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URINARY INFECTION
Original Article

Clinical effect of discordance in empirical treatment of cases with urinary tract infection accompanied by bacteremia

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ABSTRACT

Objective: It has been shown in previous studies that inadequate empirical treatment is associated with mortality in a variety of infections caused by Gram-negative bacteria. In this study, the clinical effect of discordance in empirical treatment was investigated in patients with urinary tract infection (UTI) accompanied by bacteremia.

Material and methods: We retrospectively reviewed the files of adult (>18 years old) patients who were diagnosed with UTI in our clinic between January 2014 and December 2015. Cases in which the same causative microorganism grew in both blood and urine cultures were included in the study. Patients using ceftriaxone and carbapenem as empirical antibiotic therapy (EAT) were compared as two different groups. In cases that the ethiologic agents were extended- spectrum beta lactamase (ESBL)-producing *Klebsiella pneumoniae* and *Escherichia coli* isolates, if the microorganism was resistant to initial antibiotic treatment the situation was defined as EAT discordance, and if it was sensitive it was defined as EAT concordance.

Results: After the exclusion criteria were applied, 65 of the 266 cases examined were taken into the study. Clinical and laboratory features of cases of ceftriaxone and carbapenem groups were similar. There was no statistically significant difference between the two groups in terms of hospital stay and survival ($p>0.05$). Of 28 cases of ESBL-producing *E. coli* and *K. pneumoniae*, 18 were EAT discordant and 10 were EAT concordant. Clinical and laboratory features of EAT concordant and EAT discordant groups were similar. No statistically significant difference was found between the two groups in terms of hospital stay and survival ($p>0.05$).

Conclusion: It was considered that ceftriaxone can still be a viable option in the EAT of UTI, which is accompanied by bacteremia without severe sepsis and septic shock findings. It was concluded that EAT discordance may not have a negative effect on the duration of hospital stay and survival rates in neither total cases nor ESBL positive ones.

Keywords: Bacteremia; empirical antibiotic therapy; urinary tract infection.

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Introduction

Urinary tract infection (UTI) is the most frequently seen bacterial infection in adults, and bacteremia accompanies this infection in 20-40% of the cases.[1-3] Bacterial agent is most often *Escherichia coli*, while Gram-negative cocci, enterococci, and *Staphylococcus saprophyticus* may also cause this infection.[4] In recent studies, extended- spectrum beta-lactamase (ESBL) producing strains have been detected in *E.coli* isolates at a higher frequency, both in the world, and in our country.[5,6] In the treatment of the infections caused by ESBL -producing strains, inadequacy of the antibiotics other than carbanepems in addition to their high-

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er mortality rates have been also indicated.[7] However, together with increased resistance of members of *Enterobacteriaceae* family, and *P. aeruginosa* isolates against carbapenems, ways of using carbapenems at a lesser frequency have been investigated.[8] In infections caused by Gram-negative bacteria, inadequacy of initial empirical treatment have been associated with high rates of mortality in some studies.[9] However these studies have encompassed not only cases with UTI, but also bloodstream infections, and pneumonia with higher mortality rates. It has been reported that in cases with acute pyelonephritis discordance in empirical antibiotherapy (EAT) has no effect on treatment outcomes, and mortality, however it has unfavourable effects on early clinical response, and hospital stay.[10]

In this study, in cases with UTI coursing with bacteremia, the impact of discordance in empirical treatment on treatment outcomes, survival, and hospital stay was investigated.

Material and methods

The study was performed after written approval (01.19.2016 decree # 1178) from the Ethics Committee of Clinical Research Center of Şişli Etfal Training and Research Hospital was obtained. Medical files of adult patients (>18 years) hospitalized with the diagnosis of UTI between January 2014, and December 2015 in The Clinics of Infectious Diseases, and Clinical Microbiology of our tertiary training and research hospital with 700 patient beds were reviewed. The cases whose blood, and urine cultures demonstrated the growth of the same agent were included in the study. The patients whose cultures did not reveal the presence of any causative agent or only in urine cultures bacterial growth was detected, in cases who had more than one bacterial agent in their culture media, and those with another different comorbidity were excluded from the study.

Before antibiotherapy, urine and blood samples were obtained from the patients twice for antibiotic susceptibility tests. For the identification of bacteria BD Phoenix™ automated system (Becton Dickinson, USA) or Matrix-assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) (Bruker Daltonics, Germany) was used. Antibiotic susceptibility tests were performed using BD Phoenix™ automated system or Kirby Bauer disk diffusion method in compliance with the criteria established by Clinical Laboratory Standarts Institute (CLSI).[11]

The decision to initiate EAT treatment with carbanepem or ceftriaxone was made by the clinician. The cases were divided into two groups based on their EAT as ceftriaxone and carbapenem (ertapenem, imipenem, and meropenem) users. Clinical and laboratory findings of both groups were compared as for their hospital stay, and survival rates.

If the microbial agent is found to be *in vitro* resistant against initial antibiotherapy, then EAT was defined as discordant. In cases where bacterial agent was found to be *in vitro* resistant against initial antibiotherapy, then EAT was defined as discordant antibiotherapy. In cases where ESBL –producing, ceftriaxone –resistant *K. pneumoniae* and *E. coli* isolates were found, ceftriaxone was replaced by ertapenem on the third day of treatment. These cases were classified as discordant EAT group. Cases where these bacteria were the causative pathogen, and so carbapenem was initiated as an empirical treatment were classied as EAT concordant group.

Improvement in clinical symptoms, and signs, and sterile urine culture obtained 7-9 days after completion of treatment was defined as criterion of treatment response.[12] Hospital records of the patients were examined retrospectively to determine the reasons of the patients for their presentation to the hospital after termination of their treatment, and the treatment they received. Development of UTI caused by a different pathogen 28-31 days after the treatment was defined as reinfection.[13] If the causative agent was the same as previously treated, then this condition was termed as relapse. Isolation of one or more than one different agent in the culture of the patient during treatment or a short time after the treatment was defined as superinfection.[14] Urinary system catheterization, urinary system malignancies, diabetes mellitus, neurogenic bladder, benign prostatic hyperplasia, and nephrolithiasis were evaluated as complicating factors.

Statistical analysis

For statistical analysis Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 15.0 Windows program was used. Descriptive statistics were expressed as numbers, and percentages for categorical variables, and means, and standard deviation for numerial variables. In comparisons between two independent groups for numerical variables with normal distribution Student *t* test, for those with non-normal distribution Mann-Whitney U test were used. Chi-square analysis was employed to test rates of categorical variables between groups. When required conditions could not be achieved Monte Carlo Simulation was applied. Level of statistical significance was accepted as $p<0.05$.

Results

Characteristic features of 266 cases followed up within the specified time interval were retrospectively examined and in 97 cases causative microorganism was not detected. From the remaining 169 cases, 104 patients met the exclusion criteria, and finally the study was conducted with 30 female, and 35 male patients. Clinical, and demographic findings of the patients in the ceftriaxone (n=47), and carbapenem

Table 1. Comparison of ceftriaxone, and carbapenem groups

Characteristics of the cases	Carbapenem group (n=18)	Ceftriaxone group (n=47)	p
Age Mean SD (year)	74.5±12.0	71.9±14.7	0.607
Gender, n (%)			
Female, n (%)	8 (44.4)	22 (46.8)	0.864
Male, n (%)	10 (55.6)	25 (53.2)	
Admission complaints, n (%)			
Fever, n (%)	15 (83.3)	41 (87.2)	0.699
Confusion, n (%)	6 (33.3)	14 (29.8)	0.782
Dysuria, n (%)	7 (38.9)	14 (29.8)	0.782
Flank pain, n (%)	3 (16.7)	11 (23.4)	0.740
Vomiting, n (%)	4 (22.2)	18 (28.3)	0.220
History			
Hospitalization within the last 3 months, n (%)	9 (50.0)	12 (25.5)	0.059
Antibiotic use within the last 10 days, n (%)	5 (27.8)	9 (19.1)	0.507
Physical examination			
Tachycardia (HR>100 bpm), n (%)	8 (44.4)	18 (38.4)	0.651
Tachypnea (>24/min), n (%)	7 (38.9)	12 (25.5)	0.289
Hypotension (SBP<90), n (%)	0 (0)	5 (10.6)	0.311
Costovertebral angle tenderness, n (%)	8 (44.4)	15 (31.9)	0.344
Suprapubic tenderness, n (%)	0 (0)	5 (10.6)	0.311
Complicating factors			
Urolithiasis, n (%)	0 (0)	6 (12.8)	0.175
Urinary system malignancy, n (%)	1 (5.6)	3 (6.4)	1.000
Benign prostatic hyperplasia, n (%)	1 (5.6)	4 (8.5)	1.000
Nephrostomy, n (%)	1 (5.6)	1 (2.1)	0.480
Neurogenic bladder, n (%)	0 (0)	2 (4.3)	1.000
Indwelling urinary catheterization, n (%)	0 (0)	1 (2.1)	1.000
Intermittent catheterization, n (%)	0 (0)	1 (2.1)	1.000
Diabetes mellitus, n (%)	4 (2.2)	14 (29.8)	0.758
Laboratory parametres			
Pyuria, n (%)	18 (100)	44 (93.6)	0.555
Leucocytes, median	15.977.20	14.454.40	0.525
Neutrophils, median	13.696.10	12.523.80	0.758
Platelets, median	218444.4	217297.9	0.964
Hemoglobin, median	11.8	11.1	0.211
CRP, median	180.4	215.4	0.195
Hospital stay (days) Mean±SD	11.1±6.1	10.0±5.3	0.586
Health state at discharge n (%)			
Cure	17 (94.4)	43 (91.5)	1.000
Referral to ICU	0 (0)	2 (4.3)	
Death	1 (5.6)	2 (4.3)	

SD: standard deviation; SBP: Systolic blood pressure; CRP: C-reactive protein; ICU: intensive care unit

(n=18) groups were comparable. A total of 21 (32%) cases [9 (25.5%) in the carbanepem, and 12 (50%) in the ceftriaxone group] were hospitalized within the last 3 months without any statistically significant intergroup difference (p=0.059). In 12 (32%) cases a complicating factor as urinary system malignancy, benign prostatic hyperplasia, urinary catheterization, neurogenic bladder, and urolithiasis was detected. As a comorbidity diabetes mellitus was detected in 4 (22.2%) carbapenem, and 14 (29.8%) ceftriaxone users (p=0.758). Any statistically significant was not found between ceftriaxone, and carbanepem groups as for comorbidities, and urologic complicating factors (Table 1). Besides, hospital stay, and survival rates were comparable between groups (p=0.586, and p=1.000, respectively).

Most frequently growth of *E.coli* (63%) was detected as a causative agent, and 43% of Gram-negative agents consisted of ESBL-producing bacteria. Forty and 44.6% of Gram-negative agents were resistant to ciprofloxacin, and cotrimoxazole, respectively (Table 2). ESBL-positivity was detected in 19 (19/41) *E. coli* isolates, while ESBL-positivity was detected in 7 (58%) out of 12 *K. pneumoniae* isolates. Eighteen (44%) *E. coli* isolates were resistant to ciprofloxacin, and cotrimoxazole. Three (3/12) *K. pneumoniae* isolates were resistant to ciprofloxacin, and 7 of them were resistant to cotrimoxazole. Resistance against ampicillin (6.1%) was not detected in patients whose cultures demonstrated growth of *Enterococcus faecalis*. Three of these cases were in ceftriaxone, and one in carbepenem group. Resistance against ceftriaxone was not detected in patients whose cultures demonstrated growth of *Proteus mirabilis* (n=4) or *Enterobacter cloacae* (n=1). All of ESBL producing *E. coli* and *K. pneumoniae* isolates were resistant to ceftriaxone.

In the ceftriaxone group EAT of 24 (51.0%) cases was discordant, while concordance was detected in EAT in 23 (49.0%) cases (Figure 1). In two patients growth of *K. pneumoniae* resistant to carbapenems was detected. One of these patients was transferred to intensive care unit (ICU), and the other one died on the 5. day of colistin+meropenem treatment. Severe sepsis developed in 5 cases. The characteristic features of these cases are shown in Table 3. One of the cases in the carbapenem group, disease relapsed.

In a total of 28 cases whose cultures revealed the presence of ESBL producing *E. coli*, and *K. pneumoniae* EAT was discordant in 18, and concordant in 10 patients. Clinical, and demographic characteristics of both groups were similar (p>0.05). Hospital stay and survival rates of these cases were not statistically significantly different (p=0.765, and p=1.000, respectively). One patient from each group died, while one case from discordant EAT group was transferred into intensive care unit (Table 4).

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Discussion

Bacteremia is an important indicator in the approach to the cases with UTI which demonstrates the severity of the disease. Bacteremia is more frequently associated with cases manifesting symptoms of severe sepsis, and septic shock. In some studies, risk factors for bacteremia have been determined. In cases with complicated acute pyelonephritis, advanced age has been detected as a risk factor for bacteremia.[2] On the other hand, malignancy, and indwelling urinary catheter have been demonstrated as independent risk factors for bacteremia.[15] These risk factors for bacteremia were also observed in our cases. Our series consisted of relatively older patients (median ages were 74.5, and 71.9 years in ceftriaxone, and carbapenem groups, respectively), and 8 patients had also concomitant urinary system malignancies, and indwelling urinary catheters.

In cases with urinary system infections *E. coli* is the most frequently detected microbial agent, and in 20-27% of them it has ESBL-producing strains.[4,5,16] Based on the 2013 data released by National Antimicrobial Resistance Surveillance System (UAMDS) in Turkey, ESBL-producing strains were detected in 44.9% of *E. coli,* and 49.9% of *K. pneumoniae* isolates. In our study the most frequent microbial agent was *E. coli* (63.1%). Overall ESBL-producing rate among *E. coli*, and *K. pneumoniae* isolates was detected as 43.1 percent. In Turkey increasingly higher rates of carbanepem resistance among *Enterobacteriaceae* strains have been reported in recent years.[17] In our study, carbanepem- resistant *K. pneumoniae* strains were detected in 2 cases in the ceftriaxone group. Resistance rates against quinolone antibiotics are gradually increasing among Gram-negative urinary pathogens.[16] Based on 2013 UAMDS data rates of resistance against ciprofloxacin among *E.coli* and *K. pneumoniae* isolates were 44.0, and 43.0%, respectively. Similarly, in our study 40%, and 44.6% of all Gram-negative agents were resistant to ciprofloxacin, and cotrimoxazole, respectively. According to Infectious Diseases Society of America guidelines antibiotics with regional resistance rates above 20 % are not recommended in empirical treatment of UTIs.[18] In this case, use of ciprofloxacin in our

Table 2. Distribution of gram-negative agents, and resistance rates

		Carbapenem group (%)	Ceftriaxone group (%)	Total
Microorganisms	*E. coli*	9 (50)	32 (68)	41 (63.1)
	K. pneumoniae	5 (27)	7 (16)	12 (18.4)
	Proteus mirabilis	2 (11)	4 (8)	6 (9.2)
	P. aeruginosa	0 (0)	1 (2)	1 (1.5)
	E. cloacae	1 (6)	0 (0)	1 (1.5)
ESBL				
Resistance against:		10 (62.5)	18 (40.0)	28 (43.1)
Carbapenem		0 (0)	2 (4.4)	2 (3.1)
Quinolone		4 (25.0)	20 (44.4)	24 (40.0)
Cotrimoxazole		9 (56.3)	20 (44.4)	29 (44.6)

ESBL: extended-spectrum beta-lactamase

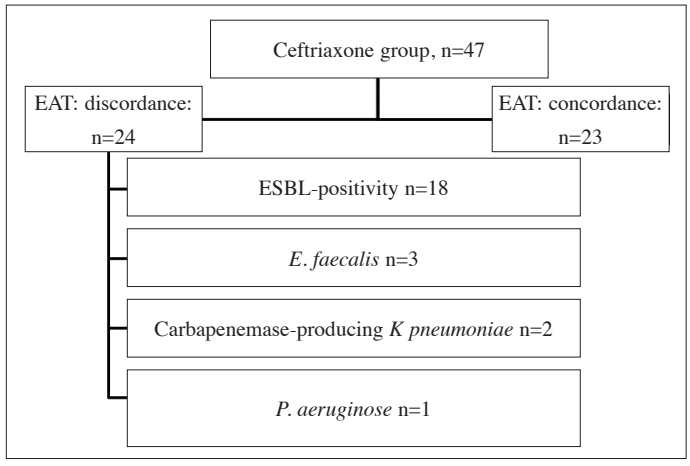

Figure 1. Causes of discordance in EAT among cases in the ceftriaxone group
EAT: empirical antibiotherapy; ESBL: extended-spectrum beta- lactamase

Table 3. Characteristics of the patients who were referred to intensive care units (ICUs), and those exited

Patients, n	Concordance to EAT	Age (year)/gender	Agent	The state of resistance	Concomitant disease	Outcome
1	Concordant	81 / Female	*K. pneumonia*	ESBL producing	None	Exitus
2	Discordant	98 / Male	*Enterococcus faecalis*	Susceptible to penicilline	None	ICU
3	Discordant	49 /Male	*K. pneumonia*	Resistant to all antibiotics	Bladder carcinoma	Exitus
4	Discordant	69 /Male	*K. pneumonia*	Carbapenemase	DM, cardiovascular disease	ICU
5	Discordant	83 /Female	*E. coli*	ESBL producing	DM	Exitus

ESBL: extended–spectrum beta-lactamase; EAT: empirical antibiotherapy; DM: diabetes mellitus; ICU: intensive care unit

Table 4. Comparisons among ESBL-positive cases

Characteristics of the cases	Discordant empirical treatment (n=18)	Concordant empirical treatment (n=10)	p
Age Mean.±SD (year)	66.8±13.8	71.2±13.8	0.424
Gender, n (%)			
Female	7 (38.9)	3 (30.0)	0.703
Male	11 (61.1)	7 (70.0)	
Admission complaint, n (%)			
Fever	17 (94.4)	9 (90.0)	1.000
Confusion	3 (16.7)	2 (20.1)	1.000
Dysuria	5 (27.8)	4 (40.0)	0.677
Flank pain	5 (27.8)	3 (30.0)	1.000
Vomiting	10 (55.6)	4 (40.0)	0.430
History			
Hospitalization within the last 3 months	9 (50.0)	4 (40.0)	0.705
Antibiotic use within the last 10 days	7 (38.9)	1 (10.0)	0.194
Physical examination			
Tachycardia (100 bpm)	9 (50.0)	5 (50.0)	1.000
Tachypnea (>24 /min)	5 (27.8)	4 (40.0)	0.677
Hypotension (SKB<90)	3 (16.7)	0 (0)	0.533
Costovertebral angle tenderness	4 (22.2)	6 (60.0)	0.097
Suprapubic tenderness	4 (22.2)	0 (0)	0.265
Complicating factors			
Urolithiasis	2 (11.1)	0 (0)	0.524
Urinary system malignancies	3 (16.7)	0 (0)	0.533
Benign prostatic hyperplasia	0 (0)	1 (10.0)	0.357
Nephrostomy	1 (5.6)	1 (10.0)	1.000
Neurogenic bladder	1 (5.6)	0 (0)	1.000
Indwelling catheterization	1 (5.6)	0 (0)	1.000
Intermittent catheterization	0 (0)	0 (0)	
Diabetes mellitus	7 (38.3)	2 (20.0)	0.417
Laboratory parametres			
Pyuria	17 (94.4)	10 (100)	1.000
Leucocyte, median	13490	16687	0.338
Neutrophil, median	11833.9	13996	0.533
Platelet, median	232777.8	231400	0.968
Hemoglobin, median	11.1	12.1	0.268
CRP, median	208.4	220.1	0.749
Hospital stay (days) Mean±SD	12.7±5.2	12.0±7.4	0.765
Health state at discharge n (%)			
Cure	16 (88.9)	9 (90.0)	1.000
Referral to ICU	1 (5.6)	0 (0)	
Death	1 (5.6)	1 (10.0)	

SS: standard deviation; ESBL: extended–spectrum beta-lactamase; SBP: Systolic blood pressure; CRP: C-reactive protein; ICU: intensive care unit

country for empirical treatment of cases with UTI associated with bacteremia will not be an appropriate choice.

In a study by Tamma et al.[7] carbapenem, and tazobactam (TZB) were compared in the treatment of cases with bacteremia caused by ESBL-producing microorganisms. In this study TZB was found to be less effective, and 20% of sources of bacteremia were UTIs. However in some recent studies, effectiveness of antibiotics other than carbapenems in the treatment of UTIs caused by ESBL-producing bacteria has been reported.[19,20] In another study, in patients with severe sepsis, and septic shock caused by resistant Gram-negative microorganisms, inappropriate initial empirical antibiotics was demonstrated to be related to mortality. In this study, as a source of sepsis, cases with UTI constituted 19.5% of all cases.[9] All of our study population consisted of cases with UTI, and did not include patients with symptoms of severe sepsis, and septic shock at admission.

A study which investigated clinical effects of inappropriate empirical antibiotherapy, demonstrated that discordance in empirical treatment in cases with community-acquired UTI had no effect on treatment outcome, and mortality, however it exerted unfavorable effects on hospital stay, and early clinical response.[10] In our study EAT was found to be effective in 23 (49.0%) cases in the ceftriaxone group, so the same EAT was maintained. While in the remaining 24 (51.0%) cases EAT was ineffective, so antibiotherapy was changed. Based on the treatment outcomes, in 2 out of 5 cases who developed severe sepsis, growth of carbapenemase-producing *K. pneumoniae* was detected. Advanced age, and an complicating factor were noted in 3 exited cases. Still in 2 cases transferred to the intensive care unit advanced age, and inappropriate EAT were observed. Relapse developed in one patient in the carbapenem group. However, in the carbapenem, and ceftriaxone groups, hospital stays, and survival rates of the cases were nearly identical. Discordance in EAT had no effect on survival, and hospital stay. Besides, we compared patients with USI caused by ESBL-producing agents which received appropriate, and inappropriate EAT, and we couldn't find any significant difference as for longevity of hospital stay, and survival rates. In our study since relapse rates were estimated based on registration data recorded at admission, we think that these data did not reflect actual relapse rates. Retrospective design, dubious relapse rates, and relatively small number of cases are limitations of our study.

In conclusion, considering gradually increasing number of carbapenem –resistant *Enterobacteriaceae* isolates, one may think of decreasing the use of carbapenems in the empirical treatment of UTI. In cases with UTI without any evidence of severe sepsis, and septic shock and concomitant bacteremia, ceftriaxone may be an alternative. It has been detected that in all cases, and also in ESBL-positive cases discordant EAT might not effect

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hospital stay and survival rates unfavorably. Prospective randomized studies should be performed on this issue with higher number of case series.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Şişli Hamidiye Etfal Training and Research Hospital.

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