

The *adeH* and *adeS* Efflux Pump Genes in Imipenem and Colistin-Resistant *Acinetobacter baumannii* Clinical Isolates

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ABSTRACT

Introduction: *Acinetobacter baumannii* is one of the most important causes of nosocomial infections. In this bacteria, several mechanisms contribute to resistance against antimicrobial agents. The present study investigated the prevalence of *adeS* and *adeH* genes and the role of efflux pumps in imipenem and colistin-resistant *A. baumannii* clinical isolates. **Methods:** This study included 60 *A. baumannii* isolates collected from medical centers affiliated with the Shahid Beheshti University of Medical Science, Tehran, Iran. The antibiotic susceptibility pattern was examined using the broth microdilution MIC method according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Also, the *adeS* and *adeH* genes were amplified by PCR. **Results:** The isolates were 100% imipenem-resistant and 86.7% colistin-resistant. All isolates were positive for the *51-blaOXA* gene. The *adeH* and *adeS* genes were detected in 95% and 80% of the isolates. **Conclusion:** The high frequency of *adeS* and *adeH* efflux pump genes and the high drug resistance in *A. baumannii* clinical isolates indicated that *adeS* and *adeH* efflux pump genes contribute to antibiotic resistance in this species. Therefore, our results provide essential information about high drug resistance in *A. baumannii* clinical isolates that can help limit the horizontal and vertical transmission of efflux pump genes in antibiotic-resistant *A. baumannii* isolates that causes nosocomial infections in susceptible strains.

INTRODUCTION

A. baumannii is a nonfermenting Gram-negative bacillus and poses a severe threat, particularly in intensive care units (ICUs) [1-3]. This species can cause blood, respiratory tract, urinary tract (UTI), and ventilator-associated infections, which are severe medical challenges [4, 5]. Bacterial antibiotic resistance is of great concern for public health authorities, particularly for bacteria causing nosocomial infections [6]. High multidrug-resistant (MDR) *A. baumannii* infections in Iran are challenging health problems [7, 8]. The bacterium is typically multidrug-resistant and shows resistance to aminoglycosides, fluoroquinolones, and third-generation cephalosporins [9, 10].

In MDR *A. baumannii* strains, the enzymes such as beta-lactamases and efflux pump genes are involved in resistance to various antibiotics [11-13]. Efflux pumps may lead to inherent bacterial resistance by expelling a wide range of toxic substrates such as antibiotics, biocides, and chemicals from bacteria [14].

Overexpression of efflux pumps in *A. baumannii* is a common MDR mechanism. Efflux pumps increase the minimum inhibitory concentration (MIC), resulting from the intracellular reduction of the antibiotic [15].

A. baumannii encodes *AdeA*, *AdeB*, and *AdeC* genes through the *adeABC* operon, which are involved in the resistance-nodulation-division (RND) efflux systems [16, 17]. The RND efflux systems are found only in Gram-negative bacteria and are effective in antibiotic resistance against fluoroquinolones and other antibiotic groups, such as those affecting the bacterial cell walls [18].

Knowledge of RND efflux systems and their relationship to antibiotic resistance in *A. baumannii* can be helpful from different perspectives, e.g., reducing antibiotic resistance in *A. baumannii*-resistant isolates.

The current study investigated the relationship between the RND efflux pump system and the imipenem and colistin resistance to provide essential information about high drug resistance in *A. baumannii* clinical isolates that

can help limit the horizontal and vertical transmission of efflux pump genes in antibiotic-resistant *A. baumannii* isolates that causes nosocomial infections in susceptible strains.

Material and Methods

Bacterial Isolation and Identification. In this cross-sectional descriptive study, from October 2018 to April 2019, among 200 clinical samples collected from the medical centers of Shahid Beheshti University of Tehran, Iran, 60 isolates from blood and wound specimens were identified as *A. baumannii*. Samples were cultured on general and specific culture media such as MacConkey Agar (Merck Company, Germany) and incubated for 24 hours at 37 °C. The isolates were examined by Gram staining and biochemical tests such as motility, fermentation, catalase, oxidase, hemolysis, citrate, Methyl Red, and Vogues-Proskauer (MR and VP). Then, the housekeeping 16S rRNA gene was amplified to confirm the identity of *A. baumannii* isolates [19]. The amplification program included an initial cycle at 95 °C for 5 min, followed by 30 cycles of 95 °C for 45 s, 85 °C for 55 s, 72 °C for 60 s, and a final cycle at 72 °C for 5 min.

Amplification of *blaOXA-51*-like. A PCR assay was used to amplify *blaOXA-51*-like gene to confirm *A. baumannii* diagnosis. Bacterial DNA was first extracted using a DNA extraction kit (DENAzist Bacterial DNA isolation kit), followed by amplification using specific primers [20]. The amplification program included a cycle at 95 °C for 5 min, followed by 30 cycles at 95 °C for 45 s, 85 °C for 55 s, 72 °C for 60 s, and a final cycle at 72 °C for 5 min. The standard *A. baumannii* strain, ATCC®19606TM, was used as a positive control. PCR products were then electrophoresed in 2% agarose gel containing SYBR-safe dye and visualized under a gel documentation device.

Amplification of *adeS* and *adeH* genes. The standard *A. baumannii* strain, ATCC®19606TM containing *adeS* and *adeH* genes, was used as a control. The PCR uses proprietary primers (Table 1), and the amplification program included an initial denaturation at 94 °C for 5 min, followed by 30 cycles of denaturation at 94 °C for 1 min, annealing at 55.5 °C for the *adeH* gene and 54.5 °C for *adeS* gene C for 1 min, extension at 72 °C for 1 min, and a final extension at 72 °C for 7 min.

Table 1. Primers used to amplify genes encoding antibiotic resistance in *A. baumannii* isolates.

Genes	Primers	Sequence (5' to 3')	Size (bp)	References
<i>adeS</i>	adeS-F	GGTCGTTTACAAGGCATCATC	130	This study
	adeS-R	CAATATACAGGAGTGGAAGTTAGG		
<i>adeH</i>	adeH-F	GTTACACCGCATCTCGTTCC	120	This study
	adeH-R	CGCCGTTGATTGACTCTTCG		

Antimicrobial susceptibility testing. The efflux pump is involved in resistance to various antibiotics in *A. baumannii*. However, due to high resistance to imipenem and colistin in Iran. The minimum inhibitory concentration (MIC) for these two antibiotics (Sigma Aldrich Co. USA) was tested according to Clinical and Laboratory Standards Institute (CLSI 2020) guidelines [21]. The MIC value was determined in microplate wells containing the newly prepared Mueller Hinton broth culture medium (Merck, Co., Germany) using serial dilution, as previously described [22]. The final bacterial concentration was 5×10^5 CFU/mL in the 100 µl final volume. The microplates were placed at 37 °C and examined for bacteria growth through turbidity after 24 h. *Escherichia coli* ATCC®25922TM and *Pseudomonas aeruginosa* ATCC®27853TM were used as positive controls [23].

Statistical method. Data analysis was performed using SPSS statics 23.0. Classified variables were compared using the chi-square or Fisher's exact test. The *P*-value <0.05 was considered statistically significant.

This study followed the Declaration of Helsinki. Informed written consent was obtained from all the participants, and the Ethics Committee of Shahed University of Medical Sciences approved this study (Code No.: IR.SHAHED.REC.1397.058).

RESULTS

Identification of 16S rRNA and *blaOXA-51*-like genes. Sixty *A. baumannii* isolates were identified via microscopic observation of Gram-negative coccobacilli followed by biochemical tests, including motility, non-fermentation, positive catalase, negative oxidase, non-hemolysis, positive citrate, negative MR, and positive VP). Amplifying a 342-bp sequence of the 16S rRNA gene confirmed the identity of all isolates. The *blaOXA-51*-like gene was present in all samples.

Amplification of *adeS* and *adeH* genes. Of the 60 *A. baumannii* isolates, 57 (95%) had the *adeH* gene, and 48 (80%) had the *adeS* gene (Figs 1 and 2). Also, *AdeH* and *adeS* genes were observed in 59 (98.3%) imipenem-resistant *A. baumannii* isolates and 51 (85%) colistin-resistant isolates.



Fig. 1. Gel electrophoresis of PCR-amplified *adeH* gene (120 bp). Of the 60 *A. baumannii* isolates, 57 (95%) had the *adeH* gene. From left to right: 50 bp DNA ladder, positive control (C+), negative control (C-), 1-10 ...



Fig. 2. Gel electrophoresis of PCR-amplified *adeS* gene (130 bp). Of the 60 *A. baumannii* isolates, 48 (80%) had the *adeS* gene. From left to right: 50 bp DNA ladder, positive control (C+), negative control (C-), 1-7 ...

Microdilution Susceptibility testing method. All 60 isolates (100%) were imipenem-resistant, and 52 (86.7%) were colistin-resistant.

The MIC value for imipenem in 60 *A. baumannii* samples was 16 µg/ml, much higher than the 2 µg/ml for the *A. baumannii* ATCC®19606TM, the sensitive control strain. So all (100%) *A. baumannii* samples were imipenem-resistant. The MIC value for colistin in 52 samples was 6 µg/ml, which was also higher than the control strain (MIC= 0.5 µg/ml). Thus, 86.7% of samples were colistin-resistant, and 13.3% were not.

DISCUSSION

A. baumannii infections are among the most severe types of nosocomial infections. Evidence suggests that the overexpression of efflux pumps is a resistance mechanism in some bacteria, including *A. baumannii* [24]. The emergence of antibiotic-resistant *A. baumannii* is a global concern. In the present study, the results of the antibiotic resistance test showed 100% and 86.7% resistance to imipenem and colistin, respectively.

According to our results and similar studies in Iran, there seems to be a significant relationship between colistin and imipenem resistance of *A. baumannii* strains and efflux pump genes, *adeS* and *adeH*. Yousefian *et al.* (2014) showed that out of 96 clinical samples, 51 (30%) were resistant to colistin, and the MIC value of resistant strains was more than 128 µg/ml [25]. However, our study showed that the colistin resistance was 86.7%, and the MIC for resistant strains was higher than 8 µg/ml. Previous studies on the drug resistance pattern of *A. baumannii* isolates in Iran showed that 100% of strains were susceptible to colistin [26, 27], which is inconsistent with the present study. In Slovenia, 45.1% of isolates were resistant to colistin [28]. Consequently, we observed a significant increase in antibiotic resistance in the present study. Our results and similar studies in other countries indicated increased resistance in this bacteria due to antibiotic overuse.

In Iran, *A. baumannii* resistance rate to imipenem has increased from 26.6% (25) to 88.7% [29] from 2012 to 2015 and 100% in the present study. Another similar study in 2019 [26] showed an increase in imipenem resistance, which is entirely consistent with the present study, indicating that carbapenems are unsuitable for treating *A. baumannii* infections. Imipenem resistance rates of 98% and 99.4% by Angoti *et al.* (2016) in Iran and Boral *et al.* (2019) in Turkey [30, 31] disapproved of this antibiotic for *A. baumannii* infections.

In China, an evaluation of the relationship between *adeDE*, *adeM*, and *adeABC* efflux pumps among *A. baumannii* strains showed that 80% of the imipenem-resistant strains carried the *adeB*, *adeR*, *adeS*, and *adeJ* genes, indicating that efflux pumps were associated with antibiotic resistance, consistent with the results of the present study [32].

In a study by Asadolah-Malayeri *et al.*, the imipenem and colistin resistance was 97% and 0%, respectively, and 98.3% of the isolates had *adeS* gene. Moreover, the *OXA-23* gene was prevalent in 95% of the isolates [29]. According to Noori *et al.* [33], colistin was the most effective antibiotic against *A. baumannii*, with a sensitivity value of 97%, which differs significantly from the present study. Moreover, the prevalence of the *adeS* gene was 91%, which is probability consistent with the present study. The *OXA-23* and *adeH* genes were observed in all 10 (100%) MDR *A. baumannii* isolates, and the *OXA-23* gene was associated with carbapenem resistance [34].

Feizabadi *et al.* (2019) reported that the MIC value for imipenem [35] was higher than the value reported by Taheri Kalani (2008) [36], and the present study exhibited increased imipenem resistance over the years.

The most recent study identified 60 clinical isolates of *A. baumannii* and later confirmed by detecting *blaOXA-51*-like and *16S rRNA* genes. This study showed that 98.37% of *A. baumannii* isolates were 100% resistant against piperacillin, meropenem, cefotaxime, ceftriaxone, ceftazidime, ceftazidime, and ciprofloxacin. Most *A. baumannii* isolates had antibiotic efflux pumps, and more than 73% of *A. baumannii* isolates were resistant to the target antibiotics, indicating the significant role of efflux pumps in developing resistance against these antibiotics. In addition, 95% of all *A. baumannii* isolates possessed *adeH* and 80% *adeS* efflux pumps [37].

The present study revealed increasing colistin and imipenem-resistant *A. baumannii* rates in Iran, similar to previous studies. This trend is a warning sign for health systems. According to the present and other studies, efflux pumps play a significant role in resistance to different antibiotics. Thus, it is necessary to use new treatment regimens and be more alert in the timely diagnosis and control of nosocomial infections.

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CONFLICT OF INTEREST

The authors declare there are no conflicts of interest associated with this manuscript.

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