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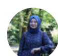

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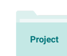

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CO-EXISTANCE OF ISABA1/BLA$_{OXA-51/23}$ IS INCREASING IN CARBAPENEM RERSISTANT *ACINETOBACTER BAUMANNII* ISOLATES IN TURKEY

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ABSTRACT

Introduction: *Carbapenem resistant Acinetobacter baumannii (A. baumannii) strains are challenging topics for hospitals. We determined the antibiotic susceptibilities and genetic resistance mechanisms of 135 A. baumannii isolates from Giresun State Hospital, Turkey between January 2013 and September 2014.*

Material and methods: *Antimicrobial susceptibility tests were performed according to the Clinical and Laboratory Standarts Institute guidelines. β-lactamase coding genes were investigated by simplex/multiplex PCR.*

Results: *High rates of multi drug resistance (51.11%) and extensively drug-resistance (48.14%) were remarkable. Colistin was seemed to be the only active compound against all clinical strains. Isolates were found 100% positive for bla$_{OXA-51}$ and 95.55% positive for bla$_{OXA-23}$. Of all the isolates, 97.05% were found to be blaTEM (n=131) positive concomitant with whether bla$_{OXA-51}$ or bla$_{OXA23}$ or both them. All strains were negative for the rest of the β-lactamase coding genes. ISAb1 element was positive in the 98.51% (n=133) of the isolates and 100% of them were located upstream of bla$_{OXA-51/23}$.*

Conclusion: *To our knowledge this study revealed the highest co-existence of bla$_{OXA-51/23}$ and also demonstrated the increase of co-existence of both bla$_{OXA-51/23}$ and ISAba1/bla$_{OXA-51/23}$ over time in Turkey. The increasing combination of these genes and element may lead more resistance against to carbapenems among A. baumannii isolates.*

Keywords: *Acinetobacter baumannii, ISAb1; bla$_{OXA-51}$ or bla$_{OXA23}$, Carbapenemase.*

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Introduction

Acinetobacter baumannii (A.baumannii) is a Gram negative, non-fermentative bacteria leading hospital acquired, severe infectious diseases including pneumonia, sepsis, menengitis, urinary tract and wound infections. Mutations and acquired resistance determinants cause increasing number of Multi Drug Resistant (MDR), Extensively Drug-Resistant (XDR) or Pan Drug Resistant (PDR) *A.baumannii* isolates worldwide[1].

A.baumannii strains that are resistant to all β-lactams, including carbapenems, are the challenging topics for medical professions in recent years.

The most frequent resistance way for β-lactams is enzymatic degredation via β-lactamase enzymes. Ambler class D β-lactamases (OXA-type) and Ambler class B metallo-lactamases (MBLs) have the leading role for carbapenemase resistance.

Especially, bla$_{OXA51/23}$ variants having ISA*ba1* insertion sequence elements at upstream,

enhance the expression of OXA-type carbapenemases and mobilize them among different strains[2].

AmpC beta-lactamases are also important enzymes, which cause resistance to cephalosporins, penicillins and beta-lactamase inhibitor-beta-lactam combinations. AmpC enzymes are inducible however *A.baumannii* starains do not have inducible AmpC beta-lactamases expression[3]. Increased expression of this enzyme in *A.baumannii* depends on the ISAba1 element[4].

Extended-spectrum ß-lactamases (ESBLs) (TEM-type, SHV-type, CTX-M-type, PER-type and VEB-type genes), which cause phenotypical resistance to penicillins and 3rd generation cephalosporins, MBLs (IMP-like, SIM-1, NDM-type and VIM-like genes) which have been described as carbapenemases, GES and KPC genes from Ambler Class A, which hydrolase various type of cephalosporins and carbapenems are also detected from *A.baumannii strains*[5, 6].

Mortality rates, duration of hospital stay and health expenditures are affected from MDR or PDR A.baumannii infected or colonised patients. Therefore molecular epidemiologic studies are important for not only hospitals alone but also countries' surveillance and the other infection control strategies[5].

The aim of this study was to characterise the susceptibility profile and genetic resistance mechanisms of *A.baumannii* collected from a state hospital in Turkey.

Material and methods

Bacterial Strains and Antimicrobial Susceptibility Testing

In this study, consecutive isolates of *A. baumannii* (n =135) isolated from clinical specimens that had been collected from Turkey between 2013 June -2014 September, were included. The isolates were collected from; respiratory tract (tracheal aspirates, sputum, bronchoalveolar lavage (BAL)), blood, urine, wound, cerebrospinal fluid (CSF), pleural fluid, cathether tip, abscess and tissue cultures. The isolates were identified by both conventional methods and Becton Dickinson (BD) Phoenix Automated Microbiology System according to the manufacturer's instructions.

Antimicrobial susceptibility testing was performed by Becton Dickinson (BD) Phoenix Automated Microbiology System. The minimal inhibitory concentrations (MICs) of carbapenems and colistin were confirmed by E test gradient method. The results were interpreted according to the 2014 Clinical and Laboratory Standards Institute (CLSI) revised supplements[7]. The study was approved by the local ethics review board of Ordu University Medical Faculty.

DNA Extraction

Genomic DNA was obtained from bacterial suspensions which were grown overnight in Luria Broth (LB) with shaking at 37°C. Suspensions were centrifuged at 13,000 rpm for five minutes, and pellets were suspended in 500 μl distilled water and than boiled for 10 minutes. Debris was centrifuged at 13,000 rpm for five minutes and 500 μl of supernatant was obtained. For PCR mixture, 5 μl of each supernatant was used as a template.

Multiplex PCR for Detection of bla$_{OXA}$ and bla$_{CTX-M}$ Genes

Multiplex PCR was used to detect bla$_{OXA-23-24-51}$ and 58-like and bla$_{CTX-M-1/M-2}$ genes using primers listed in Table 1.

	Primer	5'-3' Sequence	Amplicon Size (bp)	Tm (°C)	Reference
Group A	*bla*$_{CTX-M-1}$	F:GCGTGATACCACTTCACCTC R:TGAAGTAAGTGACCAGAATC	260	50	8
	bla$_{CTX-M-2}$	F:TGATACCACCACGCCGCTC R:TATTGCATCAGAAACCGTGGG	341	50	
	bla$_{TEM}$	F:AGTATTCAACATTTYCGTGT R:TAATCAGTGAGGCACCTATCTC	860	49	9
	bla$_{SHV}$	F:ATGCGTTATATTCGCCTGTG R:TTAGCGTTGCCAGTGCTC	843	55	10
	bla$_{GES}$	F:ATGCGCTTCATTCACGCAC R:CTATTTGTCCGTGCTCAGGA	863	56	11
	bla$_{PER-2}$	F:ATGAATGTCATCACAAAATG R:TCAATCCGGACTCACT	927	50	12
	bla$_{VEB}$	F:ATTTCCCGATGCAAAGCGT R:TTATTCCGGAAGTCCCTGT	542	55	
	bla$_{KPC}$	A: CGTTCTTGTCTCTCATGGCC B: CCTCGCTGTGCTTGTCATCC	796	52	13
Group B	*bla*$_{IMP}$	F:CATGGTTTGGTGGTTCTTGT R:ATAATTTGGCGGACTTTGGC	488	56	14
	bla$_{VIM}$	F:ATTGGTCTATTTGACCGCGTC R:TGCTACTCAACGACTGAGCG	780	58	
	bla$_{NDM}$	F:TGGAATTGCCCAATATTATGC R:TCAGCGCAGCTTGTCGGCCATGC	813	54	12
Group D	*bla*$_{OXA-51}$	F: TAATGCTTTGATCGGCCTTG R: TGGATTGCACTTCATCTTGG	353	50	15
	bla$_{OXA-23}$	F: GATCGGATTGGAGAACCAGA R: ATTTCTGACCGCATTTCCAT	501		
	bla$_{OXA-40}$	F: GGTTAGTTGGCCCCCTTAAA R: AGTTGAGCGAAAAGGGGATT	246		
	bla$_{OXA-58}$	F: AAGTAT TGGGGCTTGTGCTG R: CCCCTCTGCGCTCTACATAC	599		
	bla$_{OXA-48}$	A:TTGGTGGCATCGATTATCGG B:GAGCACTTCTTTTGTGATGGC	743		
	*ISAba*1	F: CACGAATGCAGAAGTTG R: CGACGAATACTATGACAC	549	56	16

Table 1: Primers used for amplication and sequencing in this study.

PCRs were performed in a final volume of 50 μL and included 5 μL of genomic DNA, 20 pM of each primer, 10 μL of 10X polymerase activity buffer, 3 μL of 25 mM $MgCl_2$, 200 μM of each dNTPs and 1.5 U of *Taq* Polymerase (Fermentas Thermo Fisher Scientific Inc., Waltham, USA). PCR amplification was performed using initial denaturation at 94°C for 3 min followed by 30 cycles of 25 s at 94°C, 40 s at 52°C and 50 s at 72°C for bla$_{OXA}$ genes and initial denaturation at 95°C for 2 min followed by 30 cycles of 1 min at 95°C, 1 min at 55°C and 1 min at 72°C for blaCTX-M-1/M-2 genes with a final extension of 5 min at 72°C. All PCR results were analyzed on 1% agarose containing 0.5 mg /Lethidium bromide, subsequently visualized under UV light and evaluated according to their molecular size.

PCR Amplifications of the ESBLs and, MBLs Resistance Genes and ISAba1 Element

The primers and PCR amplification conditions used to detect ESBLs and MBLs genes are shown in Table 1[8-16]. The reactions were performed in 50 μL final reaction volume using 5 μL of genomic DNA, 20 pM of each primer, 5 μL of reaction buffer, 3 μL of 25 mM MgCl2, 200 μL of dNTPs and 1 U Go *Taq* Polymerase (Fermentas Thermo Fisher Scientific Inc., Waltham, USA). Co-existence of ISAba1and bla$_{OXA51}$ was detected using the primers ISAba1-F and bla$_{OXA51}$-R. The results were run as above and evaluated according to their molecular size and PCR results of control groups which were defined as β-lactamase gene carrier bacteria in the earlier studies[9, 12, 17].

Results

A total of 135 non-dublicate clinical *A. baumannii* strains were collected from Giresun Prof. Dr. A. Ilhan Ozdemir State Hospital in Turkey over a 18 month period. The majority of the isolates were obtained from respiratory specimens (62 tracheal aspirates (45.92%), 23 sputum (17.03%), 4 bronchoalveolar lavage (2.96%)) followed by 24 blood (17.77%), 12 urine (8.88%), 4 wound (2.96%), 2 cathether tips (0.74%), 1 cerebrospinal fluid (0.74%) (n=1), 1 pleural fluid (0.74%), 1 abscess (0.74%) and 1 tissue culture (0.74%). All patients were hospitalized in several units: 110 patients (81.48%) from intensive care unit, 23 patients (17.03%) from internal units (cardiology, pulmonology, etc.) and 2 patients (1.48%) from surgery clinics. The diagnosis of the patients were cerebrovascular diseases, epilepsy, menengitis, parkinson (31.85%), chronic obstructive pulmonary disease, pneumonia, respiratory failure, pulmonary and thoracic diseases (33.33%), congestive heart failure (7.40%), myocardial infarction (8.88%), malignancy (4.44%), urinary tract infection (2.96%), acute and chronic renal failure (4.44%), diabetes mellitus (DM) (4.44%), cholecystitis (1.48%), tyroid crisis (0.74%). All strains were identified as A. baumannii by Becton Dickinson (BD) Phoenix Automated Microbiology System, conventional methods and blaOXA-51 PCR to specify the *A. baumannii* species.

High rates of *A. baumannii* resistance were observed for ampicillin-sulbactam (94.07%), ceftazidime (98.51%), cefepime (97.03%), piperacillin-tazobactam (97.77%), iprofloxacin (98.51%), levofloxacin (97.77%), gentamicin (86.62%), imipenem (98.51%), meropenem (98.51%), amikacin (94.81%) and tigecycline (10.37%). Colistin was the most active compound (100% susceptible) among all tested antibiotics (Table 2).

Antibiotic	Resistance Rate
Ampisillin-sulbactam	94,07%
Ceftazidime	98,51%
Cefepime	97,03%
Piperacillin-tazobac-tam	97,77%
Ciprofloxacin	98,51%
Levofloxacin	97,77%
Gentamicin	89,62%
Amikacin	94,81%
Tigecycline	10,37%
Imipenem	98,51%
Meropenem	98,51%
Colistin	0%

Table 2: Resistance rates of *Acinetobacter baumannii* isolates (n=135).

The samples, which were resistant to representetives of at least three major antibiotic classes (aminoglycosides, antipseudomonal penicillins, carbapenems, cephalosporins and quinolones) were defined as Multi Drug Resistant (MDR) (51.11%) and the samples which had only colistin sensivity

were defined as Extensively Drug-Resistant (XDR) (48.14%).

Isolates were found 100% positive for bla_{OXA-51} and 95.55% positive for bla_{OXA-23}. Of all the isolates, 97.05% were found to be blaTEM (n=131) positive concommitant with whether bla_{OXA-51} or bla_{OXA23} or both them. All strains were negative for the rest of the β-lactamase coding genes. ISAb1 element was positive in the 98.51% (n=133) of the isolates and 100% of them were located upstream of $bla_{OXA-51/23}$.

Discussion

Extra genetic element capability and high mutation rates give the advantage of an easy adaptation process to the new environments and an enhanced virulance to *A.baumannii*. These benefits cause MDR bacteria whose response to antibiotic treatment is decreased and that has a long life on inanimate surfaces[18]. Although there are several confusing reports about classification of resistant A.baumannii strains, generally the strains resistant to at least three most used antibiotic groups for A.baumannii including aminoglycosides, antipseudomonal penicillins, carbapenems, cephalosporins and quinolones are called MDR[1].

Recently, hospital-acquired infections with MDR *A.baumannii* strains have been reported from all over the world in an increasing rate[5]. MDR A. baumannii are usually known with their high resistance rates to cephalosporins, aminoglycosides and quinolones[1]. Also in our study, 51.11% of all strains were MDR and in a correlation with the literature the resistance rates were; 98.51% for ceftazidime, 97.03% for cefepime, 98.51% for ciprofloxacin, 97.77% for levofloxacin, 86.62% for gentamicin and 94.81% for amikacin.

Although colistin and tigecycline are the last options for MDR and XDR *A.baumannii* strains, incerasing resistance rates have been declareted for these antibiotics[1]. During 2015, the resistance rates of tigecycline and colistin have been reportedto be 45.5% from Taiwan and 50% from USA, respectively[18]. There are also some studies from Turkey declerating that tigecyclin and colistin resistance rates were increased to 27.4% and 6%, respectively[19, 20].

In our study, tigecycline resistance rate was 10%. In addition there were no colistin resistant strains. The differences in the resistance rates might be related with excessive usage of these antibiotics against MDR *A.baumannii*. However colistin still seems to be the best choice for the treatment of XDR *A.baumannii*.

Ambler class D β-lactamase enzymes are examined in four phylogenetic groups: $OXA_{23\text{-like}}$, $OXA_{24/40\text{-like}}$, $OXA_{58\text{-like}}$ ve OXA_{51}. OXA_{51} is originally intrinsic to *A. baumannii* and in our work it was determined 100% positive. It was also used for validation of *A. baumanni* identification. $OXA_{23\text{-like}}$ gene is the best known source of carbapenemase resistance and it is transfered via plasmid or chromosomally[5]. The highest OX_{A23} enzyme production was reported by Keskin with resistance rate 91.5% from Turkey up to know[20]. In our study this resistance rate was 95.55%. If we consider the 85% resistance rate reported from Kuwait, $OXA_{23\text{-like}}$ enzyme production in Turkey is quite a bit higher than the Far and Middle East countries[21]. These results have been observed in MDR A. baumannii strains and this can be interpreted as $OX_{23\text{-like}}$ gene existence may show a correlation with carbapenem resistance.

ISA*ba1* insertion sequence elements have been found in A. baumannii strains, which can enhance the expression of OXA-type carbapenemases and mobilize them among different strains[2]. The main resistance mechanism was the presence of the ISAbaI/$bla_{OXA-51/23}$ gene in the *A. baumannii* isolates. In an earlier study from Turkey, the ISAba1 element was shown at upstream of bla_{OXA-51} in 80% of A. baumannii strains, and this combination has been shown to confer high levels of carbapenem resistance[12].

To our knowledge our study revealed the highest co-existence of $bla_{OXA-51/23}$ in *A. baumannii* isolates from Turkey and also demonstrated the increase of co-existence of $bla_{OXA-51/23}$ and ISA*ba*1/*bla*$_{OXA-51/23}$ over time in Turkey. Our results are consistent with the previous studies that report high carbapenem resistance in *A. baumannii* strains from Turkey with OXA-type carbapenemases and ISA*ba1* element predominancy. It seems that the increasing combination of these genes and element may lead to an increase in resistance rate against carbapenems among *A. baumannii* isolates.

Usually $OXA_{58\text{-like}}$ producers are reported from Asia and Middle East countries. The highest OXA58-like enzyme production was detected from India as 15% up to now[22]. On the other hand the highest resistance rate from Turkey was 53.3%[23].

In our study we couldn’t determine any $OXA_{58\text{-like}}$ producer. It is obvious that $OXA_{58\text{-like}}$ production changes even within countries. In our study there was no $OXA_{24/40\text{-like}}$ producer strain however Vali et al. detected high rates of this enzyme production with 85% from Kuwait and also another center from Turkey detected $OXA_{24/40\text{-like}}$ pruduction as 2%[20]. Studies from Turkey indicate that $OXA_{24/40\text{-like}}$ production is very rare. The fact that majority of cases about $OXA_{24/40\text{-like}}$ and $OXA_{58\text{-like}}$ are beeing reported from Asian and Middle East countries points that these strains are spreading to the world from these regions.

Conclusion

The study results show that many carbapenemase producing strains are mainly located in Mediterrenean, Middle East and Asian countries. Due to the migration paths, Turkey has a strategic geographic location in spreading of these isolates to the whole world. In order to control emerging MDR, XDR and PDR A. baumannii strains, new strategies and further epidemiological studies are needed.

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