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Arising Prevalence of OXA-48 producer *Escherichia coli* and OXA-48 with NDM co-producer *Klebsiella pneumoniae* Strains

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Abstract

***Background/aim**: This prospective study aimed to determine the presence of the most common carbapenemase genes, blaOXA-48, blaKPC, blaIMP, blaVIM and blaNDM on carbapenem resistant clinical K.pneumoniae and E.coli isolates. **Materials and methods**: Isolates were selected according to EUCAST guideline; gradient test and disc diffusion with both meropenem and ertapenem discs. Resistance rates of these isolates to other antimicrobial agents were also examined by disc diffusion method. Carbapenem resistance gene were investigated by using Real-Time PCR. **Results**: A total of 3845 E. coli and 1689 K.pneumoniae isolates from clinical samples between January 2015 and April 2017 were evaluated. The 419 isolates were found as carbapenem resistant but only the first resistant isolate (n=155; 126 K.pneumoniae and 29 E.coli) of each patient were included. Carbapenem resistant isolates were most frequently isolated from intensive care units (48.8%). Colistin was the most effective antibiotic (91.0%). The 121 (78.1%) of the tested isolates were positive for OXA-48 (103 K.pneumoniae and 18 E.coli) and 9 K. pneumoniae carrying blaNDM were also positive for blaOXA-48. VIM, IMP and KPC type carbapenemases were not detected in any isolates. **Conclusion**: Carbapenem-resistant pathogens have been shown to be able to develop resistance mechanisms with more than one carbapenemase encoding gene.*

***Keywords:** Klebsiella pneumoniae, Escherichia coli, carbapenem resistance, antimicrobial resistance, Enterobacterales*

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Introduction

Intestinal microbiota includes *Enterobacterales* and members of this order are the most common types of human pathogens which cause both community-acquired and hospital-acquired infections, such as cystitis, pyelonephritis, septicemia, pneumonia, peritonitis, meningitis and catheter-related infections (1,2). Nowadays, carbapenem resistance in *Enterobacteriacea* has become the most common antibiotic resistance problem worldwide (2,3). Being the major contributors to carbapenemase-producing enterobacterial infections, *Klebsiella pneumoniae* and *Escherichia coli* include other resistance genes as well as carbapenem resistance genes. Acquisition of resistance to last resort drugs has also increased the incidence of mortality and morbidity rates by nullifying existing treatment options (3,4). Determination of the resistance mechanisms of these clinically important isolates is critical both in terms of infection control and public health measures and in understanding the geographical distribution of these isolates and risk factors (3). In this study, we aimed to investigate $bla_{\text{OXA-48}}$, bla_{KPC}, bla_{IMP}, bla_{VIM} and bla_{NDM} genes, which are the most common carbapenemase producer genes worldwide in carbapenem resistant *K.pneumoniae* and *E.coli* isolates. As one of the largest-capacity 1,500-bed training and research hospital, our results would provide information on the broad distribution of resistance in this region.

Materials and Methods

Isolate Profile

Between January 2015 and April 2017, carbapenem resistant *K.pneumoniae* and *E.coli* isolates from various clinical specimens sent to the laboratory of Gulhane Training and Research Hospital were collected. Identification of isolates were performed by using MALDI-TOF MS (Brucker, USA). Carbapenemase producing isolates were selected according to EUCAST guideline by gradient test and disc diffusion test with ertapenem and meropenem discs (5). The first carbapenem resistant isolates of each patient were included in the study. The isolates were stored at -20ºC in 5% skimmed milk until use.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility tests for imipenem, meropenem, ertapenem, doripenem, ciprofloxacin, levofloxacin, amikacin, gentamycin, ceftazidime, cefepime, ceftriaxone, cefotaxime, piperacillin-tazobactam, ampicillin-sulbactam, amoxicillin-clavulanic acid, aztreonam, trimethoprim-sulfamethoxazole (Oxoid, UK) were performed by disc diffusion method. In carbapenem resistant strains, gradient tests were performed with E-test for ertapenem, imipenem, meropenem and piperacillin-tazobactam (AB Biodisk, Switzerland), and broth microdilution was perfomed for colistin. *Escherichia coli* ATCC 25922 and *Escherichia coli* NCTC 13846 were used as control strains (5,6).

Detection of Carbapenemase Genes by PCR

DNA isolation from bacteria was performed by boiling bacterial suspension in ultrapure water at 95ºC for 10 min. Cell residues were removed by centrifugation. Bio-Speedy™ CRE Real Time PCR screening kit (Istanbul, Turkey) was used to detect $bla_{\text{OXA-48}}$, bla_{KPC}, bla_{IMP}, bla_{VIM} and bla_{NDM} gene region according to the manufacturer's instructions. The detection limit of the kit is 3 copies DNA/µL for the target DNA. For reproducibility studies, the compatibility rate was determined as 96-100% for all targets. All isolates were screened for the presence of $bla_{\text{OXA-48}}$, bla_{KPC}, bla_{IMP}, bla_{VIM} and bla_{NDM} gene region separately. The amplification conditions were as: pre-denaturation at 95°C 180 seconds and multiplication (40 cycles) at 95ºC for 10 seconds and 55ºC for 40 seconds. *K.penumoniae* ATCC 1705 blaKPC, *K.penumoniae* NCTC 13440

blaVIM-1, *K.penumoniae* CDC 529 blaNDM-1, *K.penumoniae* CDC309 blaIMP-2, and *K.penumoniae* blaOXA-48 confirmed positive strains were used as positive control strains.

Interpretation of PCR Results

Cycle threshold (CT)> 38 was interpreted as the reaction was inhibited or there might be contamination that inhibits the qPCR reaction in DNA isolation. In this case, DNA isolation was performed again. CT <38 was interpreted as absence of any inhibition from the sample, indicating that the reagents were working. One of the $bla_{\text{OXA-48}}$, bla_{KPC}, bla_{IMP}, bla_{VIM} and bla_{NDM} target gene regions tested by Real-Time PCR was interpreted as having a positive result in the corresponding gene in the bacterial isolate.

Statistical Analysis

Statistical analysis was performed using 95% confidence interval using SPSS version 15.0, similarity between ratios by chi-square test.

Results

A total of 419 (39 *E.coli* and 380 *K.pneumoniae*) carbapenem resistant isolates were detected among 3845 *E.coli* and 1689 *K.pneumoniae* isolates. 155 (126 *K.pneumoniae* and 29 *E.coli)* carbapenem resistant isolates of the first isolate of each patient were included the study. Of these 155 patients, 74.2% were male (n = 115) and 25.8% (n = 40) were females. Urine (n=45; 29%) was the predominant sample followed by respiratory (n=41; 26.5%), blood (n=34; 21.9%), wound/tissue (n=21; 13.5%) and sterile body fluid samples (n=14; 9.1%). The 95.5% of the isolates were resistant to meropenem and 97.4% to imipenem. The MIC levels of *E.coli* strains were 16-256 mg/l for imipenem, 8-128 mg/l for meropenem. The MIC levels of *K.pneumoniae* strains were 8-256 mg/l for imipenem, 8-256 mg/l for meropenem. The most effective antibiotic against these isolates was colistin (91%) (MIC levels of resistant *K.pneumoniae* strains were 8-128 mg/l), followed by amikacin (52.9%) and gentamicin (34.8%). Resistance rates of *K.pneumoniae* are much higher than *E.coli* strains. The increase in colistin resistance in recent years is noteworthy (11.1%). *E.coli* isolates did not show resistance to colistin. As shown in Table 1, the resistance rate of the β-lactam/β-lactamase inhibitor combination was 100%. Resistance rates of ceftriaxone, ceftazidime, cefotaxime and cefepime were determined at a high rate of 94.2-99.4%. Co-trimoxazole resistance was close to that of *E.coli* and *K.pneumoniae*, which were found as 72.4% and 75.4%, respectively. In Table 1, resistance rates were given to all agents tested both on the isolate basis and on total.

The studied isolates were most frequently isolated from the patients admitted to intensive care unit (ICU) (n=75), followed by surgical clinics (n=27), internal medicine clinics (n=24), and haematology/oncology (n=11), burn care unit (n=11), pediatrics (n=5) and emergency service (n=2). The majority of carbapenem resistant *K.pneumoniae* were isolated from respiratory tract specimens (31.0%), followed by urine samples (29.4%) and blood culture (20.6%).

According to the Real-Time PCR results, 121 (78.1%) of the 155 isolates studied for target gene regions were found to have OXA-48 positivity. Of these, 103 were *K.pneumoniae* and 18 were *E.coli* (Table 2). No target resistance gene was detected in 34 (21.9%) isolates (11 *E.coli*, 23 *K.pneumoniae*). The bla_{NDM} was detected in 9 (7.1%) *K.pneumoniae* isolates, co-carrying $bla_{\text{OXA-48}}$ gene region as well. The bla_{NDM} gene was not found in any *E.coli* isolates, and VIM, IMP and KPC were not detected on any isolates. In Table 3, the numbers and ratios of the target genes in the isolates are given. Both OXA-48 and NDM positive isolates showed higher rates of resistance to antimicrobial agents (Table 3).

Table 1. Antimicrobial resistance rates

Antimicrobials	*K.pneumoniae*		*E.coli*		Total	
	R (%)	n (126)	R (%)	n (29)	R (%)	n (155)
ETP	100.0	126	100.0	29	100.0	155
MEM	95.2	120	96.6	28	95.5	148
IMP	96.8	122	100.0	29	97.4	151
AK	54.8	69	13.8	4	47.1	73
GN	70.6	89	41.4	12	65.2	101
CIP	98.4	124	75.9	22	94.2	146
LEV	93.7	118	72.4	21	83.2	139
CAZ	96.0	121	86.2	25	94.2	146
FEB	97.6	123	89.7	26	96.1	149
CTX	99.2	125	100.0	29	99.4	154
CRO	97.6	123	96.6	28	97.4	151
AMC	100.0	126	100.0	29	100.0	155
SAM	100.0	126	100.0	29	100.0	155
ATM	95.2	120	93.1	27	94.8	147
FOX	93.7	118	89.7	26	92.9	144
PTZ	100.0	126	100.0	29	100.0	155
SXT	75.4	95	72.4	21	74.8	116
CL	11.1	14	0.0	0	9.0	14

ETP; ertapenem, MEM; meropenem, IMP; imipenem, AK; amikacin, GN; gentamicin, CIP; ciprofloxacin, LEV; levofloxacin, CAZ; ceftazidime, FEB; cefepim, CTX; Cefotaxime, CRO; ceftriaxone, AMC; amoxicillin-clavulanic acid, SAM; ampicillin-sulbactam, ATM; aztreonam, FOX; cefoxitin, PTZ; piperacillin / tazobactam, SXT; trimethoprim / sulfamethoxazole, CL; Colistin. R; resistant, n; number.

Table 2. The rates and numbers of target genes in isolates

Target Gene	*K.pneumoniae* (n=126)		*E.coli* (n=29)		Total (n=155)	
	%	n	%	n	%	n
blaOXA-48	81.7	103	62.1	18	78.1	121
blaNDM	7.1	9	0	0	5.8	9
blaVIM	0	0	0	0	0	0
blaIMP	0	0	0	0	0	0
blaKPC	0	0	0	0	0	0
TOTAL	88.9	112	62.1	18	83.9	130

n=number

Discussion

E.coli and *K.pneumoniae* are the major contributors to carbapenem-resistant *Enterobacterales* (CRE) infections worldwide and they may contain other resistance genes besides carbapenemase resistance genes, which causes almost all available treatment options to be, therefore, ineffective (7). In Turkey, CRE seem to become a problem for less than a decade. In 2009, imipenem resistance was 3.1% for *K.pneumoniae* and had not yet been detected in *E.coli* isolates according to HITIT2 study (8). In another study in 2011, imipenem susceptibility was reported as 100% and 94% in ESBL positive *E.coli* and *K.pneumoniae* isolates, respectively (9). However, by 2016, imipenem resistance in *E.coli*

Table 3. Resistance rates of isolates carrying blaOXA-48, co-carrying blaOXA-48 and blaNDM and absence of any carbapenemase gene

Anti-microbials	OXA-48+ NDM (n=9)	OXA-48 (n=112)	NEG-ATIVE (n=34)
	R %	R %	R %
ETP	100	100	100
MEM	100	98.2	85.3
IMP	100	99.1	91.2
AK	88.9	45.5	41.2
GN	88.9	62.5	67.6
CIP	100	92.9	100
CAZ	100	92.0	100
FEB	100	94.6	100
CTX	100	99.1	100
CRO	100	96.4	100
AMC	100	100	100
AMP	100	100	100
SAM	100	100	100
ATM	100	100	100
FOX	100	91.1	94.1
PTZ	100	100	100
SXT	88.9	75.0	76.5
CL	44.4	8.9	0

ETP; ertapenem, MEM; meropenem, IMP; imipenem, AK; amikacin, GN; gentamicin, CIP; ciprofloxacin, LEV; levofloxacin, CAZ; ceftazidime, FEB; cefepim, CTX; Cefotaxime, CRO; ceftriaxone, AMC; amoxicillin-clavulanic acid, SAM; ampicillin-sulbactam, ATM; aztreonam, FOX; cefoxitin, PTZ; piperacillin / tazobactam, SXT; trimethoprim / sulfamethoxazole, CL; Colistin. R; resistant

and *K.pneumoniae* isolates isolated from urinary tract infections had been reported as 3.2% and 36.4%, respectively, and recently, resistance rates show a rise in current studies (10). According to the last CAESAR surveillance report, resistance/intermediate susceptibility rates for *E.coli* and *K.pneumoniae* among blood and cerebrospinal fluid isolates in Turkey were 5% and 41% respectively. Although lower rates were reported from western European contries, similar higher threats in Turkey can clearly be observed for third-generation cephalosporin-resistant *E. coli*, multidrug resistant *K.pneumoniae* and *Acinetobacter* spp., and finally carbapenem resistant *E.coli* and *K.pneumoniae* (11). Imipenem and meropenem resistance rates in *K. pneumoniae* isolated from our blood cultures increased in the last 5 years compared to the previous 5-year period, from 4.7% to 33.3% and 32.0%, respectively, showing a statistically significant increase ($p < 0.001$). In *E.coli*, the resistance rates were 4.7% for both carbapenems over the last 5 years (12). Carbapenem resistance of *K.pneumoniae* was reported as <1% in countries such as UK, Ireland, Norway, Germany, but 33% in Italy, 7% in Bulgaria and 62% in Greece (13). It is obvious that our data are compatible with the countries that are geographically in the same region, and the increase in carbapenem resistance has become a global problem in *E.coli,* as well.

CRE isolates are a serious risk for inpatients and develop resistance to many other antibiotic classes. All of the isolates included in the study were highly resistant and the rate of resistance to the most effective agent, colistin, increased to 11.1% in *K.pneumoniae* isolates. Polymyxins, some aminoglycosides, and tigecycline are generally "last resort drugs" with in vitro activity against CRE (14). Currently, colistin, tigecycline and aminoglycosides in treatment protocols are the main options for the treatment of invasive CRE infections and combination therapy may be superior to monotherapy (15). In our study, the tigecycline susceptibility test was not performed, but the status of colistin and aminoglycoside resistance is worrying.

In enteric bacteria, carbapenem resistance is mainly developed by two mechanisms. The first one is the acquisition of carbapenemase genes encoding enzymes that hydrolyze carbapenems. The other one is the structural and/or quantitative deficiency of porin expression. The most important carbapenemases leading to high levels of resistance to carbapenems can be subdivided into three groups; Metallo-β-lactamases (MBL);

Klebsiella pneumoniae carbapenemase (KPC) and oxacillinases (OXA) (2).

In Turkey, IMP-1 was reported in 2006 from *K.pneumoniae* isolate, and VIM-5 in 2003 (16,17) followed by sporadic cases and the prevalence of VIM was reported as 4.0% in the 2017 EUSCAPE report (3). Our isolates did not produce IMP and VIM enzymes. Until recently, the most common MBLs found in *Enterobacterales* were VIM and IMP, while in 2008, NDM was identified in the *K.pneumoniae* isolate and has spread worldwide. In Turkey, the first NDM-1 was detected in *K.pneumoniae* isolate in 2011 (18) and Turkey was located among the countries with regional spreads (19). Until 2015, isolates carrying both the OXA-48 and NDM-1 resistance genes were reported only from Morocco, Tunisia and Switzerland (20-22), suggesting that NDM-1 was carried to Turkey by refugees from Syria according to the reported case (23). Of the 155 isolates included in this study, bla_{NDM} was detected in 9 (5.8%) *K. pneumoniae* isolates which carried also bla_{OXA-48}. Significant phenotypic resistance was also observed in these strains with high MIC levels (64-256 mg/l for both imipenem and meropenem).

KPCs are the class of the fastest geographically distributed carbapenemases and the first KPC isolate in Turkey was reported in 2014 (24). In our study, KPC was not detected from any strain, the same as in the previous rectal swab screening report from Turkey (25). Despite the high prevalence rates of *K.pneumoniae* isolates in Greece and Italy, and *E.coli* isolates in geographycally close countries such as Greece, Italy and Cyprus (3), KPC-positive pathogens in our country were limited to sporadic cases.

Although other carbapenemases are reported, the most common carbapenemase in our country is OXA-48, which is endemic for Turkey (19). The 103 (81.7%) of the 126 carbapenem resistant *K.pneumoniae* isolates, and 18 (62.1%) of 29 *E.coli* isolates were OXA-48 positive. In a multicenter study in Turkey, OXA-48 enzyme was determined to be 84.6% (26). The prevalence of bla_{OXA-48} in carbapenem resistant *K.pneumoniae* isolates was reported as 79% and in carbapenem resistant *E.coli* isolates as 86.4% (3), which is actullay statistically similar with our study (p=0,438). There were 34 (21.9%) isolates (23 *K.pneumoniae* and 11 *E.coli*) that carried none of the target genes. Although carbapenem resistance in *Enterobacterales* is largely developed by the acquisition of genes encoding carbapenemases, it should be remembered that carbapenem resistance may develop from alternative mechanisms such as variability in permeability. In the European CRE surveillance report of 2017, carbapenem resistance mechanism for the isolate that does not carry any of the genes was indicated on reduction of permeability (3). iIn our study, these strains were not further evaluated for defining other carbapenem resistance mechanism, which was the limitation of this study. Another limitation is that it is not a multicenter surveillence study. Thus, prevalence may not represent all regions of Turkey; however it is important to observe multi-carbapenemase-producer strains and their arising condition.

In this study, bla_{KPC}, bla_{VIM}, bla_{OXA-48}, bla_{NDM} and bla_{IMP} resistance genes were screened in carbapenem-resistant *E.coli* and *K.pneumoniae* isolates by Real-time PCR method. Carbapenem resistant isolates were found to be multi-drug resistant and developed high resistance against other antibacterial agents, as well. Even in the last option of treatment of CRE, such as colistin, resistance to antibiotics has been observed. It has been found that some of our isolates carry more than one resistance mechanism and they have higher resistance rates.

Ethical Approval

Ethical approval is not required for this study.

Conflict of Interest

The Authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Authors' contribution

Aylin Uskudar-Guclu (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing –review & editing)
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