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Antimicrobial Original Research Paper

Retrospective evaluation of the patients with urinary tract infections due to carbapenemase producing *Enterobacteriaceae*

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In this study, we aimed to investigate retrospectively the patients with carbapenem-resistant *Enterobacteriaceae* urinary tract infections (UTIs) in the terms of demographic findings, antibiotic sensitivity patterns and clinical features along with the treatment options. This study was performed at a tertiary-care educational university hospital. Adult (>18 years old) patients diagnosed with culture proven UTI due to carbapenem-resistant *Klebsiella pneumoniae* (between December 2016 to December 2017) were included in the study. Antimicrobial susceptibility testing of the isolates was performed with the VITEK 2 system (bioMérieux). Resistance to imipenem, ertapenem, and meropenem was tested by E-test (bioMérieux). The results were interpreted according to the EUCAST criteria. A total number of 100 patients (34% female, mean age 61.69 ± 1.65 years) were included in this study. One month all-cause mortality rate was 19%. Microbiologic eradication rate was 88.7% while it was significantly higher in combination therapy (65/70 vs. 14/19, $p = 0.019$) and carbapenem long-lasting (4 h) infusion subgroups (54/56 vs. 2/56, $p = 0.005$). Relapse and reinfection rates were 61.7 and 29.7%, respectively. Logistic regression analysis for mortality risk factors resulted as history of ertapenem usage (OR: 4.74, 95% CI: 0.678–33.201, $p = 0.117$), lack of microbiologic eradication (OR: 21.7, 95% CI: 1.906–247.375, $p = 0.013$) and ICU stay (OR: 54.8, 95% CI: 4.145–726.324, $p = 0.002$). Combination, carbapenem long-lasting infusion and double carbapenem therapies seem to result in higher microbiologic eradication rates and thus may effect the mortality rates of these group of patients. Randomized-controlled studies should be performed in this critical patient group to confirm these results.

Keywords: Urinary tract infection, carbapenem resistance, *Klebsiella pneumoniae*, treatment, risk factors, prognosis

Introduction

The infections due to Gram-negative pathogens with extended-spectrum beta-lactamases and carbapenemases effect especially the hospitalized or immunosuppressive patients in recent years.[1–5] Well-planned retrospective or prospective studies related to treatment as well as clinical presentation and prognosis of carbapenem-resistant *Enterobacteriaceae* (CRE) infections are limited.[3–5]

In this study, we aimed to investigate retrospectively the patients with urinary tract infections (UTIs) due to CRE in terms of demographic data, antibiotic sensitivity patterns and clinical features.

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Methodology

Selection of the patients

Both inpatient and outpatient patients with UTI due to CRE and followed up/consulted by the Department of Infectious Diseases and Clinical Microbiology in a tertiary care university hospital, were recorded between 20 December 2016 and 20 December 2017. Case assessment forms including data related to demographical and clinical findings as well as culture results, microbiological clinical response to treatment regimens and mortality were recorded. UTIs were investigated according to clinical criteria[6] as upper and lower UTIs via using the case assessment forms. Septic shock was defined by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia.[7]

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Table 1 Demographical data of the patients

Age (year ± standard deviation)	61.69 ± 1.65
Gender (female/male)	34/66
Comorbidities (%)	
Malignancy	40
Hypertension	32
Chronic renal failure	22
Diabetes mellitus	20
Coronary heart disease	18
Nephrolithiasis	9
Renal transplantation	3
Liver transplantation	1
Intensive care unit follow-up (%)	
Yes	36
No	64
Geriatric patients (%)	
≥65 years	47
<65 years	53
History of surgical operation (%)	70
Urological operation type, *n* (%)	
Double J stent	15/70 (21.4)
Ureterorenoscopy (URS)	11/70 (15.7)
Transurethral resection-bladder (TURB)	9/70 (12.8)
Nephrostomy	7/70 (10)
Nephrolithotomy (PNL)	5/70 (7.1)
Transurethral prostate resection (TURP)	4/70 (5.7)
Nephrectomy	4/70 (5.7)
Prostatectomy	3/70 (4.2)
Endoscopic internal urethrotomy	3/70 (4.2)
Cystectomy	2/70 (2.8)
History of antibiotic usage during the last 1 month (%)	73
History of carbapenem-resistant *Enterobacteriaceae* (CRE) infection (%)	13

Inclusion criteria

- 18 years old or above (adult patients were included).
- Urinary culture positivity for CRE and diagnosed as UTI.

Exclusion criteria

- Presence of an infection source other than urinary tract.
- Asymptomatic or colonized patients.

Microbiological evaluation and sensitivity tests

Mid-stream urine samples were collected into a sterile container and transported immediately to Clinical Microbiology Department, Bacteriology Laboratory where quantitative urine cultures were done. Peripheral blood cultures were inoculated to aerobic and anaerobic culture bottles, (BacT/ALERT, BioMérieux, Durham, USA) and automated microbial detection system (BacT/ALERT 3D, BioMérieux, Durham, USA) was used. MALDI-TOF mass spectrometry, (VITEK MS, BioMérieux, France) was used for microbial identification. Antibiotic sensitivity tests were performed by VITEK2 (BioMérieux, France) system according to EUCAST criteria.[8] Carbapenem minimum inhibitory concentration (MIC) levels were determined by gradient tests (E test, BioMérieux, France).

Local Institutional Review Board approved the study (18-3/33 on the 06 March 2018).

Statistical analysis

Statistical analysis was performed by using SPSS 20.0 program. Comparison of values between the two categorical groups was performed by Chi-square test, on the other hand *t*-test was performed for the numerical values of the independent groups. Chi-square test of the variables for mortality was performed and the variables which had significant *p* values were analysed by simple linear and logistic regression analysis. A p value <0.05 was considered to be statistically significant.

Results

A total of 100 patients (34% female and mean age 61.69 ± 1.65 years) who fulfilled our inclusion criteria were included in the study. Mean duration of hospitalization was 26.6 ± 2.8 days and ICU admission rate was 36%. Demographical data of the patients are shown in Table 1.

The most commonly used antibiotics in the previous 1 month were fluoroquinolones (36/73, 49.3%), ertapenem (21/73, 28.8%) and third generation of cephalosporins (21/73, 28.8%).

Table 2 Simple linear regression analysis of independent variables on mortality (1 month)

Risk factors		Mortality, yes (*n*)	Mortality, no (*n*)	*p* value
History of ertapenem usage	Present	6 (28.6%)	15 (71.4%)	0.067[a]
	Absent	5 (9.6%)	47 (90.4%)	
History of quinolone usage	Present	6 (16.7%)	30 (83.3%)	0.961[b]
	Absent	5 (13.5%)	32 (86.5%)	
Age $\geq$ 65	Present	9 (19.1%)	38 (80.9%)	1.000[b]
	Absent	10 (18.9%)	43 (81.1%)	
Chronic renal failure	Present	6 (27.3%)	16 (72.7%)	0.355[a]
	Absent	13 (16.7%)	65 (83.3%)	
Nephrolithiasis	Present	0 (0%)	9 (100%)	0.201[a]
	Absent	19 (20.9%)	72 (79.1%)	
Diabetes mellitus	Present	2 (10%)	18 (90%)	0.348[a]
	Absent	17 (21.3%)	63 (78.7%)	
Hypertension	Present	7 (21.9%)	25 (78.1%)	0.818[b]
	Absent	12 (17.6%)	56 (82.4%)	
Coronary heath disease	Present	4 (22.2%)	14 (77.8%)	0.958[b]
	Absent	15 (18.3%)	67 (81.7%)	
Malignancy	Present	8 (20%)	32 (80%)	1.000[b]
	Absent	11 (18.3%)	49 (81.7%)	
ICU admission	Present	18 (50%)	18 (50%)	$p_2<0.001$[b,*]
	Absent	1 (1.6%)	63 (98.4%)	
History of CRE infection	Present	1 (7.7%)	12 (92.3%)	0.453[a]
	Absent	18 (21.2%)	67 (78.8%)	
Monotherapy	Present	3 (15%)	17 (85%)	0.757[a]
	Absent	16 (20%)	64 (80%)	
Microbiological response	Present	9 (11.4%)	70 (88.6%)	0.036[a,*]
	Absent	4 (40%)	6 (60%)	
Double carbapenem regimen	Present	8 (15.1%)	45 (84.9%)	0.423[b]
	Absent	11 (23.4%)	36 (76.6%)	
Colistin-based regimen	Present	11 (28.2%)	28 (71.8%)	0.106[b]
	Absent	8 (13.1%)	53 (86.9%)	
Tigecycline containing regimen	Present	8 (26.7%)	22 (73.3%)	0.317[b]
	Absent	11 (15.7%)	59 (84.3%)	
Carbapenem treatment with long infusion	Present	9 (14.8%)	52 (85.2%)	0.275[b]
	Absent	10 (25.6%)	29 (74.4%)	

[a]Fisher's Exact test.
[b]Continuity (Yates) correction.
[*]$p < 0.05$.

When the patients were clinically evaluated, upper UTI were identified in 70 patients, whereas lower UTI were identified in the other 30 patients. The most common UTI symptoms of the patients were fever (69%), dysuria (54%) and flank/inguinal pain (29%). Urinary catheter, central venous catheter and nephrostomy were in 73, 18 and 14 patients, respectively, while 19 cases presented with septic shock in initial presentation.

Antibiotic susceptibility rates and MICs of the some antibiotics for urinary and concomitant peripheral blood culture isolates are shown in Tables S1 and S2. A total number of 18 patients had concomitant peripheral blood culture positivity for carbapenem-resistant *Klebsiella pneumoniae*.

At the initial assessment, 10 of each upper and lower UTI patients were started monotherapy. Treatment change rates were noted as 35% (7/20) for monotherapy group and 30% (24/80) for combination treatment group ($p = 0.787$).

Microbiological response during or after the treatment could be evaluated in 89 patients and only 10 were still culture positive. Microbiological response rates were higher in combination therapy subgroup vs. monotherapy subgroup [92.8% (65/70) vs. 73.6% (14/19)] ($p = 0.019$). When we analysed the different treatment regimens in terms of microbiologic response, the rates were 46/49 vs. 33/40 for double carbapenem given versus others ($p = 0.106$), 32/36 vs. 47/53 for colistin based regimen given versus others ($p = 0.627$), 22/26 vs. 57/63 for tigecycline containing regimen given versus others ($p = 0.470$) and 54/56 vs. 25/33 for carbapenem long infusion treatment given versus others ($p = 0.005$).

The total number of 47 patients whose control cultures could be sent within the 30 days of the treatment or post-treatment period after the first negative culture results, were evaluated and relapse rate was found as 61.7% (29/47) with reinfection rate as 29.7% (14/47). Among these 47 patients, only 23.4% (11/47) had no relapse or reinfection. Mean duration of relapse and reinfection were 14.04 ± 8.78 days and 11 ± 7.32 days, respectively.

All-cause mortality rate 1 month after the end of treatment (EOT) was 19% while this was 22.2% (4/18) for the concomitant CRE bacteremia subgroup.

Table 3 Logistic regression analysis of the independent variables on the mortality (1 month)

Variable	Odds ratio	95% confidence interval	*p* value
History of ertapenem usage	4.744	0.678–33.201	0.117
Absence of microbiological response	21.714	1.906–247.375	0.013
Intensive care unit admission	54.867	4.145–726.324	0.002

Overall mortality (all-cause mortality during therapy or on 30 days follow up) rates were 15% (3/20) in monotherapy group versus 20% (16/80) in combination treatment group ($p = 0.757$). Mortality rates in patients with upper UTI were 20% (2/10) for monotherapy group versus 23% (14/60) for combination treatment group ($p = 0.590$). On the other hand, in patients with lower UTI, mortality rates were 10% (1/10) in monotherapy group versus 10% (2/20) in combination treatment group ($p = 0.749$) all due to cardiopulmonary arrest. A total of 5 presented with septic shock in initial presentation while another 14 developed septic shock during treatment. Two of these had concomitant CRE bacteremia and 57.8% (11/19) resulted in mortality.

Chi-square tests of independent variables versus mortality (1 month after EOT) showed that ICU admission (18/36 vs. 1/64; $p < 0.001$) and presence of microbiologic response (9/79 vs. 4/10, $p = 0.036$) were significantly associated with mortality (Table 2).

Mortality rate was higher in patients with a history of ertapenem usage (28.6%) versus others (9.6%) in Chi-square test ($p = 0.067$). However, linear regression test for mortality versus prior ertapenem therapy received cases versus others showed a significant result (OR: 3.760; 95% CI: 1.003–14.096). In linear regression analysis, mortality rate was also higher in patients with ICU admission (50%) versus others (1.6%) (OR: 63.000; %95 GA: 7.865–504.629, $p = 0.000$), and significantly lower for patients with microbiological response (11.4%) versus others (40%) (OR: 5.185; %95 GA: 1.225–21.951, $p = 0.036$). Other risk factors were not found as statistically significant effect on the mortality ($p > 0.05$) (Table 2).

The logistic regression analysis was performed with the variables of history of ertapenem usage, absence of microbiological response and ICU admission and the model was found as significant ($p = 0.000$; $p < 0.01$) and Negelkerke $R^2 = 0.598$ with explanation coefficient as good as 90.4%. In this model, microbiological unresponsiveness and ICU admission were found as significant variables (Table 3, $p < 0.05$).

Discussion

CRE emerge as a major global healthcare problem. As distinct from a systematic review which showed that *Escherichia coli* was the most frequently isolated CRE species from Turkey,[9] all CRE isolates detected in our study were *K. pneumoniae*.

In a multicenter study from United States of America, a total number of 266 hospital's data were analysed and fluoroquinolone usage was reported to be a significant risk factor for CRE infections ($p = 0.0007$) in contrast to carbapenem usage.[10] In our study, history of fluoroquinolone usage rate was 49.3% and carbapenem usage was 46.5%. In addition to this, history of ertapenem usage was found as a risk factor for mortality ($p = 0.067$) in contrast to history of meropenem usage ($p = 0.454$). Especially in recent years, the term of 'colleteral damage' appears as an important healthcare problem due to unnecessary usage of the antibiotics and the selection of multidrug antibiotic-resistant pathogens. Although the fluoroquinolones were the usual suspects for colleteral damage, we found that the history of ertapenem usage as a risk factor for mortality. Thus, we believe that unnecessary usage of ertapenem should be avoided and indications for ertapenem treatment should be carefully determined.

Since treatment regimen for the CRE infections needs to be tailored according to antibiotic susceptiblity patterns of the infecting strain, no standart regimen exists and published data are confined to single or multicenter cohorts in which different treatment regimen subgroups are compared. Falagas et al. conducted a systematic evaluation of 20 non-randomized controlled studies with a total number of 692 patients that compare the combination regimens in terms of mortality rate. They revealed the mortality rates as 67% for colistin-carbapenem combination, 64% for colistin-tigecycline combination, 50% for tigecycline-gentamycine combination, whereas 57% for colistinmonotherapy and 80% for tigecyclinemonotherapy.[11] Souli et al. conducted a study from Greece with 16 UTIs out of 27 carbapenemase producing (KPC-2) *K. pneumoniae* infections that were treated with dual carbapenem rescue treatment.[12] They reported the total clinical and microbiologic success rates as 77.8% and 74.1% while crude mortality rate was 29.6%.[12] In our study, regardless of the combination or monotherapy treatment given groups, 30 day crude mortality rates were 15% for double carbapenem regimen, 28% for colistin based regimens, 26% for

tigecycline containing regimens and 14.7% for the long-infusion carbapenem containing regimens. Besides, microbiological success rates were as high as 93.8% for double carbapenem regimen and 96.4% for long-infusion carbapenem containing regimens in our study. The reasons of lower mortality rates compared to literature in our study, may be explained by well-defined UTI group of patients and by the probably different carbapenemase enzyme characteristics.

The surveillance report of the European Center for Disease Prevention and Control (ECDC) in 2015 revealed that the bla (OXA-48) was endemic in Turkey but also reported an increase of the isolates with bla (NDM-1) and bla (KPC) especially in the border cities of Syria like Sanliurfa.[13–20] In our retrospectively designed study, one of the main limitations was lack of the molecular identification of carbapenemase genes. Tekintas et al. recently investigated a total of 54 carbapenem (either one of the ertapenem, meropenem or imipenem) resistant *K. pneumoniae*isolates from our hospital between the years of 2015–2016 by using molecular methods. They reported the carbapenemase genes in study strains as 33 (61.1%) for bla (OXA-48), 19 (35.1%) for both bla (OXA-48) and bla (NDM-1), 2 (3.7%) for bla (NDM-1) alone while no bla (IMP), bla(VIM) and bla (SIM) genes were detected.[21] These data reveal that the most common enzyme is OXA-48 in our setting. Galani et al. showed the synergistic effect of the double carbapenem treatment for the isolates of OXA-48 positive *K. pneumoniae.*[22] Thus, we believe that one of the main reasons for the different rates of clinical, microbiologic response rates from the literature is due to differences in the epidemiology of these carbapenemase enzyme types.

In another study from our hospital, Cilli et al. investigated the rectal colonization in CRE-infected patients and decolonization rates in CRE colonized patients. They reported that 25 (78%) of 32 CRE-infected cases had rectal colonization and only 7 of 46 cases (52.2%) with rectal colonization had decolonization during weekly follow-up.[23] In our study, 13% of our patients had a history of previous CRE infection. Previous studies that analysed recurrent UTIs in women, reported 30–44% of the patients had a recurrent UTI during the six months after the first episode,[24,25] but in our study these rates were found higher as 61.7% for relapse and 29.7% for reinfection rate among the 47 patients whose control cultures could be performed. The reason of these higher recurrence rates may be explained by the low decolonization rate of the CRE colonized patients. Hence, easily applicable new strategies are needed for decolonization of CRE colonized cases.

Our study has several limitations such as its retrospective design (for this reason control cultures were available in some of the patients), lack of carbapenemase gene investigation via molecular methods, lack of pharmacokinetics and pharmacodinamic evaluation via measurement of blood antibiotic levels, usage of automatized system data (VITEK) for colistin susceptibility, and lack of autopsy in order to demonstrate the exact cause of death. However, to our knowledge this is the first study that evaluates the adult CRE UTI patients clinically from Turkey as well as one of the largest datasets in terms of double carbapenem therapy.

Conclusion

These data suggest that antibiotic consumption should be carefully selected in CRE-infected patients; combination treatment should be preferred priorly; double carbapenem and/or long infusion carbapenem treatments with high rates of microbiological success should be prioritized and finally unnecessary ertapenem usage should be restricted. We suggest that double carbapenem regimen needs to be assessed in larger cohorts and/or randomized-controlled studies to be prioritized in a wider aspect.

Disclosure statement

All authors declare no conflict of interests.

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