Comparative analysis of carbapenemases, RND family efflux pumps and biofilm formation potential among *Acinetobacter baumannii* strains with different carbapenem susceptibility

Yanpeng Zhang1†, Bing Fan1†, Yong Luo1, Zhiyuan Tao1, Yongbo Nie1, Yongtao Wang2, Fanglin Ding1, Yanwu Li1* and Dayong Gu1*

**Abstract**

**Aim:** This study has conducted a comparative analysis of common carbapenemases harboring, the expression of resistance-nodulation-cell division (RND) family efflux pumps, and biofilm formation potential associated with carbapenem resistance among *Acinetobacter baumannii* (*A. baumannii*) strains with different carbapenem susceptibility.

**Methods:** A total of 90 isolates of *A. baumannii* from two tertiary hospitals of China were identified and grouped as carbapenem susceptible *A. baumannii* (CSAB) strains and carbapenem non-susceptible *A. baumannii* (CnSAB) strains based on the susceptibility to imipenem. Harboring of carbapenemase genes, relative expression of RND family efflux pumps and biofilm formation potential were compared between the two groups. Result: Among these strains, 12 (13.3%) strains were divided into the CSAB group, and 78 (86.7%) strains into the CnSAB group. Compared with CSAB strains, CnSAB strains increased distribution of bla{*OXA*−23} (p < 0.001) and IS*Aba1/bla{*OXA*−51}−like (p = 0.034) carbapenemase genes, and a 6.1-fold relative expression of adeB (p = 0.002), while CSAB strains led to biofilm formation by 1.3-fold than CnSAB strains (p = 0.021).

**Conclusions:** Clinically, harboring more bla{*OXA*−23}−like and IS*Aba1/bla{*OXA*−51}−like complex genes and overproduction of adeABC are relevant with carbapenem resistance, while carbapenem susceptible strains might survive the stress of antibiotic through their ability of higher biofilm formation.

**Keywords:** *Acinetobacter baumannii*, Carbapenemases, Efflux pump, Biofilm, Resistance

**Introduction**

*Acinetobacter baumannii* (*A. baumannii*) is emerging as an opportunistic nosocomial pathogen and clinically causes serious infections, including ventilator-associated pneumonia, urinary tract infection, surgical wound infection, pyemia, meningitis, and peritonitis [1–4]. *A. baumannii* has become a clinically successful pathogen owing to its strong tolerance to an adverse environment, complex drug resistance mechanism and plastic genome. This pathogen has caused serious public health problems globally in recent 20 years [5].

Carbapenems, including imipenem, meropenem and doripenem, are important antibiotics in treating *A. baumannii* infections [6, 7]. According to the results of the antimicrobial sensitive test (AST), clinical isolates of *A. baumannii* can be divided into carbapenem
non-susceptible *A. baumannii* (CnSAB) and carbapenem susceptible *A. baumannii* (CSAB). Even following the guidance of AST strictly, the actual treatment effects of *A. baumannii* are often not so ideal, both for CNAB and CSAB. Different strains seem to live in different ways. Carrying carbapenemases, overproduction of efflux pumps, low-expression of outer membrane proteins, and biofilm formation may be related to the survival of *A. baumannii* in the presence of antibiotics. A comparative understanding of CSAB and CnSAB pathogen characteristics is critical for adopting appropriate strategies to control their infection. To the best of our knowledge, most studies focused on the resistance mechanisms, and only a few investigations have attempted comparing CnSAB and CSAB, especially after modifying the clinical breakpoints for imipenem in 2021 (CLSI 2021, 31st Edition; Document M100). In this context, this study aims to investigate the different characterization in carbapenemases harboring, efflux pumps expression level and biofilm formation capability of CnSAB and CSAB strains of *A. baumannii*.

**Methods**

**Collection and identification of strains**

A total of 115 non-repetitive strains of *Acinetobacter calcoaceticus - Acinetobacter baumannii* complex were collected from two hospitals from July 2018 to December 2019. 90 of these strains were further identified as *A. baumannii* using *rpoB* gene sequence analysis with a previously described method [8, 9], and the primer sequences are listed in Table 1.

Among them, 48 strains were from the First Affiliated Hospital of Shenzhen University in South China, and 42 strains were from Wuhan No.1 Hospital in Central China. Specimen sources of these isolates included sputum, blood, nasal secretion, alveolar lavage fluid, urine, etc. This study was approved by the Ethics Committee of the First Affiliated Hospital of Shenzhen University (approval ID 20200511007). The data related to this study were received from the hospital’s information system, and the patient’s informed consent was exempted. Overall, the outcome of this study is expected to benefit patients with the infection of *A. baumannii* for better therapy.

**Antimicrobial susceptibility test (AST)**

AST of the above strains was determined by an automated broth microdilution method (Gram-negative susceptibility cards) through the VITEK 2 system (Biomerieux, France) according to the manufacturer’s instruction, and susceptibility interpretation was based on the clinical breakpoints from the Clinical and Laboratory Standards Institute (CLSI 2021, 31st Edition; Document M100). *Escherichia coli* ATCC 25,922 and *Pseudomonas aeruginosa* ATCC 27,853 strains were used as the control. According to the CLSI clinical breakpoint to imipenem, these strains were divided into two groups: carbapenem susceptible *A. baumannii* (CSAB) and carbapenem non-susceptible *A. baumannii* (CnSAB). In CSAB, the minimum inhibitory concentration (MIC) for imipenem was ≤ 2 µg/ml; and in CnSAB, MIC was ≥ 4 mg/L (intermediate: 4 mg/L; resistant: ≥ 8 mg/L).

**Detection of carbapenemases**

Based on the already established polymerase chain reaction (PCR) conditions [10], all these 90 strains were subjected to the detection of carbapenemase genes, including *blaSIM* (Seoul imipenemase), *blaIM* (Verona integron-encoded metallo-β-lactamases), *blaIMP* (imipenemase), *blaNDM* (New-Delhi metallo-β-lactamase), *blaOXA*—like, *blaOXA*—like, *blaOXA*—like, *blaOXA*—like, and *blaOXA*—like. The detection of ISAbal/blaOXA—like was performed using the method of Jane Turton et al [13]. All

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**Table 1** Primer sequences of targeting genes and amplicon size

| Target genes   | Primer sequence                          | Size (bp) |
|----------------|------------------------------------------|-----------|
| *rpoB*         | F: GAGCTTAAATCCGCGGTTGCTTC              | 110       |
|                | R: ATGCTTTTACCTGCTGCTTTG               |           |
| *blaSIM*       | F: TACAAGGGAAATCGGTTG                   | 570       |
|                | R: TAAATGGTTCGCCCTCCATGTG              |           |
| *blaIM*        | F: GATGGTTTGGTGCCGTTA                   | 390       |
|                | R: CGAATGCCCAGACACAG                   |           |
| *blaIMP*       | F: GGAATAGAGTGGTCTATTG                 | 232       |
|                | R: TGCATTAAAYAACACAAACACC              |           |
| *blaNDM*—1     | F: GTGGTGGCACATCTGTTTC                 | 621       |
|                | R: CGGAATGCTCATTCCACGTC                |           |
| *blaOXA—23—like| F: GAATGTCACATTCCGCTTAC                | 850       |
|                | R: TAATCTAGTGGCCACCTATCTTT             |           |
| *blaOXA—24/40—like| F: TGGTGGGAGGACTTAATAGG           | 81        |
|                | R: ACGAGTAAAGACACACATCTCTCT             |           |
| *blaOXA—31—like| F: TAATGTTGGTACGGGCTTGT                | 353       |
|                | R: TGGATTGACCTGATCTTCTG                |           |
| *blaOXA—58—like| F: GACAATACCCTACACAAAGAAG             | 599       |
|                | R: AAACCCACATACACACC                   |           |
| ISAbal/bloXOXA—51| F: CAGGAATGCAAAGATG            | 1200      |
|                | R: CTTCTGTTGCTCGTTCG                  |           |
| *adeB*         | F: GCAGACGCTAATCGGAAAG                 | 101       |
|                | R: CCATTAGGAGACATCGCAT                 |           |
| *adeG*         | F: GGTGATTTCACTTGGGTTG                 | 86        |
|                | R: TTTTTGTACGCGCCGGAGTT                |           |
| *adeJ*         | F: TTCGCTTGTCCATCAAGGC                 | 137       |
|                | R: GGAAGGACCACTTAACGTG                 |           |
| *16S rRNA*     | F: AGCTAACCGGATTAAGGACC                | 137       |
|                | R: GTCAAGGCGAGTGTTTC                  |           |
PCR primers targeting resistance genes and mobile elements used in this study are shown in Table 1.

Relative expression of RND family efflux pumps
The relative gene expressions of adeB, adeI and adeG were used to evaluate the relative expressions of adeABC, adeFGH and adeIJK efflux pumps, respectively. The preparation methods of RNA templates and quantitative real-time PCR assays were performed based on the earlier reported conditions [10]. The 16 S rRNA gene as control and A. baumannii ATCC 17,978 as a reference strain were used to measure the relative expression levels. All the reactions were carried out in triplicate.

Detection of biofilm production capacity
The biofilm formation assay was performed according to the previous method [14]. A. baumannii strains were cultured overnight and diluted to a density of 0.5 on the McFarland scale. 100 µl of the diluted culture was introduced into the wells of 96-well plate and incubated for 24 h at 37 °C without shaking. All wells were washed three times, and the planktonic bacteria were removed. 125 µl (0.1%) crystal violet solution was then added into each well and incubated for 10 min at 25 °C. The wells were then washed and dried at room temperature. Each well was then added 200 µl of 95% ethanol and incubated for 10 min at 25 °C. The obtained ethanol-crystal violet solution in each well was transferred to a new 96-well plate to determine the optical density (OD) at 550 nm.

Statistical analysis
Data entry and analysis were performed with Stata/SE 15.1 for windows version 16.0 (Stata Corp LLC, Texas, USA). Categorical variables were described as frequency numbers (percentages). The distribution of sources of samples, age and gender, were compared using Pearson's chi-square test. Harboring of resistance genes, relative expression of efflux pumps, and biofilm formation between the CSAB and CnSAB groups were compared using the Fisher-Exact or independent t-test. The association of relative expression of RND family efflux pumps and biofilm formation were analyzed using multivariate regression. All tests were two-tailed, and a p < 0.05 was considered statistically significant.

Results
Clinical characteristic of strains
The clinical characteristics of the 90 isolates of A. baumannii are listed in Table 2. In this study, the patients who suffered from the infection of A. baumannii consisted of 72 (80.0%) males and 18 (20.0%) females. Among them, 52 (57.8%) were over 60 years old (including 60), and 38 (42.2%) were less than 60 years old. Respiratory tract specimens were the most frequent source. These respiratory tract specimens included sputum, bronchoalveolar lavage fluid and nasal secretion, and their respective proportions were 71.1%, 8.9 and 5.6%, respectively. Five of these strains were isolated from a blood specimen.

Antimicrobial susceptibility test
Based on the susceptibility to imipenem, strains were divided into CnSAB and CSAB. Of the 90 strains, 13.3% (12/90) were carbapenem susceptible (CSAB), and the rest (86.7%, 78/90) were classified as CnSAB.

Distribution of carbapenemases
As shown in Table 3, no blaSIM, blaVIM and blaIMP genes were detected in these 90 isolates. An intrinsic carbapenemase gene to A. baumannii species, blaOXA−51–like was present in all the 90 (100%) isolates. The blaOXA−23–like, blaOXA−24/40–like and blaOXA−58–like were present in 83.3% (75/90), 1.1% (1/90), and 2.2% (2/90) isolates, respectively. The blaOXA−23–like was detected positive in 33.3% (4/12) of the CSAB group and 91.0% (71/78) of CnSAB, respectively. Compared with CSAB strains, CnSAB showed a statistically significant increasing distribution of blaOXA−23–like (p < 0.001). For another carbapenemase gene, ISAba1 blaOXA−51–like was detected in 28.2% (22/78) in CnSAB group (p = 0.034). The blaOXA−24/40–like and blaOXA−58–like genes were noted in 1 and 2 strains, respectively. blaNDM–1 gene was detected in 6.4% (5/78) of CnSAB strains.

Relative expression of RND family pumps
The relative expression of three RND family efflux pumps genes was measured using quantitative

### Table 2: Characteristics of 90 isolates of A. baumannii

| Variables          | CSAB  | CnSAB  | P-value | Number |
|--------------------|-------|--------|---------|--------|
| Age                |       |        | 0.22    |        |
| <60                | 7 (58.3%) | 31 (39.7%) | 38 (42.2%) |        |
| ≥ 60               | 5 (41.7%) | 47 (60.3%) | 52 (57.8%) |        |
| Gender             |       |        | 0.73    |        |
| Female             | 2 (16.7%) | 16 (21%) | 18 (20.0%) |        |
| Male               | 10 (83.3%) | 62 (79%) | 72 (80.0%) |        |
| Specimen types     |       |        | 0.28    |        |
| Sputum             | 8 (66.7%) | 56 (71.8%) | 64 (71.1%) |        |
| Urine              | 1 (8.3%) | 4 (5.1%) | 5 (5.6%) |        |
| Blood              | 2 (16.7%) | 3 (3.8%) | 5 (5.6%) |        |
| Bronchoalveolar lavage fluid | 0 (0.0%) | 8 (10.3%) | 8 (8.9%) |        |
| Nasal secretion    | 1 (8.3%) | 4 (5.1%) | 5 (5.6%) |        |
| Skin and soft tissue | 0 (0.0%) | 3 (3.8%) | 3 (3.3%) |        |
real-time PCR (qRT-PCR) (Fig. 1). Compared with CSAB, the relative expressions of adeB, adeJ, and adeG genes in CnSAB were increased by 6.1, 0.9, and 0.9 times, respectively. The relative expression of adeB was significantly increased ($p = 0.003$), but the relative expressions of adeG ($p = 0.709$) and adeJ ($p = 0.340$) were not significantly increased.

**Biofilm forming capacity**
The biofilm-forming potential of strains was measured through violet crystalline dying. As shown in Fig. 2, CSAB strains produced biofilm with an OD of $0.29 \pm 0.04$, while CnSAB strains produced biofilm with an OD of $0.23 \pm 0.02$. The biofilm produced by CSAB strains was 1.3 times higher than that of CnSAB. There was significant difference in biofilm forming capacity between the two groups ($p = 0.021$).

**Association between the relative expression of RND family efflux pumps and biofilm formation**
The regression analysis results of the correlation between the relative expression of RND family efflux pumps and biofilm formation are shown in Table 4. The relative expressions of three proteins, adeB, adeG, adeJ, demonstrate no significant association with biofilm formation capacity ($p = 0.128, 0.218$, and $0.601$, respectively).

**Discussion**
*A. baumannii* is an important pathogen of nosocomial infections. This decade witnessed a series of clinical infections events and led to high clinical mortality...
designed to compare the characterization of carbapenem resistance. The most important carbapenemases harboring efflux pumps and biofilm formation capability in the A. baumannii strains with different carbapenem susceptibility. For this, 90 isolates of A. baumannii obtained from two hospitals were identified and were divided into CSAB and CnSAB groups based on their imipenem susceptibility. The obtained results indicate that CnSAB strains increased distribution of bla_{OXA-23} (P<0.001) and ISAba1/bla_{OXA-51–like} (p = 0.034) carbapenemase genes, and a 6.1-fold relative expression of adeB (p = 0.002) was noted compared with CSAB strains, while the biofilm produced by CSAB strains was 1.3 times higher than that of CnSAB, (p = 0.021).

Production of multiple carbapenemases is effective for carbapenem resistance. The most important carbapenemases in A. baumannii include class B metallo-β-lactamases (MBLs) and class D oxacillinases (OXAs). OXAs include bla_{OXA-51–like}, bla_{OXA-23–like}, and bla_{OXA-58–like} and MBLs include blaSIM (Seoul imipenemase), blaVIM (Verona integron-encoded metallo-beta-lactamases), blalMP (imipenemase), blaNDM-1 (New-Delhimetallo-β-lactamase) [23, 24, 25].

Whereas the composition of different carbapenemases was different in different regions, the most common mechanism for carbapenem resistance was harboring bla_{OXA-23} in A. baumannii. Janak Koirala et al. reported bla_{OXA-23–like} (52%) and bla_{OXA-24/40–like} (28%) were the most common genes in CnSAB in central Illinois, the United States. [26] Sunil Kumar et al. found a high prevalence of bla_{OXA-23–like} (97.7%) among the carbapenem-resistant strains followed by bla_{NDM-1} (29.1%) and bla_{OXA-58–like} (3.5%) in India [27]. Udomluk Leung-tongkam found a pattern of bla_{OXA-23} (82.6%), bla_{NDM-1} (9.1%), bla_{OXA-24/40–like} (0.3%), and bla_{OXA-58–like} (6.5%) in 339 A. baumannii in Thailand [24]. In the current study, a pattern of bla_{OXA-23–like} (83.3%), ISAba1/bla_{OXA-51–like} (24.4%), bla_{NDM-1} (5.6%), bla_{OXA-24/40–like} (1.1%), and bla_{OXA-58–like} (2.2%) was detected in CnSAB. CnSAB strains showed a statistically significant increase of harboring of bla_{OXA-23} (p < 0.001) compared with CSAB strains.

Another interesting finding was that harboring the ISAba1/bla_{OXA-51–like} gene might be another important factor in carbapenem resistance. The chromosome encoded bla_{OXA-51–like} gene is intrinsic, but the solitary OXA-51 enzyme only showed a weak hydrolyzing activity to carbapenems. While with an additional genetic element ISAba1/bla_{OXA-51–like} complex may result in OXA-51 over-production which confers resistance to carbapenems. In this study, a significant difference in the carrying of

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**Table 4** Association between the relative expression of RND family efflux pumps and biofilm formation

| Biofilm | Coef. | Std. err. | p    | 95 % Conf. Interval |
|---------|-------|-----------|------|--------------------|
| adeB    | −0.004| 0.002     | 0.128| −0.008 to 0.001    |
| adeG    | −0.010| 0.008     | 0.218| −0.026 to 0.006    |
| adeJ    | −0.024| 0.047     | 0.601| 0.117 to 0.068     |

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**Fig. 2** Biofilm formation capacity of CSAB and CnSAB strains. A The biofilm of A. baumannii by violet crystalline dying (under oil lens, 1000x). B Comparison of biofilm production between carbapenem susceptible (CSAB) and carbapenem non-susceptible (CnSAB) groups of A. baumannii. S, significant; NS, not significant.
resistance of carbapenems is controversial. Using con-
relationship between biofilm formation potential and
relapse of chronic infection and disease delay. The
(p = 0.034) was observed. In this study, four isolates har-
boring bla_{OXA-23-like} were found susceptible to carbape-
nem. This may be due to some mutations in bla_{OXA-23-like}
gene or decrease of expression of this gene. Based on this,
a further quantitative detection for bla_{OXA-23-like} expres-
sion is necessary to evaluate the actual contribution to
carbapenem resistance in further research.

Besides carbapenemase, overproduction of efflux
pumps could be another important factor contribut-
ing to drug resistance. Efflux pumps can extrude avariety
of antimicrobial agents and reduce the accumulation
of antibiotics in bacteria. According to the reports in this
decade, five super families of efflux pumps have been
found in A. baumannii: the resistance-nodulation-cell
division (RND) family, the ATP-binding cassette (ABC)
transporters family, the multidrug and toxic com-
pound extrusion (MATE) family, the major facilitator
super (MFS) family, and the small multidrug resistance
(SMR) family [10, 28–31]. The three RND efflux family
members, adeABC, adeFGH and adeIJK, are the most
important pumps for carbapenem resistance in A. baum-
nanii. The relative expressions of adeB, adeJ and adeG
were commonly used to evaluate the relative expres-
sion of adeABC, adeFGH, and adeIJK efflux pumps,
respectively. Also, by comparing with CSAB strains,
the relative expression of adeB, adeJ, and adeG genes in
CnSAB strains increased by 6.1-fold (p = 0.003), 0.9-fold
(p = 0.709), and 0.9-fold (p = 0.340), respectively. These
results agree with Yili Chen’s findings, where they found
a significantly increased expression of adeB from carbape-
nen-resistant A. baumannii strains compared with sus-
ceptible strains [32]. This indicates the overproduction
of adeABC efflux pump might be another potential cause
for carbapenem resistance. In this study, only RND fam-
ily pumps were discussed, but the contribution of other
efflux family pumps needs to be examined further.

Biofilm formation of A. baumannii often leads to
relapse of chronic infection and disease delay. The
relationship between biofilm formation potential and
resistance of carbapenems is controversial. Using confoc-
alar scanning microscopy, Dahdouh et al. found
that carbapenem resistant strains could produce more
biofilm than susceptible strains [33]. In comparison,
Perez et al. reported an inverse relationship between
the biofilm formation ability and carbapenem resis-
tance level. They observed meropenem susceptible iso-
lates produced more biofilm than the resistant ones
in nosocomial A. baumannii strains [34]. This study
noticed that the biofilm produced by CSAB strains was
1.3 times higher than that of CnSAB, and the differ-
ence is significant (p = 0.021). It was indicated that the

carbapenem susceptible strains might take advantage
of the biofilm formation to survive the pressure of anti-
microbials. This explains why the clinical therapy for A.
baumannii sensitive strains is often not so ideal, even
following the guide of AST strictly in vitro.

The relative expression of RND efflux pumps influ-
encing biofilm formation is controversial. Yoon et al.
reported that mutants with up-regulation expression of
the AdeABC, AdeFGH and AdeIJK efflux pumps reduced biofilm formation compared with wild strains.
In contrast, He et al. reported that overexpression of
the AdeFGH efflux pump is beneficial for biofilm for-
mation in A. baumannii. In this study, a regression
analysis was attempted. No relationship between the
relative expressions of adeB, adeG, and adeJ, as well
as biofilm formation capacity in these 90 isolates, was
found out.

Besides the above observations, this study has sev-
eral limitations. Firstly, the sample size was relatively
small, and the source of the strains was only from two
hospitals. Secondly, this study only discussed the rela-
tionship of overproduction of three members of the
RND family, but other efflux pump families and outer
membrane proteins were not involved. Thus, the exper-
imental data analysis might be influenced by these limi-
tations. Thirdly, different resistance mechanisms may
have synergistic or antagonistic effects, and the inter-
actions between those resistance mechanisms have not
been considered in this study.

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Authors’ contributions
DG, YZ and BF conceived and designed the experiment, YZ, BF, ZT, YL, YN and
YW performed the experiment, YZ, BF and YL analyzed the data, YZ, FD, and
BF participated in its design and coordination and helped to draft the manu-
script. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published
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Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the First Affiliated Hos-
pital of Shenzhen University, and all methods were performed in accordance
with the relevant guidelines and regulations (Approval ID: 20200511007).

Consent for publication
Not applicable since there are no details on individuals reported within the
manuscript.
Competing interests
The authors declare no competing interests.

Author details
1 Department of Clinical Laboratory, Shenzhen Institute of Translational Medicine, The First Affiliated Hospital of Shenzhen University, Shenzhen Second People’s Hospital, No. 3002, Sungang Xi Road, Shenzhen 518035, China.
2 Department of Clinical Laboratory, Wuhan No.1 Hospital, Zhongshan Road, Wuhan, China.

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