Original Article

Emerging Challenges: High frequency of Antiseptic Resistance Encoding Genes and Reduced Biguanide Susceptibility in Antibiotic-Resistant *Acinetobacter baumannii* in Iran

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ABSTRACT

Acinetobacter baumannii (A. baumannii) has been identified as a prevalent infectious agent that is frequently reported from patients in hospital intensive care units (ICUs). Annually, multi-drug-resistant (MDR) isolates pose a significant clinical challenge. The present study aimed to determine the prevalence of antiseptic resistance genes and the level of resistance to quaternary ammonium and biguanide compounds in A. baumannii isolates obtained from patients of north Khorasan province. All obtained A. baumannii isolates were examined for in The presence of genes that encode for resistance to antiseptics, including qacE, qacEΔ1, and blaOXA-23, was investigated. The broth microdilution method was utilized to determine the Minimum Inhibitory Concentrations (MICs) against antiseptic compounds. The study found that the majority of A. baumannii infections were observed in ICU patients (n=63, 84%). MDR and extensively drug-resistant (XDR) phenotypes were present in 53.2% and 46.7% of cases, respectively. Among 75 isolates, 48 (64%) had at least one resistance gene, including 24 (32%) isolates with only the qacE gene and 5 (6.7%) isolates with the qacEΔ1 gene. Furthermore, the coexistence of the qacE and qacEΔ1 genes was observed in nine (25.3%) isolates. Statistically significant differences were identified in the mean minimum inhibitory concentration (MIC) of chlorhexidine digluconate (CHG) between isolates with and without antiseptic resistance genes (81.4 µg/ml versus 27.9 µg/ml, P=0.001). The heightened minimum inhibitory concentration (MIC) levels exhibited by A. baumannii isolates against antiseptic agents constitute a significant medical concern. The presence of antiseptic-resistant genes and elevated MIC levels against antiseptic agents in MDR and XDR A. baumannii underscores the imperative for comprehensive monitoring of all A. baumannii isolates in hospital settings to ensure efficacious infection control measures.

Keywords: *Acinetobacter baumannii*, Multi-Drug Resistant, Antiseptic Resistance, Biguanide Compound, *qac*E, *qac*EΔ1.

1. Introduction

Acinetobacter baumannii is a colonizer of the human ecosystem and a nosocomial infectious agent (1). It is responsible for a variety of infections in the hospital setting, including pulmonary infection, urinary tract infection and meningitis.Multi-Drug Resistance (MDR) and carbapenems resistance among A. baumannii isolates from Intensive Care Units (ICU) is a universal dilemma (2). The carbapenem resistance that is the result of genes such as those encoding oxicillinase (OXAs) has led to this class of antibiotics being withdrawn from the first-line drugs of choice for the treatment of A. baumannii infections (3).The insertion of gene sequences in the upstream regions of blaOXA-23 genes is responsible for the regulation of carbapenem resistance among A. baumannii (4).This highlights the importance of the effective prevention strategies against this microbial species in hospitals. In healthcare settings, disinfectants containing quaternary ammonium compounds (QACs), such as benzethonium chloride (BTC) and benzalkonium chloride (BKC), as well as biguanide compounds like chlorhexidine digluconate (CHG), are widely employed to prevent nosocomial infections. The mechanisms of action of chlorhexidine and QAC, including cytoplasmic membrane disruption and phospholipid bilayer damage, further underscore their efficacy (5). However, it is crucial to acknowledge that prolonged utilisation of these antiseptic agents can lead to the development of resistance in A. baumannii through the acquisition of genes such as qacA/B, qacC/D, and qacE (6). Gram-negative bacteria that possess the qacE and qacEΔ1 genes exhibit resistance to QAC (7).The acquisition of antiseptic resistance genes by bacteria that are already resistant to other antibiotics is an evolving issue in hospital settings, necessitating attention and action (8,9). In the present study, the potential correlation between the presence of antiseptic resistance genes and an elevated resistance phenotype against primary antiseptic agents was investigated. To this end, the prevalence of antiseptic resistance genes (according to the most prominent resistance genes) and the Minimum Inhibitory Concentration (MIC) were analysed. rations (MIC) of quaternary ammonium compounds and biguanide compounds in A. baumannii isolates obtained from various infections in hospitalized patients at the Imam Hassan Hospital (the primary and referral teaching and care facility in the North Khorasan province, Iran).

2. Materials and Methods

2.1. Study Samples

During the study period, all A. baumannii isolates responsible for infections in hospitalized patients at Imam Hassan Hospital in North Khorasan Province, Iran, were identified to the species level in the hospital laboratory. This identification was further validated in the microbiology laboratory at the Faculty of Medicine using Gram staining, oxidase testing, motility testing, and assessing their ability to grow at 42°C, following the Clinical and Laboratory Standard Institute (CLSI) guidelines. Confirmation at the gene level as A. baumannii was achieved through the use of a BlaOXA51-like PCR assay. All specimens were stored at -30°C in Trypticase Soy Broth (TSB) with 20% glycerol added. Chromosomal DNA was isolated using a DNA extraction kit from Povagene Azma, Iran, in accordance with the manufacturer's guidelines for subsequent molecular analyses.

2.2. Antiseptic Susceptibility Testing

The assessment of susceptibility to QACs and biguanide compounds (CHG; Sigma-Aldrich, Steinheim, Germany) was conducted utilizing the Mueller–Hinton broth microdilution method (BMD).

2.3. Antibiotic Susceptibility Testing

Antimicrobial susceptibility testing (AST) was conducted on Mueller–Hinton agar from Merck, Germany, utilizing the disk diffusion (Kirby–Bauer) method. The interpretation of zone sizes was based on Clinical and Laboratory Standards Institute (CLSI) guidelines. The following 11 antimicrobial agents were used to differentiate the isolates of A. baumannii: cephalosporins (Cefepime, Ceftazidime), carbapenems (Doripenem, Meropenem, Imipenem), tetracyclines (Tigecycline), b-lactamase inhibitors (Ampicillin+Sulbactam, Piperacillin+Tazobactam), aminoglycosides (Amikacin, Tobramycin) and fluoroquinolones (ciprofloxacin).The isolates were classified as extensively drug-resistant (XDR) if they demonstrated resistance to one or more antimicrobial agents in at least six categories, or if they were resistant to all antibiotics except one or two. Bacteria were grouped as multi-drug resistant (MDR) if they demonstrated resistance to one or more agents in three or more categories.

2.4. Detection of Genes

The screening of all collected samples was conducted in accordance with established methodologies for the identification of antiseptic and antibiotic resistance genes, including the qacE, qacEΔ1, and blaOXA-23 genes (8). The primer sequences employed are enumerated in Table 1.

2.5. Statistics

The data analysis was conducted utilizing the SPSS 17 for Windows (SPSS Inc., Chicago) software. The determination of differences among the isolates was accomplished through the implementation of One-way ANOVA, with P-values less than 0.05 being designated as statistically significant.

3. Results

In the present study, 75 A. baumannii isolates were utilized, with the understanding that these isolates were obtained from a variety of clinical specimens, including urine (2 isolates, 2.6%), wounds (5 isolates, 6.6%), blood (4 isolates, 5.3%), and tracheal aspirates (63 isolates, 87%) (Table 2). The demographic profile of the infected patients revealed that 60% of the subjects were male (n=45/75), with a mean age of 65.4 years (range: 22-92 years). The mean age for males was 67.7 years (range: 22-92 years), while for

Table 1. Primer sequence for studied genes.

NO	Oligo Name	Seq(5-3)
1	*bla OXAlike-51F*	TAATGCTTTGATCGGCCTTG
2	*bla OXAlike-51R*	TGGATTGCACTTCATCTTGG
3	*qac E F*	ATGAAAGGCTGGCTT
4	*qac E R*	TCACCATGGCGTCGG
5	qacEΔ1 *F*	TAGCGAGGGCTTTACTAAGC
6	qacEΔ1 *R*	ATTCGAAATGCCGAACACCG

Table 2. Demographic data of *A. baumannii* infections.

Gender	Age(year)	Ward							Site of infection				
		No./percent							No./percent				
No (%)	Mean	ICU			NERO	EMR	INF	CARD	LC	WC	BC	UC	other
	Rang	I	II	III									
Male 45(60)	67.7 22-92	30 40	6 8	0 0	3 4	3 4	2 2.6	1 1.3	36 48	3 4	4 5.3	2 2.6	0 0
Female 30 (40)	63.1 22-83	16 21.3	10 13.3	1 1.3	1 1.3	1 1.3	1 1.3	0 0	27 36	2 2.6	0 0	0 0	1 1.3
Total 75 (100)	65.4 22-92	46 61.3	16 21.3	1 1.3	4 5.3	4 5.3	3 4	1 1.3	63 84	5 6.6	4 5.3	2 2.6	1 1.3

ICU: Intensive care unit, CARD: Cardiology, EMR: Emergency, INF: Infectious diseases, NERO: Neurology, LC: tracheal aspirate culture, BC: blood culture, UC: urine culture, WC: wound culture

females it was 63.1 years (range: 22-83 years) (Table 2). The preponderance of A. baumannii infections was observed to occur in the ICU (n=63, 84%), with a further breakdown of ICU I (n=46, 61.3%), ICU II (n=16, 21.3%), and ICU III (n=1, 1.3%). The remaining A. baumannii infections were detected in the Neurology ward (n=4, 5.3%), the Emergency ward (n=4, 5.3%), the Infectious Diseases ward (n=3, 4%), and the Cardiology ward (n=1, 1.3%). The primary isolation sites of A. baumannii isolates were the lungs (84%), followed by wounds (6.6%), blood (5.3%), urine (2.6%), and other (1.3%) (Table 2).

3.1. Antibiotic Susceptibility Test (AST)

The present study examined the antibiotic resistance patterns of A. baumannii isolates. The results revealed that the majority of the isolates (96%) demonstrated resistance to at least nine out of the twelve tested antibiotics. The highest and lowest resistance rates were observed for CAZ (98.7%) and TGC (34.7%), respectively. The analysis identified five distinct antibiotic resistance patterns (A-E). Four of these patterns included XDR phenotypes, with pattern A being the only exception (Table 3). Pattern A was the most prevalent resistance pattern, being detected in 31 isolates (41.3%). The A. baumannii isolates exhibiting pattern A demonstrated resistance to ten antibiotics (Table 3).XDR isolates were identified among pattern B (11 antibiotics) (N=19, 25.3%), pattern C (nine antibiotics) (N=12, 16%), pattern D (10 antibiotics) (N=6, 8%), and pattern E (11 antibiotics) (N=3, 4%) (Table 2). Four isolates demonstrated a unique resistance pattern. The ICU patients exhibited the highest number of A. baumannii infections (75 patients in total, with 63 infections, constituting 84%). Among these patients were 36 males (57%) and 27 females (43%). The majority of cases exhibited MDR (Multi Drug Resistant) and XDR (Extended Drug Resistant) phenotypes, with 62 cases (98.4%) demonstrating these traits (53.2% MDR and 46.7% XDR).

3.2. Antiseptic Resistance Gene Distribution

In the present study, a total of 75 isolates were analysed, of which 48 (64%) were found to have at least one antiseptic resistance gene. This included 24 isolates (32%) with the qacE gene, five isolates (6.7%) with the qacEΔ1 gene, and nine isolates (25.3%) where both qacE and qacEΔ1 genes were detected simultaneously. The highest prevalence of antiseptic resistance genes (qacE and qacEΔ1) was detected in pattern D (100%), followed by pattern B (68.4%), pattern A (64.5%), and pattern C (58.3%). The most prevalent single occurrence of qacE (83.3%) and qacEΔ1 (66.7%) genes was observed in pattern D, while in pattern D, there was a simultaneous occurrence of resistance genes at the highest rate of 50%.

3.3. Antibiotic Resistance Gene Distribution

The BlaOXA-23 gene was identified in 63 (84%) of the isolates examined, with the majority of these isolates also possessing at least one antiseptic resistance gene (n=41/63, 65%). The highest occurrence of the BlaOXA-23 gene was among pattern D (100%), followed by pattern B (89.4%), pattern A, and pattern C (83.3%) isolates (Table 3).

3.4. MICs for Antiseptics

It is noteworthy that there was no statistically significant variation among the isolates with respect to BTC and BKC resistance levels, suggesting a uniformity in the patterns of resistance exhibited. The MICs for various antiseptics ranged from 3.9 to 31.2 µg/ml for BTC, from 3.9 to 62.5 µg/ml for BKC, and from 31.2 to 250 µg/ml for CHG. The mean MIC for CHG in isolates with antiseptic resistance

genes was found to be significantly higher than in isolates without these genes (81.4 µg/ml versus 27.9 µg/ml, P=0.001). Furthermore, a statistically significant difference in mean MICs for CHG was observed among isolates harboring qacE (63.8 µg/ml), qacEΔ1 (56.2 µg/ml), and qacE+qacEΔ1 (111.8 µg/ml) in comparison to those not possessing these genes (27.9 µg/ml, P=0.001). Moreover, the investigation revealed that 63 out of 75 (97.3%) isolates possessed the blaOXA-23 gene, with 41 out of 63 (65%) of these isolates also harboring at least one additional antiseptic resistance gene (Table 4).

4. Discussion

The present study results illustrate the correlation between the antiseptic resistance genes (qacE and qacEΔ1) and minimal inhibitory concentrations (MICs) against CHG.The prevalence of multidrug resistance (MDR) and extensively drug resistance (XDR) (94.6%) is higher than reported from other parts of Iran. The MDR prevalence ranges between 32.7% and 93% (2001 to 2011 among Iranian A. baumannii isolates reported by seven studies) (10). A recent study by Mirzayi and colleagues (2020) reported 74.8% and 73.1% prevalence of MDR and XDR, respectively (11). The MDR phenotype rate was reported from 50% to 85% from Latin American countries, Africa, Asia, and North American countries (12). The high prevalence of MDR isolates from intensive care unit (ICU) wards noted in this study aligns with findings from other research, except in North American countries (12). Resistance against carbapenems detected in the current study was reported differently in European and Arabian countries (13). Elevated resistance against carbapenems was also reported in Iran (14). The prevalence of the qacEΔ1 gene reported in the present study is significantly lower than in several other studies conducted in Iran (49.5%, 59%, and 91%) and other countries (63% - 96.07% (15,16)). Some Iranian studies reported a higher frequency of the qacE gene (40% - 47.5%) (17,18), while its rate was reported to be lower (4% - 17%) in other Iranian studies (19). The prevalence of the qacE gene among A. baumannii isolates has been reported to be higher in other countries (33.3% from Saudi Arabia) (20), 45.5% and 52% from Egypt (21), and 73% from Malaysia (22). However, a lower prevalence has been reported in China (30.48% and 31.37%) (8,16).The elevated prevalence of the blaOXA-23 gene and its carbapenems resistant phenotype documented

Table 3: Antibiotic resistance patterns versus antiseptic and antibiotic resistance gene distribution among *A. baumannii* isolates.

Pattern No. (%)	Resistant to antibiotic	Sensitive	having at least a gene	*qac*E	*qac*EΔ1	*qac*E+ *qac*EΔ1	*Bla*OXA-23
			No (%)				
A(MDR) 31(41.3)	SAM, FEP, AMI, TOB, PI+TZ, CAZ, MEM, IMI, DOR, CIP 10	TGC 1	20 64.5	17 54.8	12 38.7	9 29	26 83.8
B (XDR) 19 (25.3)	SAM, FEP, AMI, TOB, PI+TZ, CAZ, MEM, IMI, DOR, CIP, TGC 11	- 0	13 68.4	13 68.4	5 26.3	5 26.3	17 89.4
C (XDR) 12 (16)	FEP, AMI, TOB, PI+TZ, CAZ, MEM, IMI, DOR, CIP 9	SAM, TGC 2	7 58.3	6 50	3 25	2 16.6	10 83.3
D (XDR) 6 (8)	FEP, AMI, TOB, PI+TZ, CAZ, MEM, IMI, DOR, CIP, TGC 10	SAM, 1	6 100	5 83.3	4 66.7	3 50	6 100
E (XDR) 3 (4)	SAM, FEP, AMI, TOB, PI+TZ, CAZ, MEM, IMI, DOR, CIP, TGC 11	- 0	1 33.3	1 33.3	0	0	1 33.3

Doripenem(DOR)(10mg), Meropenem(MEM)(10mg), Tigecycline(TGC)(15mg), Imipenem(IMI)(10mg), Ceftazidime(CAZ)(30mg), Ampicillin+Sulbactam (SAM) (20mg), Cefepime(FEP) (30mg), Amikacin(AMI)(30mg) ,Tobramycin(TOB)(10mg), Ciprofloxacin (CIP), Piperacillin+Tazobactam (PI+TZ).

Table 4. Distribution of antiseptic resistance genes and MIC level among *A. baumannii* isolates.

gene	BTC		BKC		CHG		resistance gene	BTC	BKC	CHG	*Bla*OXA-23
	Mean (µg/ml) rang	*P*	Mean µg/ml Rang	*P*	Mean µg/ml rang	*P*	distribution pattern	Mean (µg/ml)			
							No. (%)		rang		No. (%)
Positive 48 (64%)	14.4 3.9-31.2	0.276	20.2 3.9-62.5	0.41	81.4 31.2-250	0.001	*qac*E 24 (50%)	13.02 (3.9-31.2)	18.8 (7.8-31.2)	62.5 (31.2-125)	20 49.3
							*qac*EΔ1 5 (10.4%)	16.4 (3.9-31.2)	16.4 (3.9-31.2)	56.2 (31.2-62.5)	5 28.7
							*qac*EΔ1+*qac*E 19 (39.5%)	15.6 (7.8-31.2)	22.8 (3.9-62.5)	111.8 (62.5-250)	16 21.9
Negative 27 (36%)	11.5 3.9-31.2		14.6 1.9-62.5		27.9 1.9-62.5			11.5 (3.9-31.2)	14.6 (1.95-62.5)	27.9 (1.9-62.5)	

*Bla*OXA-23: Antibiotic resistance gene, P: One way ANNOVA test, bold text: significant.

in this study is of particular interest (23). The co-occurrence of antiseptic and antibiotic resistance in our isolates, likely attributable to their co-location within the same class I integron, is a significant concern. This discovery highlights the potential difficulties in eliminating these isolates, emphasising the need for further research in this critical area (24). The frequent detection of antiseptic resistance genes among the blaOXA-23-harbouring isolates poses a significant challenge to the eradication of these isolates. A statistically significant increase in the MIC against CHG was detected among qacE- and qacEΔ1-positive A. baumannii isolates. Guo et al. documented a statistically significant increase in the MIC against CHG in qacE-positive isolates in China (16). Conversely, Liu et al. observed a non-statistically significant increase in the MIC against BKC among qacE-positive A. baumannii isolates (8). Contrary to these findings, studies conducted in Saudi Arabia (20) reported no increase in MIC values among A. baumannii isolates against CHG and BTC (8). It is fortunate, however, that the recommended concentration of use for CHG in commercial disinfectants (5000 µg/ml) is still higher than the highest measured MIC in the current study (25). Nevertheless, the increased MIC among A. baumannii isolates from our region is a significant clinical concern. The presence of A. baumannii isolates with MDR and XDR phenotypes, which possess antiseptic resistance genes and elevated MICs against antiseptic agents, underscores the necessity for meticulous monitoring of all A. baumannii isolates in hospital settings.

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Authors' Contribution
Conceptualization, Project Administration, Writing _Original Draft Preparation; HGM.
Investigation and laboratory works, NF; Investigation and Resources; M R.
Project Administration; MM.
Investigation and Resources, and AvB. Writing – Review and Editing, scientific advice; AA.

Ethics
The collection of samples was carried out in strict accordance with the guidelines approved by the Ethical Committee of Islamic Azad University, Damghan, Iran (ethics code: IR.IAU.DAMGHAN.REC.1401.001).

Conflict of Interest
The authors have no relevant financial or non-financial interests to disclose.

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Data Availability
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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