% of the urinary tract infections.[8]

Gradually increasing rates of development of resistance against frequently used antibacterial drugs have become more and more important health problem with time.[4] This developing resistance is transferred among species of bacteria.[1] Because of this important issue of resistance, identification of the antibiotic susceptibilities of the infectious agents aids in the treatment of infections.[2]

Extended- spectrum beta-lactamases (ESBLs) manifest themselves with point mutations in amino acids. Beta-lactamases produced by gram-negative bacteria, hydolyze beta-lactamase ring which inactivates beta-lactam antibiotics.[1,9,10] *E. coli,* and *Klebsiella spp.* belonging to the *Enterobacteriacea* family rank on top in terms of ESBL production.[10]

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Therefore, determination of antibiotic susceptibilities of UTI pathogens, and also ESBLs are important in order to achieve successful treatment outcomes.[1]

Material and methods

Blood samples of 7145 patients sent to Microbiology Laboratory of Merdivenköy Outpatient Clinics of Göztepe Training and Research Hospital between January 1, and December 31, 2010 were included in the analysis.Midstream urine samples were implanted using quantitative methods on 5% sheep blood agar, and McConkey Agar media contained in sterile urine containers. Under aerobic conditions, following 18-24 hours of incubation at 37°C, urine samples with growth of ≥100.000 CFU /mL were accepted as the presence of urinary tract infection. The isolated strains were identified using classical methods. Antibiograms of *E. coli* were evaluated using Kirby-Bauer disk diffusion method in Müller-Hinton agar in line with recommendations of NCCLS. Rates of resistance to amikacin, amoxicillin-clavulanate, gentamicin, imipenem, meropenem, nitrofurantoin, piperacillin-tazobactam, cefazolin. cefepime, cefaperazone-sulbactam, cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, trimethoprim-sulfamethoxazole were estimated.

Double-disk synergy test was used to identify the presence of extended-spectrum beta-lactamase enzyme. To that end, in the center of the Müller- Hinton agar, amoxicillin-clavulanate (20/10 μg) disk, and 20 mm away from its center ceftazidime (30 μg), ceftriaxone (30 μg), cefotaxime (30 μg), and aztreonam (30 μg) disks were placed. Enlargement of inhibition zone of any disk facing amoxicillin-clavulanate disk was evaluated in favour of ESBL positivity.[11]

Statistical analysis

Descriptive method was used for statistical analysis. In the analysis of data, "SPSS for Windows 15" package program was employed. In descriptive statistics, continuous variables were expressed as mean ± standard deviation, and categorical variables as percentages (%).

Results

In our study, urine cultures of a total of 7145 [4884 (68.4%) females, and 2261 males] patients were evaluated. In urine cultures of 1210 (24.8%) female, and 471 (20.8%) male patients bacterial growth was detected. In 1681 urine samples a total of 1715 microorganisms were grown. In 98% of the samples, only one strain grew. In urine cultures of 17 female, and 17 male patients only two strains grew. Bacterial growth rates in female, and male patients are summarized in Table 1.

In the urine samples of the female patients, most frequently isolated microorganisms were *E. coli* (65.1%), *Enterococcus spp.* (9.9%), *Klebsiella spp.* (6.8%), streptococci (4.4%), and *Candida spp.* (2.9%) in order of decreasing frequency. The most frequently isolated microorganisms in urine samples of male patients were *E. coli* (48.1%), *Enterococcus spp.* (11.2%), *Pseudomonas spp.* (10.1%), *Klebsiella spp.* (8.3%), and *Enterobacter spp.* (5.1%) In all urine cultures the most frequently grown microorganism was *E.coli* (60.6%). The distribution of isolated microorganisms grown in urine cultures according to gender is seen in Table 2.

Any resistance of *E. coli* strains to meropenem was not detected. Minimal resistance was detected against imipenem (0.2%), amikacin (0.7%), piperacilin-tazobactam (1.2%), and cefoperazone-sulbactam (1.4%). In our study, *E. coli* strains demonstrated maximal resistance (45.1%) against ciprofloxacin. Microorganisms were also resistant to trimetoprim-sulfamethoxazole (44.8%), amoxicillin-clavulanate (31.6%), cefazolin (29.2%), and gentamicin (24.4%). Antibiotics least effective on *E. coli* strains are shown in Table 3. One of enterococcal strains isolated from one of the female patients, resistance to vancomycin was detected. In our study, rate of resistance of *E.coli* strains to ESBL was found to be 14 percent.

Discussion

UTIs which are the most frequently seen infectious diseases, are important in that they lead to loss of productivity, and higher treatment expenditures.[1] Antibiotic resistance because of inappropriate antibiotic use has become increasingly encountered health problem.[4]

Kaya et al.[12] applied a survey study on 47 primary care physicians working in the primary health care centers in the city center of Sivas, and concluded that these physicians had encountered mostly UTIs, after respiratory tract infections.All the physicians participated in the survey indicated that they had devoid of facilities of performing urine cultures. In the empirical treatment of acute cystitis, 66% of the participating physicians stated that they had preferred to use trimethoprim-sulfamethoxazole

Table 1. Urine culture results according to gender of the patients

	Female patients (n=4884) (%)	Male patients (n=2261) (%)	Total (n=7145) (%)
No growth	3674 (75.2%)	1790 (79.2%)	5464 (76.5%)
Evidence of growth	1210 (24.8%)	471 (20.8%)	1681 (23.5%)
Growth of a single bacterium	1193 (98.6%)	454 (96.4%)	1647 (98.0%)

Table 2. Distribution of microorganisms grown in urine cultures

	Female patients (n=1227) (%)	Male patients (n=488) (%)	Total (n=1715) (%)
E. coli	799 (65.1%)	240 (49.1%)	1039 (60.6%)
Enterococcus spp.	121 (9.9%)	55 (11.2%)	176 (10.3%)
Klebsiella spp.	84 (6.8%)	41 (8.3%)	125 (7.3%)
Pseudomonas spp.	32 (2.6%)	50 (10.1%)	82 (4.8%)
Streptokoklar	54 (4.4%)	2 (0.4%)	56 (3.3%)
Enterobacter spp.	20 (1.6%)	25 (5.1%)	45 (2.6%)
Candida spp.	36 (2.0%)	8 (1.5%)	44 (2.6%)
Proteus spp.	24 (2.0%)	13 (2.6%)	37 (2.2%)
Citrobacter spp.	16 (1.3%)	18 (3.6%)	34 (2.0%)
MSCNS*	17 (1.4%)	13 (2.6%)	30 (1.7%)
MRCNS**	9 (0.7%)	9 (1.7%)	18 (1.0%)
MSSA***	4 (0.3%)	3 (0.6%)	7 (0.4%)
Acinetobacter spp.	2 (0.2%)	5 (1.0%)	7 (0.4%)
MRSA****	4 (0.3%)	2 (0.4%)	6 (0.3%)
Morganella spp.	2 (0.2%)	2 (0.4%)	4 (0.2%)
S. maltophilia	-	2 (0.4%)	2 (0.1%)
Haemophilus spp.	2 (0.2%)	-	2 (0.1%)
Serratia spp.	1 (0.1%)	-	1 (0.1%)
Total:	1227 (100%)	488 (100%)	1715 (100%)

*MSCNS, Meticilline-susceptible coagulase negative staphylococci; **MRCNS, Meticilline-resistance coagulase negative staphylococci,***MSSA, Meticilline-susceptible *S. aureus;* **** MRSA, Meticilline-resistance *S. aureus*

Table 3. Antibacterial resistance rates to *E. coli*

Antibiotic	Resistance (%)
Meropenem	0.0
Imipenem	0.2
Amikacin	0.7
Piperacillin-tazobactam	1.2
Cefoperazone-sulbactam	1.4
Nitrofurantoin	9.3
Cefepime	12.7
Ceftazidime	13.8
Cefotaxime	20.2
Ceftriaxone	20.6
Gentamicin	24.4
Cefazoline	29.2
Amoxacilline-clavulanate	31.6
Trimethoprim-sulfamethoxazole	44.8
Ciprofloxacin	45.1

or quinolone group of antibiotics, and in pyelonephritis 53.2% of the physicians also opted for the same treatment modality.[12] As is seen, since in most of the health care institutes providing primary health care services, urine cultures can not be performed, generally empirical treatment is used for patients presenting with UTI. In empirical treatment, the antibiotic is preferred according to the physicians'routine. From time to time, in other conditions confused with signs, and symptoms of UTI, unnecessary antibiotic use can occur. Treatments initiated for patients consulting to health care institutes without obtaining urine cultures can cause treatment failures, and development of resistance against antibiotics. To be able to preclude this condition, urine cultures should be obtained from all patients presenting with UTI signs, and symptoms, and based on the antibiotic susceptibility of the isolated microorganism, appropriate treatment should be selected.

Urinary tract infections frequently caused by a single pathogen namely *E. coli*.[2,3,6,7,13,14] Also in our study we isolated only *E. coli*. as a single UTI pathogen in 60.6% of the cases. In various studies reported in our country, *E.coli* has been indicated as the most frequently encountered UTI agent in 43-80.4% of the cases.[1,2,4,6,15-20] In ECO-SENS 2000 Project which contained shared common data retrieved in Canada, and sixteen European countries, *E. coli*.was reported as the most frequently isolated UTI pathogenic agent with an incidence rate of 79.5 percent.[21]

In our study, the pathogens were mostly (45.1%) resistant against ciprofloxacin. Kaya et al.[12] indicated that they had priorly preferred quinolone group of antibiotics in their empirical treatment., Temiz et al.[4] detected resistance to ciprofloxacin in 38.1% of the patients consulted to the outpatient clinics, emphasized careful use of this antibacterial class of drugs. Ciprofloxacin is one of the most studied antibiotic so as to reveal resistance to antibacterials. Gündüz et al.[5] declared their incidence of resistance to antibiotics among patients who consulted to outpatient clinics as 6.5 percent. Still from our country various authors reported different antibacterial resistance rates among ambulatory patients (Yılmaz et al.[2] 17.5%; Rifaioğlu et al.[15] 15.4%; Küçükbayrak et al.[16] 23%; Demirtürk et al.[19] 21%, Ay et al.[6] 21%; Kibar et al.[7] 25%; Tolun et al.[20] 11.62%, and Alım et al.[8] 16%). These rates are below our antimicrobial resistance rates. Altoparlak et al.[1] reported higher resistance rate (56.7%) than ours. In the ECO-SENS 2000 report which mostly contain data retrieved from European countries, resistance of *E. coli* strains to ciprofloxacin was reported to be 2.9%, while its incidence of resistance indicated by the same study

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group in 2003 report was 2.3 percent.[21,22] These rates are far below those reported in our country. Among these countries, resistance to ciprofloxacin was not encountered in Austria, Canada, Denmark, Ireland, Norway, and Sweeden.Among these countries the highest rates of ciprofloxacin resistance (14.7%) were reported for Spain.[22]

As quinolone group of antibiotics, trimethoprim-sulfamethoxazole is a frequently preferred antibiotic in the empirical treatment of UTI. In our study resistance to trimethoprim-sulfamethoxazole was seen in 44.8% of the patients. This antibiotic is also frequently used in the empirical treatment of UTI in our country. Gündüz et al.[5], and Tolun et al.[20] found antibacterial resistance to this drug as 22%, and 31.2%, respectively which were still lower than our findings. In other studies, resistance rates have changed between 42, and 91.5 percent.[1,2,4-6,15,16,19] The highest incidence of resistance (91.5%) was encountered in a study by Demirtürk et al.[19] In the ECO-SENS survey, resistance to trimethoprim-sulfamethoxazole (14.6%) was quite below those reported in our country.[21]

In our study, rate of antimicrobial resistance to amoxicillineclavulanate was 31.6 percent. Gündüz ve ark.[5] 27%, Alım et al.[8] (27.3%), Küçükbayrak et al.[16] (28%) reported resistance rates closer to our results. In similar studies, compared to our results relatively higher rates of resistance to this antibiotic ranging between 40, and 65.7% have been detected.[1,4,5-7,15] In ECO-SENS 2003 survey data, reported rate of resistance (3.4%) to this antibiotic was far below those detected in our country.[21] In ECO-SENS report, any incident of resistance to this drug was not encountered in two participating countries, Spain, and Portugal, However in ECO-SENS 2003 report, corresponding rates of resistance to this drug were 9.3, and 4.2%, respectively.[21,22]

In our study rate of resistance to cefazolin was 29.2 percent. In various studies resistance rates have ranged between 14, and 35 percent.[7,15,17] However, Altoparlak et al.[1] reported a higher rate (56.4%) for cefazolin-resistance.

Aminoglycosides have been used prevalently in the treatment of various infections, mostly for infections caused by gram-negtative bacteria.[5] In our study rates of resistance to gentamicin, and amikacin were 24.4, and 0.7%, respectively. Yılmaz et al.[2] (9.8%), and Tolun et al.[20] (5.2%) reported relatively lower resistance rates, while in various studies, indicated gentamicin-resistance rates have ranged between 17.6, and 28.5% which were closer to our findings.[1,4-6,17,19] Resistance to amikacin has been detected at a lower rate (0.7%) relative to gentamicin. In various studies performed in our country, reported rates of resistance to amikacin ranged between 3, and 5.3% which were comparable to our results.[1,5,7,8,15,16,20] Ay et al.[6] reported relatively higher rates of amikacin-resistance in Malatya. In the ECO-SENS 2003 report gentamicin-resistance rate was reported as 1.0 percent. This survey study couldn't detect gentamicin-resistance in Denmark, France, Luxemburg, Norway, Sweeden, and UK. Among the participating coıuntries, the highest resistance was reported for Spain (4.7%).[22]

In our study rate of antimicrobial resistance against ceftriaxone was found to be 20.6 percent. In similar studies rates of resistance to ceftriaxone ranged between 3, and 41.5 percent.[1,2,4-7,19] Tolun et al.[20] reported that only 8 (0.9%) isolates of *E. coli* among 804 *E. coli* strains were resistant to this antibiotic.

In many studies performed in Turkey, rates of antimicrobial resistance of *E. coli* against cefotaxime and ceftazidime were reported as 13.7, and 41.1% vs. 2, and 34%, respectively.[1,4,6,7,15] Our corresponding resistance rates were 20.2, and 13.8%, respectively. Rates of antimicrobial resistance against cefepime was 12.7 % in our study, while Altoparlak et al.[1] reported its incidence as 34.6 percent.

Antimicrobial resistance rate against nitrofurantoin is relatively lower. In various studies performed in our country rates of antimicrobial resistance against nitrofurantoin were reported between 9.3, and 14.1 percent.[4,6,7,17] Aydos et al.[18] indicated that all *E. coli* strains grown in the urine cultures of the patients who presented with complaints of cystitis were susceptible to nitrofurantoin, and conluded that nitrofurantoin is effective against this microorganism. In our study, rates of antimicrobial resistance against this drug was 9.3 percent. Temiz et al.[4] associated this lower rate of resistance to nitrofurantoin probably with its seldom use as a first-line therapy in UTIs.

In our study we detected relatively lower rates of resistance against cefoperazone-sulbactam (1.4%), and piperacillin-tazobactam (1.2%). Similarly Rifaioğlu et al.[15] also reported lower resistance rates against piperacillin-tazobactam (4.2%), and cefoperazone-sulbactam (4.0%) Still similarly, Tolun et al.[20] presented lower resistance rates (2%) against cefoperazone-sulbactam, while Gündüz et al.[5] analyzed 155 *E. coli* urinary isolates in urine cultures of ambulatory patients, and indicated lack of any antimicrobial resistance against this drug. On the other hand in some studies higher resistance rates against piperacilline-tazobactam (35.2-36.8%), and cefoperazone- sulbactam (42.9%) have been reported.[1,4,23]

In our study the lowest rates of resistance were related to carbapenem group of antibiotics. Meropenem-resistance was not detected, while only in two isolates of 1039 *E.coli* strains imi-

penem-resistance was found. In similar studies, lower resistance rates against imipenem, and meropenem were reported (0-8% vs. 0-10.3%).[1,4-7,15,16,19,20] Deveci et al.[23] presented data about 57 urinary isolates of *E. coli* with antimicrobial resistance in patients who consulted to outpatient clinics, and reported rate of imipenem-resistance as 49.1 percent. Antimicrobial resistance rates of *E. coli* strains reported in ours, and similar studies are summarized in Table 4.

Extended-spectrum beta-lactamase (ESBL) positive strains have been isolated at an increasing rate both in nosocomial, and community-acquired infections. Surgical procedures, catheterization, ICU stay, prolonged hospitalization, use of cephalosporins and/or aminoglycosides are risk factors for the production of ESBL.[24] ESBL mediated resistance can be transferred between bacterial species via plasmids, and lead to emergence of epidemics.[10] Most of the resistance seen against antibiotics develops as a result of beta-lactamase production.[25] Production of ESBL in *E. coli* strains isolated in community-acquired UTI increases significantly.[26] Increase in the production of ESBL leads to treatment failures, and increases in the incidence rates of mortality, and morbidity.

In our study ESBL producing *E. coli* was detected in 14% of our cases. Kuzucu et al.[24] reported that majority (n=184) of 239 *E. coli* strains identified in various clinical samples were isolated from urine samples, and indicated that they retrieved ESBL positive *E. coli* strains in 30% of the isolates in cases with community-acquired infections. Bülüç et al.[9] reported that ESBL detection rate in various clinical samples including urine samples (37% in all) as 14% for *E. coli* strain. In a similar study, Albayrak et al.[25] detected ESBL positivity rate of 17.9% in *E. coli* strains isolated from 61.6% of urine samples. Deveci et al.[10] indicated a prevalence rate of 13% for ESBL producing *E. coli* grown in urine cultures.

We obtained regional outcomes which did not reflect our country in general. In studies performed in various regions of our country, quite different antimicrobial resistance/susceptibility rates have been reported. In patients presenting with complaints of UTI, use of appropriate antibiotic till urine culture results are available is a very important issue for the clinician. Selection of the appropriate antibiotic effects not only treatment success, but also development of resistance which is closely related to treatment costs. Significantly higher rates of resistance have developed in recent years against some of the antibiotics used

Table 4. Antimicrobial resistance rates of *E. coli* strains isolated from urine samples of the patients presented to our outpatient clinics of our hospital with manifestations of UTI, and antimicrobial resistance rates of E. coli strains indicated in similar studies expressed in percentages (%)

	CIP	TMP SXT	AMC	CZ	GEN	AK	CRO	CTX	CAZ	FEP	NIT	CES	TZP	IMI	MER
Our hospital	45.1	44.8	31.6	29.2	24.4	0.7	20.6	20.2	13.8	12.7	9.3	1.4	1.2	0.2	0
Temiz et al.[4]	38.1	54.6	68.8		41.2		41.5		34		13.2		32.4		0
Gündüz et al.[5]	6.5	22	27		20	3.2	10.3					0		0	
Yılmaz et al.[2]	17.5	47.8			9.8		7.6								
Rifaioğlu et al.[15]	15.4	52.6	54.7	23.8		1.3		13.7	11.8			4.0	4.2	0.4	0.5
Küçükbayrak et al.[16]	23	55	28			2.0								0	
Demirtürk et al.[19]	21	91.5			22.1		12.1							3.3	
Ay et al.[6]	21	42	33		31.3	13	3.0		2.0		13			0	
Kibar et al.[7]	25	64	56	27		3.0	5.0		20		10			8	
Tolun et al.[20]	11.6	31.2			5.2	0.9						0.2		0	0
Alım et al.[8]	16		27.3												
Altoparlak et al.[1]	56.7	41	56.7	56.4	28.2	5.3	28.2	41.1		34.6		42.9		1.3	10.3
ECO-SENS 2000[21]	2.9	14.6	0												
ECO-SENS 2003[22]	2.3		3.4		1.0										
Çitil et al.[17]				35	17.6						9.3				
Deveci et al.[23]													36.8	49.1	

CIP: ciprofloxacin; TMP-SXT: trimethoprim-sulphamethoxale; AMC: amoxacilline-clavulonate; CZ: cefazoline; GN: gentamicin; AK: amikacin; CRO: ceftriaxone; CTX: cefotaxime; CAZ: ceftazidime; FEP: cefepime; NIT: nitrofurantoin; CES: cefaperazone-sulbactam; TZP: piperacillin-tazobactam; IMI: imipenem; MER: meropenem

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in the treatment of especially gram-negative infections which necessitated overview of treatment protocols. In consideration of the regional differences in the rates of resistance, we think that antibacterial resistance/susceptibility rates of each geographic region should be declared at certain intervals in order to be able to cut treatment costs, select the appropriate antibiotic till urine culture results are available, and decrease mortality, and morbidity rates.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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