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First report of OXA-143-lactamase producing *Acinetobacter baumannii* in Qom, Iran

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ABSTRACT

Objective(s): Antibiotic resistance in *Acinetobacter baumannii* and outbreaks caused by this organism have been reported from several areas of the world. The present study aimed at determining the antibiotic susceptibility profiles and the distribution of OXA-type beta-lactamases among Iranian *Acinetobacter baumannii* isolates from Qom of Iran.

Materials and Methods: For this study, 108 non-duplicate *A. baumannii* isolates were obtained from clinical specimens in four teaching hospitals in Qom in the central of Iran. The antimicrobial susceptibility of isolates was tested by standard disk diffusion and prevalence of *bla* OXA genes was investigated by PCR method.

Results: Among 97 carbapenem non-susceptible isolates of *A. baumannii*, 90.72% (88 isolates) isolates showed extensive drug resistance to multiple antibiotics. Among carbapenem resistant isolates, 100% carried *bla*$_{OXA-51-like}$, 82.47% carried *bla*$_{OXA-23-like}$, 55.67% carried *bla*$_{OXA-58-like}$, 22.68% carried *bla*$_{OXA-40-like}$ and 14.43% had *bla*$_{OXA-143-like}$ resistance genes.

Conclusion: This study demonstrated high genetic diversity of OXA genes among isolates of *A. baumannii* in Qom, Iran.

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Introduction

Acinetobacter baumannii is a glucose non-fermentative, Gram-negative bacillus classified as a significant opportunistic pathogen and is usually involved in infectious outbreaks originating in intensive care units (1). The infections caused by *A. baumannii* include bacteremia, ventilator-associated pneumonia, meningitis, urinary tract and wound infections (2). The number of multidrug resistant (MDR) strains of *A. baumannii* has increased in recent years and therefore treatment of this organism is complicated (3). The terms of pan drug resistance (PDR), extensive drug resistance (XDR) and multidrug resistance (MDR) were explained as, resistance of an isolate to all antibiotics in all antimicrobial categories, resistance to at least one antibiotic in all expect one or two antimicrobial categories and resistance to at least one antibiotic in ≥3 antimicrobial categories, respectively.

The antimicrobial categories were included aminoglycosides, carbapenems, cephalosporins, fluoroquinolones, penicillins, monobactams and polymyxins (4).

Carbapenems are considered a last-line agent for the treatment of important Gram-negative bacilli, but resistance to these compounds in *A. baumannii* has been increased worldwide within the past decade (5, 6). Several mechanisms involved in resistance to carbapenem antibiotics in *A. baumannii* among them OXA-type beta-lactamases are the most widespread mechanism (7). At the present five main groups of OXA-type beta-lactamases have been identified in *A. baumannii*: *bla*$_{OXA-23-like}$; *bla*$_{OXA-40-like}$; *bla*$_{OXA-51-like}$; *bla*$_{OXA-58-like}$ and *bla*$_{OXA-143-like}$ (8, 9). The OXA-type beta-lactamases contain between 243 and 260 amino acids residues, with a molecular mass ranging from 23 to 35.5 kDa (10). The first report of OXA-type beta-lactamases in *A. baumannii* was from Scotland in 1985 that named ARI-1 (*Acinetobacter* Resistant to Imipenem) (11) and later designated as OXA-23 (12). Nowadays, this gene has been discovered from many countries of the world (13). The second group of OXA-type beta-lactamases is *bla*$_{OXA-40-like}$, originally called OXA-24, which was initially found in *A. baumannii* from Spain (14).

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This gene encoded chromosomally or by plasmid and has 60% identity with OXA-23 (1). The largest group of OXA-type beta-lactamases is the *bla*$_{\text{OXA-51-like}}$, which corresponds to chromosomal encoded enzymes and therefore naturally occurs in *A. baumannii* (15). The fourth group is *bla*$_{\text{OXA-58-like}}$ that was identified in France (16). These enzymes often located on plasmids, which may explain their wide distribution (1). Recently, Higgins *et al*. reported a new OXA-type beta-lactamase, the OXA-143, which isolated from a carbapenem resistant *A. baumannii* in Brazil. This gene has been identified in plasmid and so far was not reported from other countries of the world (8). The purpose of this study was to access the antibiotic susceptibility profile and the rate of MDR, XDR and PDR *A. baumannii* isolated from different hospitals in Qom in center of Iran and to investigate the distribution of OXA-type beta-lactamases among *A. baumannii*.

Materials and Methods

Bacterial isolation and identification

A total of l08 non-duplicate isolates of *A. baumannii* were collected from clinical specimens of hospitalized patients in (four teaching hospitals in Qom, Iran) Shahid-beheshti hospital (a 530-bed referral hospital with three 12-bed ICUs), Nekoei Hospital (a 170-bed referral hospital), Kamkar Hospital (a 150-bed referral hospital) and Valiasr Hospital (a 158-bed referral hospital) between November 2012 and October 2013. The isolates were obtained from clinical specimens, including tracheal aspirate, urine, blood, wounds and cerebrospinal fluid. The identification of the isolates was performed using standard microbiological and biochemical tests such as Gram stain, colony morphology, glucose oxidation, citrate utilization, oxidase tests and growth at 44 °C (17). In addition, identification of *A. baumannii* was confirmed using *bla*$_{\text{OXA-51}}$ PCR (18).

Antibiotic susceptibility testing

Susceptibility to a panel of 18 antimicrobial agents was determined by Kirby-Bauer disc diffusion according to Clinical and Laboratory Standard Institution (CLSI) guideline (19). Antibiotics used were ceftriaxon (30 µg), ceftazidime (30 µg), gentamicin (10 µg), amikacin (30 µg), ciprofloxacin (5 µg), piperacillin (100 µg), piperacillin–tazobactam (100/10 µg), imipenem (10 µg), meropenem (10 µg), aztreonam (30 µg), cefepime (30 µg), levofloxacin (5 µg), ampicillin-sulbactam (10/10 µg), trimethoprime-sulfamethoxazole (25 µg), ticarcillin-clavulanic acid (75/10 µg), tobramycin (10 µg), colistin (10 µg), polymyxin B (30 unit) (MAST, Merseyside, United Kingdom). *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as controls. Intermediate sensitivity was considered as resistance.

DNA extraction and PCR assay

All *A. baumannii* isolates were grown for 24 hr at 37 °C in MacConkey agar then pure colonies were isolated and cultured in the LB broth medium and DNA was extracted by boiling method (20). Detection of *bla*$_{\text{OXA-23-like}}$, *bla*$_{\text{OXA-40-like}}$, *bla*$_{\text{OXA-51-like}}$, *bla*$_{\text{OXA-58-like}}$ and *bla*$_{\text{OXA-143-like}}$ in clinical isolates of *A. baumannii* was carried out by PCR with specific primers (8, 21-23). PCR amplification conditions were as follows: Initial denaturation at 94 °C for 4 min, followed by 35 cycles of denaturation for 1 min at 94 °C, annealing at specific temperature for each gene for 1 min, and extension at 72 °C for 1 min with a final extension at 72 °C for 7 min. PCR products were analyzed by gel electrophoresis in 1.2 % agarose gel at 85 V. *A. baumannii* reference strain NCTC 12516, NCTC 13305, NCTC 13304 and NCTC 13302 were used as positive control for the *bla*$_{\text{OXA-51-like}}$, *bla*$_{\text{OXA-58-like}}$, *bla*$_{\text{OXA-23-like}}$ and *bla*$_{\text{OXA-40-like}}$ respectively. PCR product of *bla*$_{\text{OXA-143-like}}$ gene was extracted from the gel, purified and sequenced using an automated sequencer. DNA sequence was compared to the national center for biotechnology information (NCBI) database.

Results

A total of 108 *A. baumannii* isolates were recovered from clinical specimens collected in four teaching hospitals in Qom, Iran. Clinical samples were tracheal aspirate (81 isolates, 75%), urine (17 isolates, 15.74%), blood (7 isolates, 6.48%), wounds (2 isolates, 1.85 %) and cerebrospinal fluid (1 isolate, 0.93%).

The age ranges of the patients were from 20 to 90 years old with a median of 52 years. Seventy-five (69.44%) patients were male and thirty-three (30.56%) were female. *A. baumannii* isolates were collected from different hospital wards as follows; ICU wards (92 isolates, 85.19%), burn wards (2 isolates, 1.85%), trauma and emergency wards (7 isolates, 6.48%), general surgery wards (2 isolates, 1.85%) and internal wards (5 isolates, 4.63%). Analysis for presence of *bla*$_{\text{OXA-51-like}}$ gene with PCR method showed that all isolates were positive for this gene and confirmed them as *A. baumannii*. *A. baumannii* isolates showed 100% resistance to aztreonam and ticarcillin-clavulanic. In addition, 41.6% and 12% of the isolates were resistant to colistin and polymixin B, respectively (Table 1). In addition, among 108 *A. baumannii* isolates screened 12 isolates (11.11%) were multidrug resistant (MDR), 89 isolates (82.4%) were extensive drug resistant (XDR) and 6 isolates (5.55%) were pandrug resistant (PDR). Of the total 108 *A. baumannii* collected in this study, 97 isolates (89.81%) were found non-susceptible to imipenem and meropenem.

Table 1. Antibiotic resistance of *Acinetobacter baumannii* isolates

Antimicribial agents	Resistance (%)
Ceftriaxone	97.22
Ceftazidime	94.44
Gentamicin	81.48
Amikacin	93.51
Ciprofloxacin	93.51
Piperacillin	97.22
Piperacillin-Tazobactam	94.44
Imipenem	89.81
Meropenem	89.81
Colistin	41.66
Polymyxin B	12.03
Azotreonam	100
Cefepime	93.51
Levofloxacin	91.66
Tobramycin	47.22
Ampicillin-Sulbactam	92.59
Ticarcillin-Clavulanic acid	100
Cotrimoxazole	95.37

The results of PCR assays for 97 carbapenem non-susceptible isolates of *A. baumannii* showed that 80 isolates (82.47%) carried $bla_{\text{OXA-23-like}}$, 54 isolates (55.67%) carried $bla_{\text{OXA-58-like}}$, 22 isolates (22.68%) carried $bla_{\text{OXA-40-like}}$ and 14 isolates (14.43%) had $bla_{\text{OXA-143-like}}$ genes (Figure 1). The sequencing and alignment results for PCR product of $bla_{\text{OXA-143-like}}$ gene was showed that sequence of this gene was 100% similar to sequences of $bla_{\text{OXA-143-like}}$ genes recorded in the GenBank and registered in GenBank with accession number KX349208. Table 2 shows the genotypic profiles of OXA-type beta-lactamase genes in carbapenem resistant *A. baumannii* isolates.

Discussion

Nosocomial infections are an important origin of mortality and morbidity in hospitalized patients. *A. baumannii* plays a significant role in these infections especially in ICU wards due to its resistance against multiple classes of antibiotics (24). The finding of this study showed that 85.18% of *A. baumannii* isolates were recovered from hospitalized patients in ICU wards. This result is in line with previous report about the role of *A. baumannii* in ICU infections (25, 26). Findings of this study showed that 89.81% of *A. baumannii* isolates were resistant to imipenem and meropenem. Previous reports from Iran showed the resistant rate to imipenem in 50.7% (25), 52% (27) and 62% (28) of *A. baumannii* isolates which indicates an increase in the rate of resistance to carbapenems. Results of other studies also show that resistance rate to carbapenems in recent years has been increased (29, 30). Results of PCR amplification

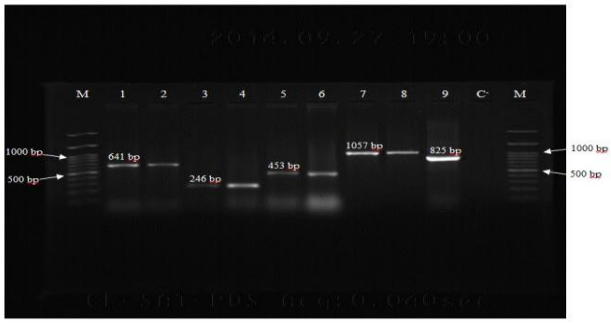

Figure 1. PCR amplification for the detection of OXA-type beta-lactamase genes among Acinetobacter *baumannii* isolates. Lane M: DNA size marker (100 bp plus), Lane 1: OXA-51 positive control (*A. baumannii* NCTC12516), Lane 2: OXA-51 (641 bp) positive isolate, Lane 3: OXA-40 positive control (*A. baumannii* NCTC 13302), Lane 4: OXA-40 (246 bp) positive isolate, Lane 5: OXA-58 positive control (*A. baumannii* NCTC 13305), Lane 6: OXA-58 (453 bp) positive isolate, Lane 7: OXA-23 positive control (*A. baumannii* NCTC 13304), Lane 8: OXA-23 (1057 bp) positive isolate, Lane 9: OXA-143 (825 bp) positive isolate, Lane C- negative control

for detection of $bla_{\text{OXA-51-like}}$ revealed that all *A. baumannii* isolates had $bla_{\text{OXA-51-like}}$ gene. This finding supports the proposal that detection of $bla_{\text{OXA-51-like}}$ gene can be used as a simple and valid method to differentiate *A. baumannii* strains from other species (18). In addition, we found considerable levels of multiple-resistance to antimicrobials tested in our study. The distribution of XDR and PDR among our isolates was found to be 82.4% and 5.55% which was much lower than the rate of XDR (89%) and PDR (11%) reported from Arak in central part of Iran (31). These results explain that the appropriate choices for the treatment of infection caused by *A. baumannii* are limited. Our data indicated that 82.47% (80 isolates) of the carbapenem non-susceptible isolates of *A. baumannii* contained $bla_{\text{OXA-23-like}}$ gene. The distribution of $bla_{\text{OXA-23-like}}$ gene in *A. baumannii* isolates from the Iran (central part of Iran) was shown to be 25% in 2008 (25). In other studies, increasing level of $bla_{\text{OXA-23-like}}$ gene was reported so that, 84% of the isolates were found to have the $bla_{\text{OXA-23-like}}$ gene in the capital of Iran in 2011(32) and 88.7% of the isolates had this gene in Northwest of Iran on 2012 (28). The comparison in the rate of $bla_{\text{OXA-23-like}}$ gene in these three regions could be explained by an increased distribution of $bla_{\text{OXA-23-like}}$ gene. Outbreaks of $bla_{\text{OXA-23}}$ producing carbapenem resistant *A. baumannii* isolates have been reported from many countries and this gene has found a worldwide dissemination (33). In studies conducted by Mak *et al.* and Zhou *et al.* 87.5% and 94% of carbapenem resistant isolates had $bla_{\text{OXA-23-like}}$ gene, respectively (34, 21). In our study, 22.68% of carbapenem non-susceptible *A. baumannii* isolates had $bla_{\text{OXA-40-like}}$ gene. This result is similar to the rate of $bla_{\text{OXA-40-like}}$ gene reported from central part of Iran (17.9%) (25), but is considerably higher than the rate of this gene reported from northwest of Iran (1.6%) (28). The highest prevalence of

Table 2. Genotypic profile of *Acinetobacter baumannii* isolates according to OXA-type beta-lactamase genes in carbapenem resistant

Resistance determinants	Cases (no.)	Percent
bla$_{\text{OXA-51-like}}$ only	10	10.30
bla$_{\text{OXA-51-like}}$+*bla*$_{\text{OXA-23-like}}$	24	24.74
bla$_{\text{OXA-51-like}}$+*bla*$_{\text{OXA-58-like}}$	6	6.18
bla$_{\text{OXA-51-like}}$+*bla*$_{\text{OXA-23-like}}$+*bla*$_{\text{OXA-40-like}}$	6	6.18
bla$_{\text{OXA-51-like}}$+*bla*$_{\text{OXA-23-like}}$+*bla*$_{\text{OXA-58-like}}$	27	27.83
bla$_{\text{OXA-51-like}}$+*bla*$_{\text{OXA-23-like}}$+*bla*$_{\text{OXA-143-like}}$	2	2.06
bla$_{\text{OXA-51-like}}$+*bla*$_{\text{OXA-23-like}}$+*bla*$_{\text{OXA-40-like}}$+*bla*$_{\text{OXA-143-like}}$	1	1.03
bla$_{\text{OXA-51-like}}$+*bla*$_{\text{OXA-23-like}}$+*bla*$_{\text{OXA-40-like}}$+*bla*$_{\text{OXA-58-like}}$	10	10.30
bla$_{\text{OXA-51-like}}$+*bla*$_{\text{OXA-23-like}}$+*bla*$_{\text{OXA-58-like}}$+*bla*$_{\text{OXA-143-like}}$	6	6.18
bla$_{\text{OXA-51-like}}$+*bla*$_{\text{OXA-40-like}}$+*bla*$_{\text{OXA-58-like}}$+*bla*$_{\text{OXA-143-like}}$	1	1.03
bla$_{\text{OXA-51-like}}$+*bla*$_{\text{OXA-23-like}}$+*bla*$_{\text{OXA-40-like}}$+*bla*$_{\text{OXA-58-like}}$+*bla*$_{\text{OXA-143-like}}$	4	4.12
Total	97	100

bla$_{\text{OXA-40-like}}$ gene has been reported from European countries such as Spain (23) and Portugal (35). In this study, we identified *bla*$_{\text{OXA-58-like}}$ gene in 55.67% of carbapenem non-susceptible *A. baumannii* isolates. The distribution of *bla*$_{\text{OXA-58-like}}$ gene in *A. baumannii* isolates from the northwest and the capital of Iran was shown to be 3.2% (28) and 21.2% (36), respectively. These rates are significantly lower than the rate found in current study. Ruiz *et al*. in Spain (23) and Stoeva *et a.l* in Bulgaria (30) reported that 19% and 27.27% of carbapenem resistant *A. baumannii* isolates contained *bla*$_{\text{OXA-58-like}}$ gene, respectively. To date, *bla*$_{\text{OXA-143-like}}$ gene has been reported only for *A. baumannii* isolates in Brazil (8, 37). Our study displayed, 14.43% (14 isolates) of the carbapenem non-susceptible isolates of *A. baumannii* carried *bla*$_{\text{OXA-143-like}}$ gene. This result is similar to the rates of *bla*$_{\text{OXA-143-like}}$ gene reported from Brazil (8.4%) (37) and 18.6% (38). However, our results are consistent with the data presented in some other studies documenting high distribution of *bla*$_{\text{OXA-23-like}}$ gene (84%, 88.7%), which followed by a lower occurrence of *bla*$_{\text{OXA-58-like}}$ gene (21.2%, 3.2%) and *bla*$_{\text{OXA-40-like}}$ gene (17.9%, 1.6%) (25, 28, 32). In the present study, we found that among carbapenem non-susceptible *A. baumannii* isolates 90.72% (88 isolates) of isolates were extensive drug resistance (XDR), 80.68% (71 isolates), 54.54% (48 isolates), 23.86% (21 isolates) and 13.63% (12 isolates) of them carried *bla*$_{\text{OXA-23-like}}$, *bla*$_{\text{OXA-58-like}}$, *bla*$_{\text{OXA-40-like}}$ and *bla*$_{\text{OXA-143}}$ genes, respectively. The current study found 10 (10.3%) isolates of carbapenem resistant *A. baumannii* isolates that contained only the *bla*$_{\text{OXA-51-like}}$ gene. Therefore, it implies that the association between *bla*$_{\text{OXA-51-like}}$ gene and resistance of *A. baumannii* to carbapenem is low and other *bla*$_{\text{OXA}}$ genes considerably involved in resistance of *A. baumannii* to carbapenems.

Conclusion

This study showed that the rate of resistance to most of the available antibiotics for treatment of infection caused by *A. baumannii* was high in the study region. This study also revealed that suceptibility to carbapenems in the population of *A. baumannii* isolates in Iran reduced and the *bla*$_{\text{OXA-23-like}}$ gene was the most prevalent types of carbapenemase among carbapenem resistant *A. baumannii* isolates in this area. The rapid identification of carbapenemase-producing isolates is important and the use of specific methods are necessary to control the further transmission of infection by these organisms.

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