

Investigation of the relationship between Antibiotic resistance pattern and class 1, 2, 3 Integrons in *Acinetobacter baumannii* isolated from clinical samples of ICU patients

Shahram Bagherabadi, Reza Habibi, Maziar Vakili amini, Mostafa Sedighi, Mahmoud Ghasemi

ABSTRACT: *Acinetobacter baumannii*, an opportunistic pathogen with high antibiotic resistance, can cause various infections, especially among hospitalized patients in burn and surgery intensive care units. This study is to investigate the relationship between Antibiotic resistance pattern and class 1, 2 and 3 Integrons in *Acinetobacter baumannii* isolated from clinical samples of ICU patients of Dr. Mohammad Kermanshahi Hospital in 2019.

Methods: This study was done on 47 *Acinetobacter baumannii* isolates. Initial identification of the isolates was performed through phenotypic methods and final confirmation based on blaOXA-51 using PCR method. Antibiotic susceptibility of the isolates was determined by Disk - diffusion standard methods. The presence of class 1, 2 and 3 Integrons was investigated

using PCR method.

Results: It can be seen that Cefepime showed the highest antibiotic resistance (100%) while Tigecycline (no resistance) and Colistin (8.51%) showed the lowest antibiotic resistance. The frequency of class 1(82.98%), 2(36.17%) and 3(no frequency) Integrons was determined.

Conclusion: We came to this conclusion that *Acinetobacter baumannii* had a high level of antibiotic resistance. There was a significant relationship between the presence of class 1, 2 and 3 Integrons and antibiotic resistance of the isolates to some kinds of antibiotics

INTRODUCTION

Acinetobacter baumannii is Gram-negative coccobacilli, catalase positive, oxidase negative, aerobic and non-fermentable. Also, it is an opportunistic pathogen with a low virulence. But, it can cause various infections through organs of respiratory system (pneumonia), sepsis, urinary tract, wound infections and contaminated catheters. During the last decade, the rate of hospital - acquired infections due to *Acinetobacter baumannii* has been increasing. The emergence of this bacterium is serious especially among hospitalized patients in burn and surgery intensive care units (1-3). *Acinetobacter baumannii*, as one the hospital-acquired infectious agent microorganisms, is an important human pathogenic bacterium which has caused many problems with respect to treatment failure and mortality occurrence of patients due to antibiotic resistance (4).

This bacterium shows a high resistance in environmental conditions so that it can survive in relative humidity of 31% for 11 days and relative humidity of 10% for 4 days. This bacterium can be seen in secretions of human body like sputum, urine, stool as well as vaginal discharges. In fact, the presence of this bacterium has been detected in skins of 25% of people and in pharyngeal regions of 7% of babies and adults (5).

Today, Antibiotic resistance is one of the biggest problems in treatment of bacterial infections. *Acinetobacter baumannii* is not exception. According to a report by centers for disease control and prevention (CDC), the emergence of *Acinetobacter* resistance to Carbapenem has increased from 9% in 1995 to 40% in 2004 and such a resistance can be transferred to other pathogenic bacteria (6-9).

In general, *Acinetobacter baumannii* shows two types of resistance: extensive drug resistance (XDR), multidrug resistance (MDR) and pandrug resistant (PDR) (10-12). According to some studies, strains of *Acinetobacter baumannii* show multi drug resistance (13). Mechanisms of antibiotic resistance in these bacteria include purines, efflux pumps, secretion of Beta-lactamase as well as resistance genes acquired from Integrons (14). Integrons are the most effective genetic elements which have a very essential role in capturing and carrying genes, particularly those responsible for antibiotic resistance. By structure, Integrons have three distinct genetic regions of which two are highly conserved the 5'-conserved segment (5'-CS) and the

3'-conserved segment (3'-CS), that flank the central variable region where the gene cassettes are located. Integrase gene (IntI) which encodes site-specific recombination is in 5'-CS gene and provokes gene cassette insertion through site-specific recombination mechanisms (15-17). Based on differences, present in Integrase gene, more than 9 classes of Integrons have been identified, 4 classes of them are related to clinical isolates. More attention has been paid to class 1 and 2 Integrons among clinical strains (18).

Raising awareness of mechanism and Antibiotic resistance pattern to antibiotics which are used for treatment of infections can accelerate quick and on time treatment of the related infections and decrease emergence of drug resistance and the cost of treatment. This study aimed at Investigation of the relationship between Antibiotic resistance pattern and class 1, 2 and 3 Integrons in *Acinetobacter baumannii* isolated from clinical samples of ICU patients of Dr. Mohammad Kermanshahi Hospital in 2019.

Material and methods: To study the probability of *Acinetobacter baumannii*, various clinical samples were isolated from blood, sputum, wound, urine, catheter and other bodily fluids collected from ICU patients of Dr. Mohammad Kermanshahi Hospital in 2019. Then, the collected samples were transported to the laboratory and placed on to culture mediums such as Blood agar and MacConcky agar. Then, they were incubated at 37°C and 42°C. Identification was done using microbiological and biochemical standard methods, including: Gram staining, catalase staining, oxidase staining, glucose oxidation, arginine hydrolase test and Esculin Hydrolysis Test, nitrate resuscitation, Lactose intolerance as well as culture onto citrate mediums, TSI, SIM as well as pigment production (19,20). At the final, 47 *Acinetobacter baumannii* isolates were identified. Polymerase chain reaction (PCR) method using blaOXA-51 was applied for final confirmation of the isolates (16,21).

Antibiogram test was performed using Disk-diffusion standard method (Kirby Bauer) based on clinical and CLSI laboratory standards institute 2014 regrading 0.5 McFarland standard (22,23). To test antibiotic susceptibility of isolated bacteria, the bacteria were placed onto Mueller-hinton agar medium (Himedia, India) and antibiotic disks (MAST, merseyside, UK) were used, including Amikacin (30 µg), ceftazidime (30 µg), Tobramycin (10 µg), Meropenem (10 µg), Imipenem (10 µg), Piperacillin- Tazobactam (10/100 µg), Gentamicin (10 µg), Doxycycline (30 µg), Cefepime (30 µg),

Kermanshah University of Medical Sciences

Corresponding author: Shahram Bagherabadi, Department of Pediatrics, School of Medicine. Dr. Mohammad Kermanshahi Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran, Tel: +989331880699; E-mail: sh_bagherabadi@yahoo.com



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Ciprofloxacin (5 µg), Ampicillin-Sulbactam (10/10 µg), Colistin (10 µg) and Tigecycline (15 µg). non-growth zone diameter was measured by a ruler and the results were reported using CLSI 2014 tables. In this study, standard strains of *Acinetobacter baumannii* ATCC 19606 and *E.coli* ATCC 25922 were respectively used for positive and negative quality control (22-24). MDR defined as the isolate resistant to at least three classes of antimicrobial agents all penicillins and cephalosporins (including inhibitor combinations), fluoroquinolones, and aminoglycosides. XDR *Acinetobacter* spp shall be the *Acinetobacter* spp isolate that is resistant to the three classes of antimicrobials described above (MDR) and shall also be resistant to carbapenems. Finally PDR *Acinetobacter* spp shall be the XDR *Acinetobacter* spp that is resistant to polymyxins and tigecycline (12). The investigation of the presence of class 1,2 and 3 Integron genes was done using specific primers (table 1) and Polymerase chain reaction (PCR) method.

Each clinical sample was purified by culture and *Acinetobacter baumannii* was isolated from all of the samples. Then the isolates were stored at -70°C in nutrient broth containing 30% glycerol v/v for further investigation (25). Genomic DNA used for PCR assays was obtained from bacterial suspension grown overnight in Luria broth (LB) with shaking incubator at 37°C. Extraction of genomic DNA from *A. baumannii* isolates was performed by boiling method. To do so, several purified bacterial colonies were dissolved in sterile water, boiled for 5 minutes, cooled and finally, centrifuged at 7000 r/min for 10 min (25-27). PCR reaction was performed with a final volume of 25 µl. PCR compounds was include of 3 µl 10X PCR buffer, 5 µl of extracted template DNA, 0.5 µl dNTPs mix (10mM), 0.8 µl MgCl₂ (50 mM), 0.6 µl DNA Taq polymerase, 1.5 µl (10 pM/µl) of each primer (forward and reverse), and 13.6 µl sterile D/W. PCR reaction was performed to identify genes Int 1, Int 2 and Int 3 in 35 cycles. Cycling conditions were: initial denaturation at 94°C for 6 min, denaturation at 94°C for 60 s, annealing at 56°C for 60 s, extension at 72°C for 45 s and final extension at 72°C for 6 min (26,28).

The program to identify gene blaOXA-51 included a 35 cycles. initial denaturation at 94°C for 3 min, denaturation at 94°C for 45 s, annealing at 60 °C for 45 s, and extension at 72°C for 60 s, as well as a final extension at 72°C for 5 min (29). PCR products were investigated using electrophoresis on a 1% agarose gel (and 80 V for 40 min) and stained with ethidium bromide (25). At final, the results and sample specifications were analyzed using SPSS software v20.

Statistical test: In the present study, the relationship between Integrons and drug resistance was investigated using SPSS software v20 and chi-square test. The level of significance was less than 0.05 (P<0.05).

Results: In this descriptive, cross-sectional study, among clinical samples isolated from blood, sputum, wound, urine, catheter and other bodily fluids collected from ICU patients of Dr. Mohammad Kermanshahi Hospital in 2018, 47 *Acinetobacter baumannii* isolates were identified using standard methods of identification. Of various understudied samples, 26 samples from males (55.32%) and 21 samples from females (44.68%) were collected. In respect of sampling frequency, 23 samples of blood (48.94%), 4 samples of sputum (8.51%), 3 samples of wound (6.38%), 9 samples of urine (19.15%), 4 samples of catheter (8.51) and 4 samples of trachea were collected. frequency of MDR and XDR isolates was 12 (25.53%) and 8 (17.02%), respectively and none were pan drug resistance.

The frequency of Integrons found in clinical samples showed that the frequencies of class 1 and 2 Integrons were 82.98% and 36.17%, respectively. In 19.14% of samples, class 1 and 2 Integrons were detected simultaneously. Class 3 Integrons were not isolated from the samples.

The final confirmation of the *Acinetobacter baumannii* with initial identification based on the emergence of blaOXA-51 gene, through PCR has been shown in Figure 1.

Discussion: *Acinetobacter baumannii* genus members have become resistant to almost all antibiotics and have an endless capacity to acquire antibiotic resistance. Numerous studies have shown that most strains of *Acinetobacter baumannii* are highly resistant to most clinically available antibiotics and their number of multi drug resistant strains of *Acinetobacter* is increasing, especially among hospitalized patients. Mobile genetic elements like Plasmids, Transposons as well as Integrons are the most effective elements which play an important role in acquiring and distributing of agents which are resistant to various Gram-negative bacteria, especially *Acinetobacter*

baumannii strains. Various studies show that multi drug resistance in these bacteria is related to the presence of Integrons and gene cassettes (30-32).

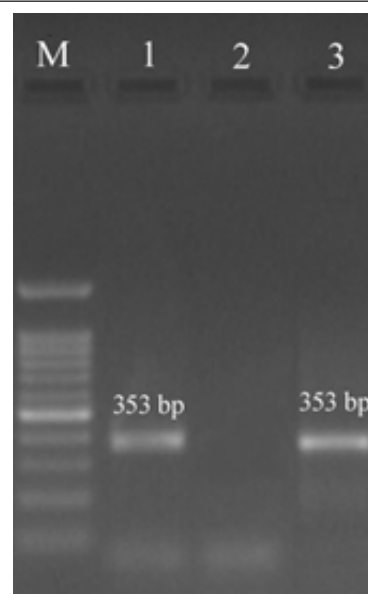


Figure 1) Agarose gel electrophoresis of PCR products of the amplification of blaOXA-51 DNA in *Acinetobacter baumannii* isolates. M) 100 bp DNA marker; 1) positive control; 2) negative control; 3) the studied samples containing the 353-bp fragment

According to the findings of the present study, the most frequent *Acinetobacter* strains isolated from clinical samples were related to the samples of blood (48.94%) this result was consistent with the results of previous studies done by Kiani and et al (2014, Ahvaz, Iran) 41.79%, Amini and et al (2015, Kermanshah, Iran) 67.2% it showed the role of the circulatory system in multiplication of bacteria but it was not consistent with the result of Izadi's study (2014, Iran) sputum 60% (19,23,25). In this study 55.32% of the samples were separated from boys and 44.68% from girls, which was consistent with the results of Amini (53.5% men), Izadi (61% men) and Deilem Salehi and et al (2015, Babol, Iran) study 53.2% women are inconsistent (19,20,25).

In this study, the isolates were MDR 25.53% and XDR 17.02% . The frequency of isolates of MDR and XDR has been reported in Izadi (MDR 29%, XDR 21%), Deilem Salehi (MDR 91.4%, XDR 58.3%), Al-Sweih (MDR 85.1%), Koczura and et al (2014, Poland) MDR 65.2% (20,25,35,36). The reason for the differences in the frequency of antibiotic resistance reported in *Acinetobacter baumannii* isolates in different studies may be due to the presence of multiple clones in the study area and the reasonable rate and level of antibiotic use (12,36).

The results from the investigation of the presence of Int 1 and Int 2 genes in samples containing *Acinetobacter baumannii* using PCR are shown in Figure 2.

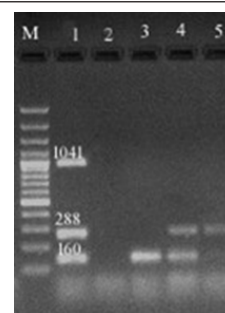


Figure 2) Agarose gel electrophoresis of PCR products of the amplification of int I, int II and int III DNA in *Acinetobacter baumannii* isolates. M) 100 bp DNA marker. 1) positive control (160,288 and 1041bp). 2) negative control. 3,4,5) the studied samples containing the 160 and 288-bp fragments

Based on the results of this study, *Acinetobacter baumannii* isolates identified by disk diffusion method showed 76.26% antibiotic resistance to the antibiotic groups used in this study like aminoglycosides, carbapenems, penicillins, tetracyclines, cephalosporins (100% resistance to cefepime) and quinolones. However, the lowest amount of antibiotic resistance was observed in glycolcyclins (no resistance to thiocyclines) and polypeptides (colistin). In fact, none of the identified *Acinetobacter baumannii* isolates were resistant to tigecycline and colistin resistance was found in only 8.51% of the isolates.

Peymani and et al (2012, Tabriz, Iran) reported in their study antibiotic resistance of *Acinetobacter baumannii* isolates identified from clinical samples to Ceftazidime (92%), Piperacillin/ Tazobactam (88%), Cefepime (85%), Gentamicin (85%), Amikacin (80%), Meropenem (56%), Imipenem (53%) (27). Amini reported antibiotic resistance of *Acinetobacter baumannii* isolates of their study to Gentamicin (77.6%) (19). but this percent was 86% for Gentamicin and Amikacin (81%) in the study of Aliakbarzadeh and et al (2013, Tabriz, Iran) which is consistent with the result from our study (33). Kiani reported antibiotic resistance of *Acinetobacter baumannii* isolates to Gentamicin (47.76%) and to Meropenem (2.98%) which was not consistent with the above results (23).

Mirnejad and et al (2010, Tehran, Iran) in their study on the investigation of antibiotic resistance pattern of *Acinetobacter baumannii* isolates, showed the isolates were resistant to Meropenem (44%), Ampicillin/ Sulbactam (62%), Imipenem (78%), Amikacin (90%), Piperacillin/ Tazobactam (48%), Ceftazidime (100%), Cefepime (100%), Gnetamicin (64%), Ciprofloxacin (92%) which are consistent to the present study (24). From above, it can be seen that antibiotic resistance of *Acinetobacter baumannii* isolates which are isolated from clinical samples in the above studies is higher than antibiotic resistance of the samples in the present study (specially to Aminoglycosides and Cephalosporins). The only effective antibiotics are Colistin and Tigecycline. In addition, the activation of more toxic antibiotics against this bacterium is a major concern and reminder of the increased attention and precision in the administration of antibiotics in the treatment of infections caused by this bacterium.

In this study, the frequency of Integrons found in clinical samples showed that the frequency of class 1 and 2 Integrons was 82.98 and 36/17%, respectively. In 19.14% of samples, class 1 and 2 Integrons were detected simultaneously. Class 3 Integrons were not isolated from the samples.

Taherikalani and et al (2011, Ilam, Iran) reported the frequency of class 1 Integrons (58%), class 2 Integrons (14%) and class 1 and 2 Integrons (9%). But they did not isolate class 3 Integrons (34). Kinani reported the frequency of class 1 (100%), class 2 (32.8%) and class 3 (4.4%) Integrons. The results from class 1 and 2 are consistent with the results from our study (23). Deylam salehi reported the frequency of class 1 (25.7%), class 2 (88.6%) and class 3 (28.6%) Integrons (20). Koczura reported the frequency of class 1 Integrons in *Acinetobacter baumannii* strains (63.5%) but they did not detect class 2 and 3 Integrons in isolates (35). Lin and et al (2013, Taiwan) reported, in their study, the frequency of class 1 Integrons (72%) but they did not detect class 2 Integrons in isolates (37).

This discrepancy may be due to the ways the researchers used antibiotics (e.g. uncontrolled prescription), differences in geographical regions (e.g. intercountry or intera country), the site of the research or differences in the materials and methods (23). the absence or the lack of class 3 Integrons may indicate that this class has no role in creation or enhancement of resistance of *Acinetobacter baumannii* strains to antibiotics.

It can be seen from the findings of the study that there was no a significant relationship between the presence of class 1 Integrons in *Acinetobacter baumannii* isolates and resistance to antibiotics ($p > 0.050$) but there was a significant relationship between the presence of class 2 Integrons in *Acinetobacter baumannii* isolates and resistance to Imipenem, Meropenem, Gentamicin, Ciprofloxacin, Ampicillin/ Sulbactam and Colistin ($p < 0.050$). in studies done by Deylam salehi (20), Mirnejad (24) and Peymani (27) a significant relationship between resistance to Ceftazidime, Amikacin, Cefepime, Piperacillin/ Tazobactam, Imipenem, Meropenem, Gentamicin,

Ciprofloxacin and Ampicillin/ Sulbactam and class 1 Integrons was reported which was not in accord to our findings. Mirnejad, Koeleman and et al (2001, Amsterdam, Netherlands) and Gaur and et al (2007, Varanasi, India) reported a significant relationship between the presence of class 2 Integrons in *Acinetobacter baumannii* Isolates and antibiotic resistance to Ceftazidime, Cefepime and Ciprofloxacin (which the Ciprofloxacin was in accord to our findings) (24,26,38). Lin and et al (2013) reported a significant relationship between the presence of Integrons and antibiotic resistance to Cefepime, Amikacin and Ciprofloxacin (37). In the cases when there is no significant relationship between the presence of class 2 Integrons and antibiotic resistance the resultant resistance can occur in different ways like defect in autolytic enzymes in cell wall or due to control plasmids or due to chromosome control (9,26).

Conclusion: The findings of the present study show the presence of the high antibiotic resistance in clinical isolates of *Acinetobacter baumannii*. In some cases, there was a significant relationship between the presence of class 1, 2 Integrons and antibiotic resistance. Since Integrons can transfer antibiotic resistance factors in to different strains, more attention should be paid to them in control protocols and treatment of infections due to *Acinetobacter baumannii* and new antibiotic resistances should be prevented by rational use of antibiotic. Colistin and Tigecycline are among effective antibiotic drugs in spite of toxicity.

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Conflict of interest

The authors declare that there is no conflict of interests

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