

## Growing OXA-23 type strains among carbapenem-resistant *Acinetobacter baumannii* and tigecycline as an alternate combination therapy

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Received: 04.08.2015 • Accepted/Published Online: 26.03.2016 • Final Version: 20.12.2016

**Background/aim:** The increasing prevalence and global spread of difficult-to-treat carbapenem-resistant *Acinetobacter baumannii* has become a serious problem. The aim of this study is to investigate the resistance patterns and tigecycline sensitivity of carbapenem-resistant *A. baumannii* strains.

**Materials and methods:** *Acinetobacter* strains that were carbapenem-resistant and collected mainly from intensive care units were included into this study. The antibiotic sensitivity/resistance of the strains to other antibiotics and tigecycline were noted. Presence of *bla*OXA-23, *bla*OXA-48, *bla*OXA-58, and NDM-1 was investigated by PCR.

**Results:** In total, 44 carbapenem-resistant *A. baumannii* strains were detected. In addition, 57% (25/44) showed resistance to netilmicin and 2% (1/43) to tigecycline. All of the strains were susceptible to colistin. *bla*OXA-58 was found only in one (2%) strain while *bla*OXA-23 was found in 14 (32%) strains. All strains were negative for *bla*OXA-48 and NDM-1.

**Conclusion:** *bla*OXA-23 was the main resistance pattern in carbapenem-resistant *A. baumannii* strains. *bla*OXA-58 was present only in one strain and no *bla*OXA-48 was found. Tigecycline susceptibility is high and it can be a treatment option for a possible combination therapy of carbapenem-resistant *A. baumannii*, especially for those for whom colistin is contraindicated because of its toxicity.

**Key words:** OXA, beta-lactamases, *Acinetobacter*, carbapenemase, drug resistance

### 1. Introduction

*Acinetobacter baumannii* has emerged worldwide as an important opportunistic nosocomial pathogen, especially in intensive care unit (ICU) patients (1). Carbapenems have been widely used to treat serious infections associated with multidrug-resistant (MDR) *A. baumannii*, but carbapenem resistance has been increasingly reported worldwide (2,3). Because of this emerging resistance, new treatment options with old antibiotics like colistin and also recent therapy combinations like with tigecycline are considered.

Resistance to carbapenem in *Acinetobacter* species occurs due to the following mechanisms: beta-lactamase production, the loss of outer-membrane porins, overexpression of efflux pumps, penicillin-binding protein alteration, and carbapenem-hydrolyzing oxacillinases (4,5). Although metallo-beta-lactamase (MBL) has been

identified in a wide variety of gram-negative species, this class of enzyme is not common in *A. baumannii*, in which the oxacillinases represent the most commonly acquired carbapenem-hydrolyzing enzymes (6). OXA-58-like and OXA-23-like carbapenemase-producing strains have been among the most detected patterns in recent years (7).

A study by the same authors of this paper regarding resistant gram-negative bacteria was conducted in a tertiary-care hospital in Turkey. Extended-spectrum beta-lactamase, AmpC, and MBL were investigated in more than 70 isolates, which included MDR *Escherichia coli*, *Klebsiella* spp. and *Acinetobacter* strains (8). After this study, the study team decided to search for further properties of the *Acinetobacter* strains.

The aim of this study is to investigate the molecular characteristics of carbapenem-resistant *A. baumannii* isolates identified in our hospital and also evaluate the

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sensitivity of the strains to other antibiotics for alternative treatment regimens for future empiric therapy options.

## 2. Materials and methods

Forty-four carbapenem-resistant *A. baumannii* strains collected at the Ankara Training and Research Hospital having 700 beds between June 2011 and June 2012 were included in this study. Phenotypic study of the strains was performed in the same hospital, but genotypic classification was performed in the microbiology laboratory of Hacettepe University. Isolates were obtained from tracheal aspirates (n = 15), urine (n = 13), catheters (n = 6), skin/mucosa (n = 6), blood (n = 2), cerebrospinal fluid (n = 1), and pleural fluid (n = 1) samples.

Multidrug resistance in *A. baumannii* is defined as nonsusceptibility to  $\geq 1$  agent in  $\geq 3$  of the following antimicrobial categories: aminoglycosides, antipseudomonal carbapenems, antipseudomonal fluoroquinolones, antipseudomonal penicillins, extended-spectrum cephalosporins, folate pathway inhibitors, penicillins + beta-lactamase inhibitors, polymyxins, and tetracyclines (8). The antibiotic use of the patients, which genera the strains belonged to, and the origin of the clinical specimens were noted. Bacterial identification was performed with the VITEK 2 system (bioMerieux, France) with the GN cards, used according to the manufacturer's instructions. Susceptibility of the isolates to antimicrobial agents was tested with AST-N174 cards and gram-negative identification cards (GNID) in the VITEK 2 system and confirmed by disk diffusion method according to 2010 CLSI standards.

Although the E-test is recommended to detect sensitivity to tigecycline, automatized results (e.g., VITEK 2) are used in routine work to start the therapy as soon as possible until E-test results are available. Since the hospital laboratory sometimes uses different methods in testing tigecycline sensitivity, tigecycline sensitivity was investigated by all three methods: disk diffusion (15 µg, Bioanalyse, Turkey) method, E-test (bioMerieux), and automatized system (VITEK 2, bioMerieux). For disk diffusion, British Society for Antimicrobial Chemotherapy limits were used ( $\geq 24$  mm: sensitive,  $\leq 19$  mm: resistant). For the E-test, the following MIC values were used, according to the US Food and Drug Administration:  $\geq 2$  µg/mL: sensitive, 4–6 µg/mL: intermediate, and  $\leq 8$  µg/mL: resistant. For the VITEK 2 system the following MIC values were used:  $\geq 2$  µg/mL: sensitive, 4–6 µg/mL: intermediate, and  $\leq 8$  µg/mL: resistant. Results of disk diffusion, E-test, and VITEK methods were compared by Spearman correlation test.

Genes encoding oxacillinases showing carbapenemase activity like OXA-23, OXA-48, and OXA-58 clusters and NDM-1 were investigated in all *A. baumannii* isolates by polymerase chain reaction (RT-PCR).

Isolation of bacterial DNA was done as described by Olsvik and Strockbine (9). A single colony of the isolate was inoculated into 2 mL of Mueller-Hinton broth and inoculated for 18 h at 37 °C. Cells from broth medium were harvested by centrifuging for 10 min in a microcentrifuge at 14,000 rpm. Then cells were resuspended in Tris-EDTA (TE) buffer (1 mM Tris, pH 7.5, and 0.5 mM EDTA, pH 8.0) and harvested by centrifuging for 10 min in a microcentrifuge. The bacterial pellet was then resuspended in TE buffer. The bacterial pellet was then boiled for 10 min and centrifuged at 10,000 rpm for 10 min, and then the DNA in the supernatant part was frozen at –80 °C until use (9).

Amplification reactions were performed in a final volume of 50 µL, containing 1X reaction buffer; 2.5 mM MgCl<sub>2</sub>; 0.2 mM each of dATP, dCTP, dGTP, and dTTP; 0.5 U of Taq DNA polymerase (Thermo Scientific, Lithuania); 30 pM each of primers OXA-23-F (5'-GAT GTG TCA TAG TAT TCG TCG-3') and OXA-23 R (5'-TCA CAA CAA CTA AAA GCA CGT-3') (10), OXA-48A (5'-TTG GTG GCA TCG ATT ATC GG-3') and OXA-48B (5'-GAC CAC TTC TTT TGT GAT GGC-3') (11), OXA-58A (5'-CGA TCA GAA TGT TCA AGC GC-3') and OXA-58B (5'-ACG ATT CTC CCC TCT GCG C-3') (12), and NDM Fm (5'-GGT TTG GCG ATC TGG TTT TC-3') and NDM Rm (5'-CGC AAT GGC TCA TCA CGA TC-3') (13) (Fermentas, Thermo Scientific); and 5 µL of sample DNA. The amplification reactions were performed in an automated thermal cycler (Flexigene, Techne, UK) programmed for denaturation at 94 °C for 5 min, 94 °C for 25 s for 30 cycles, annealing at 52 °C for 40 s and extension at 72 °C for 50 s, and a final extension at 72 °C for 6 min. PCR products (10 µL of each reaction mixture) were then separated by electrophoresis in 1.5% agarose gels with 1X TAE running buffer. After the gels were stained with ethidium bromide, they were visualized on a UV transilluminator (Kodak Gel Logic 200, USA) and photographed. As molecular weight standards, 100 bp and fx174 were used. Isolates with NDM-1, OXA-58, OXA-48, and OXA-23 phenotypes showed 621-, 528-, 743-, and 1058-bp bands, respectively. Positive and negative controls were used except for NDM-1, because the controls were not available for it.

## 3. Results

All of the carbapenem-resistant *A. baumannii* isolates showed 100% resistance to piperacillin, ciprofloxacin, ceftazidime, and cefepime. In addition, 57% (25/44) showed resistance to netilmicin and 2% (1/44) to tigecycline. All of the strains (100%) were susceptible to colistin.

According to VITEK 2, E-test and disk diffusion results, tigecycline resistance was detected in 1 (2%), 1

(2%), and 18 (40%) strains, respectively. The only strain detected as resistant by E-test was found to be sensitive by VITEK 2, while the resistant strain by VITEK 2 was found to be intermediately sensitive by E-test. Eight of 26 (31%) sensitive strains by E-test were found to be intermediately sensitive by VITEK 2. A correlation of 46% was detected between E-test and VITEK 2 results ( $R = 0.463$ ,  $P = 0.002$ ) by Spearman correlation test. No correlation was detected between disk diffusion and the other tests.

Of the 44 carbapenem-resistant *A. baumannii* isolates, 14 (32%) carried *bla*OXA-23 (Figure) and 1 (2%) carried *bla*OXA-58. None of them carried *bla*OXA-48 or *bla*NDM. Twelve (86%) of the *bla*OXA-23 carriers were isolated from patients in the ICUs (anesthesiology ICU (8.66%), neurosurgery ICU (1.8%), pediatrics ICU (1.8%), neonate ICU (1.8%), and surgical ICU (1.8%)), and two of them from patients in the orthopedics and traumatology clinic. Characteristics and sample sites of carbapenem-resistant *Acinetobacter* strains are given in the Table. Of the patients from whom *bla*OXA-23-positive strains were isolated, nine (64%) had been treated with multiple antibiotics (including carbapenem) while one (7%) had been treated with cephalosporins and one (7%) had been treated with glycopeptides, whereas three of them (21%) had not used any antibiotics before the *A. baumannii* strains were isolated.

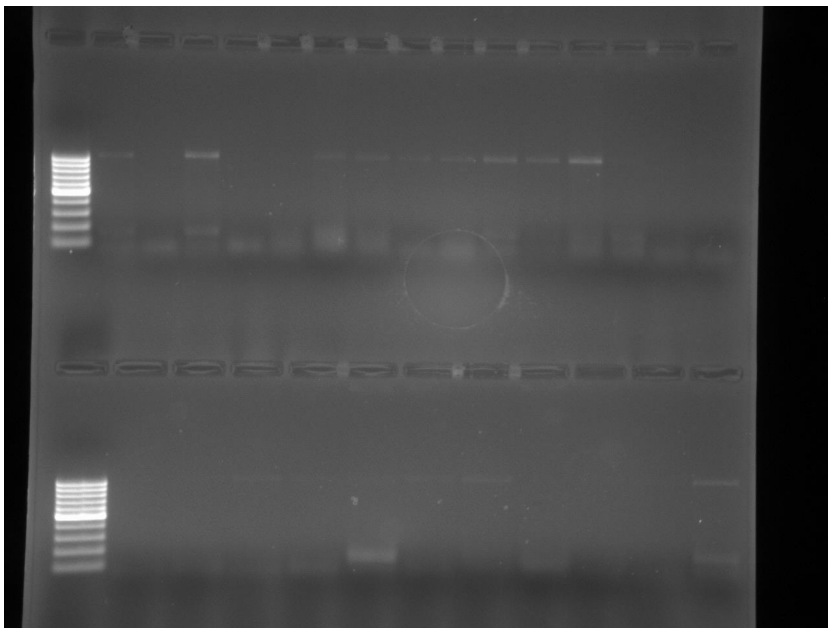
The *bla*OXA-58-positive strain was isolated from a tracheal aspirate culture of a patient who had been under quinolone therapy in the anesthesia and reanimation ICU.

**Table.** Characteristics and sample sites of carbapenem-resistant *Acinetobacter* strains (n = 44).

	n (%)	Samples, n (%)
<i>bla</i> OXA-23	14 (32)	Tracheal aspirates, 5 (36) Urine, 3 (20) Skin/mucosa, 4 (29) Catheter, 1 (7) Pleural fluid, 1 (7)
<i>bla</i> OXA-58	1 (2)	Tracheal aspirates, 1 (100)
<i>bla</i> OXA-48	0	NA
<i>bla</i> NDM	0	NA

#### 4. Discussion

There are only limited studies on the presence of oxacillinase type carbapenemases of carbapenem-resistant *A. baumannii* strains in Turkey, where MDR and panresistant *Acinetobacter* is a very common problem. It may be a threat for other European countries as well because of globalization and frequent admissions of foreign patients as a part of health tourism, which has been growing in the recent years. The growing resistance and nosocomial spread of bacteria carries a big challenge for management of the infections caused by *A. baumannii*.



**Figure.** Positive strains for OXA-23 gene amplified with PCR. Lane 1: MW marker; Lanes 2, 4, 7–13: isolates positive for OXA-23 gene; Lanes 3, 5, 6, 14–16: negative for OXA gene.

MDR *A. baumannii* clones are spreading throughout many different geographic areas and treatment options for MDR *A. baumannii* infections are limited in most cases to carbapenems (14). Carbapenem resistance may be caused by especially carbapenem-hydrolyzing beta-lactamases and the OXA-types play an especially major role. OXA carbapenemases are increasingly encountered worldwide, especially in nosocomial settings. During 1999 to 2009, *A. baumannii* strains carrying the *bla*OXA-58 carbapenemase gene predominated among carbapenem-resistant isolates of this species in the hospital flora in various Mediterranean countries including Italy, Greece, Lebanon, and Turkey (15,16). In 2006 two carbapenem-resistant *A. baumannii* isolates were *bla*OXA-23-positive in Ireland (17). Since 2009, isolation of *A. baumannii* producing the OXA-23 carbapenemase has been increasingly reported in European countries (18,19). Similarly, in our study, OXA-23 carbapenemase was the dominant resistant pattern; 32% of 44 *A. baumannii* strains were OXA 23 carbapenemase-positive. In another study from Turkey, Gür et al. showed that genes encoding oxacillinases showing carbapenemase activity (OXA-23, -24, and -58 clusters) were detected in all 44 carbapenem-resistant isolates among 75 *A. baumannii* samples collected in 2006: 26 (59.1%) strains harbored *bla*OXA-23-like genes and 18 (40.9%) carried *bla*OXA-58-like genes (7). From another European country, Greece, which is close to Turkey, Liakopoulos et al. (20) showed in their study that of 174 carbapenem-resistant *A. baumannii* isolates 125 (71.8%) carried *bla*OXA-23, 48 (27.6%) carried *bla*OXA-58, and one (0.6%) was positive for both genes. The majority of *bla*OXA-58 carriers (n = 42) were isolated during 2010. Five of the *bla*OXA-23 carriers were isolated in late 2010 from patients in ICUs. A total of 376 *Acinetobacter* isolates were collected prospectively from hospitalized patients at 15 medical centers in Germany during three surveillance studies conducted over a 5-year period (2005–2009); 25 of them were nonsusceptible to imipenem and all of them produced OXA-58-like or OXA-23-like carbapenemases (21).

After the initial report in Toulouse, France, OXA-58-producing *A. baumannii* isolates have been reported in several countries around the world, suggesting a wide distribution (12,22,23). In Europe, OXA-58-producing *A. baumannii* has been reported in Greece, Italy, Turkey, Spain, and Belgium (22–24). In our study only one (2.2%) of the strains carried OXA-58. From a neighboring country, Sonrabi et al. (25) studied 62 imipenem-resistant isolates from the northwest of Iran and showed that 3.2% carried OXA-58 and 88.7% of the strains carried OXA-23. Another study from Turkey by Ergin et al. (26) evaluated 100 nonduplicate *A. baumannii* blood culture isolates and showed that carbapenem resistance was associated with the presence of *bla*OXA-23 (31% of isolates) and *bla*OXA-58 (23% of isolates) genes. The occurrence of isolates carrying

*bla*OXA-58 genes increased between 2004 and 2009, but decreased in 2010. In contrast, isolates with *bla*OXA-23 genes increased during the 2008–2010 period.

*bla*OXA-24, *bla*OXA-40, and *bla*OXA-143, which have importance in the epidemiology of *Acinetobacter* and antimicrobial resistance, have been kept out of the scope of our study. This can be considered as a limitation of our analysis.

*A. baumannii* has developed resistance to many conventional treatments and can therefore be very challenging in terms of treatment options (3,27,28). Various antimicrobials have been used to treat *A. baumannii* infection, including carbapenems, polymyxins, tetracyclines and glycolcyclines, aminoglycosides, fluoroquinolones, and various combination therapies. Of these antimicrobial agents, carbapenems have traditionally been used as the first-line treatment of choice; however, rates of resistance to this agent are often high, rendering treatment ineffective. Polymyxins appear to be effective for treating *A. baumannii* infections, with low rates of resistance, although data from well-designed clinical trials are lacking (27,28). All of our strains were susceptible to colistin, and although aminoglycoside resistance was high, compared with other antibiotics like quinolones, to which the strains were 100% resistant, they can be still an option for combination therapy. Tigecycline, although not approved for serious infections of ICU patients, can be an option in combination therapies for patients especially in *Acinetobacter*-related skin and soft tissue infections. Jones et al. (29) showed that for *Acinetobacter* spp., applying US Food and Drug Administration tigecycline breakpoint criteria, tigecycline zone diameters (obtained by disk diffusion) and MIC results (obtained by broth microdilution) led to an unacceptable error rate of 23.3%. Thamlikitkul et al. (30) also found that if an inhibition zone diameter of  $\geq 19$  mm was a breakpoint for tigecycline susceptibility, only 44.6% of the isolates were susceptible to tigecycline, which shows a very high level of disagreement between broth microdilution and E-test results. The disk diffusion method is not useful for detecting tigecycline sensitivity of *A. baumannii*. The E-test is the standard method but sometimes the results are time-consuming. E-test and VITEK 2 results are correlated to an extent in our study and we suggest that VITEK 2 results can be used when trying to choose an alternative therapy with tigecycline for treating *Acinetobacter* infections while waiting for E-test results.

In conclusion, *bla*OXA-23 was the main resistance pattern in carbapenem-resistant *A. baumannii* strains in our hospital, like in European countries during 2008 and 2010, and mostly derived from *A. baumannii* strains of tracheal aspirates and skin/mucosa specimens. *bla*OXA-58 was present only in one strain and no *bla*OXA-48 was

found. Tigecycline susceptibility is high and it can be a treatment option for a possible combination therapy of

carbapenem-resistant *A. baumannii*, especially for those for whom colistin is contraindicated because of its toxicity.

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