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Research Article

A Molecular Diagnosis and Identification of Carbapenemase Producing *Acinetobacter Baumannii* among ICU Patients, In Khartoum State-Sudan

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ABSTRACT

Background: The emergence of carbapenemase producing *Acinetobacter baumannii* (CPAB) is increasingly reported nowadays and constitutes a major problem to the intensive care unit (ICU) patients with remarkable ability to acquire antibiotic resistance. The aim of this study was to determine the antibiotic resistance patterns, presence of carbapanemase genes of *A. baumannii* isolated from various clinical specimens, Khartoum State-Sudan.

Methods: one hundredof Gram-negative *coccobacilli* isolates were collected from ICU patients admitted to RoyalCare International Hospital and the National Ribbat Hospital. All the samples were processed using conventional microbiological and molecular methods for *A. baumanii* identification. Antimicrobial susceptibility testing was performed by dis diffusion technique. The carbapenemase-encoding genes (blaKP, blaIMP, blaVIM, blaOXA, blaNDM, blaGES, blaOXA-51 and blaOXA-23) were tested by polymerase chain reaction (PCR) method.

Results: The prevalence of *A. baumanii* was 39.0% (39/100) among ICU patients and carbapenem resistance *A. baumanii* (CRAB) was high, 97.4% (38/39) and 57.9 (22/38) of CRAB was carbapenemase gene producer. The most common carbapenemase associated with resistance was blaOXA gene followed by blaNDM and blaGES *A. baumanii* isolates. All isolates were resistance to all tested antimicrobial agents and 63.6% resistance to colistin.

Conclusion: This study shown that blaOXA followed by NDMis the predominant carbapenemase gene presenting among ICU patients of both hospitals. Here, we detected an emergent blaOXA-143 identified in two *A. baumannii* strains which reported as High-Risk Clones.Colistin no longer remains drug of choice for treatment of CRAB.This highlights the importance of national mentoring of CPAB in the hospital to avoid clone dissemination.

Keywords: Carbapenem producing *Acinetobacter baumannii* (CPAB); Intensive care unit (ICU) patients; Colistin

List of Abbreviations

ICU Intensive Care Unit

A. baumannii *Acinetobacter baumannii*

INTRODUCTION

Acinetobacter baumannii is a major cause of hospital acquire infections mainly among patients admitted at intensive care units (ICU) in many hospitals, regarding its ability to develop resistance to multiple antimicrobial agents is difficult to control and treat leading to serious therapeutic problems [1]. Carbapenems are thus often considered "last-resort antibiotics"

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for treating multi-drug resistant (MDR) bacteria and for treating *A. baumannii* serious infections [2]. However, reports of carbapenem resistant *A. baumannii* (CRAB) strains have been rising steadily during the past few years, and these isolates are often multidrug-resistant [3]. This emergence of CRAB has become a worldwide problem especially, multiresistant strains seriously challenges the treatment of these infections [4].The carbapenem resistance, most commonly caused by carbapenemases which are β-lactamases capable of hydrolysing carbapenems [7]. The Ambler classification allows differentiation of carbapenemases into class A (e.g., KPC, SME, IMI, and GES), class B (e.g., NDM, VIM, and IMP), and class D (OXA-48-like). The carbapenemases of class A and class D are serine β-lactamases, and the carbapenemases of class B are metallo-β-lactamases (MBLs) [8]. The emergence of CPAB is of special concern in developing countries, since antibiotic prescription rates and intake without prescription is markedly higher [9].

Antibiotic resistance causing increased morbidity, mortality, and economic impacts on health services especially among ICU patients as they are critically ill or debilitated patients at high risk [4]. *A. baumannii* has the ability to survive for long periods and could easily spread in hospital environments [5]. These traits could define its propensity for causing extended outbreaks [5, 6]. Consequently, there is a critical need to conduct research to estimate the burden of carbapenemase producing *A. baumanii* underlying the attributed resistance. In our region lack of systematically identification of *A. baumannii* infection among ICU patients and environments in hospital which is contributes to a poor understanding of antimicrobial resistance and limits an effective response to the problem. The present study was carried out toisolates and evaluates the antibiotic resistance of *A. baumannii* isolated from ICU patients and to evaluate the frequency of common carbapenemase-encoding genes in isolated carbapenem resistant *A. baumannii* by polymerase chain reaction (PCR).

MATERIALS AND METHODS

One hundred Gram-negative *coccobacilli* isolates were collected in 2019 from Microbiology laboratory department at Royal Care International Hospital (RCIH) and National Ribat Hospital (NRH) as identified by both microbiology laboratories, both hospitals located in Khartoum city, Sudan. The clinical specimens were sputum, blood, urine, wound swab, central-line catheter and tips then plated out on MacConkey agar.

Isolation and identification of *A. baumannii:* was done phenotypically based on cultural characteristics, Gram stains, oxidase test and conventional gram negative biochemical set following standard assay of gram negative rods at microbiology laboratory at both hospitals, and by molecular identification of *A. baumanii* was further confirmed by restriction analysis of the 16s-23s using polymerase chain reaction (PCR) amplification (Table 1). Confirmed A. *baumannii* isolates were tested for antimicrobial susceptibility and likewise screened for the presence of most common carbapenemase-encoding blagenes.

Antimicrobial susceptibility testing: Antimicrobial susceptibility test of the *A. baumannii* confirmed isolates was performed by disc diffusion method as per the (CLSI) guidelines [7], on Muller-Hinton agar (Hi-Media, Mumbai) using Ceftazidim (30 µg), ccefuroxime (30 µg), gentamicin (10 µg), cefixime (30 µg), ciprofloxacin (5 µg), amoxiclav (30 µg), meropenem (10 µg), ceftriaxone (30 µg) and colistin (10 µg)(bioanalyse, Turkey and Hi-Media, Mumbai).

The diameter of inhibition zones was measured and reported as susceptible or resistant. For quality control, standard strain of E. coli (ATCC 25922) was used.

Detection carbapenemase-encoding blagenes: *A. baumannii* isolates were screened for 6 common carbapenemase-encoding genes including blaNDM[8] blaIMP, blaKPC, blaVIM, blaOXA, blaGES [9] and forOXA-type carbapenemase-encoding genes including blaOXA-23, blaOXA-24, blaOXA-143 and blaOXA-51[10] by PCR amplification with specific sets of primers (Table 1).

PCR amplification: The deoxyribonucleic acid (DNA) was extracted by boiling technique as follow; a loopful of each *A. baumannii* isolate was emulsified in200 µl of distilled water then boiled for 15 min and centrifugation at 13,000 rpm for 10 min. Supernatant was used for PCR amplification. All PCR-Reaction conditions were prepared by using ready master mix (APSLABS,

India), 0,5 µl of each primer and 1 µl of template DNA (about 10 mg) in a total 25 µl.The PCR cycling conditions were as follows: for blaNDM comprised of initial denaturation at 94° Cfor 10 min followed by 30 cycles of 1 min denaturation at 94° C, 1 min annealing at 60°C and 1 min extension at 72°C and final extension step of 10 min at 72°C.

For multiplex (VIM, IMP and KPC) and (GES and OXA) carried out as a following: initial denaturation at 94°C for 10 min; 30 cycles of 94°C for 40 s, 55°C for 40 s and 72°C for 1 min; and a final elongation step at 72°C for 7 min. The annealing temperature of multiplex GES and OXA was optimal at 57°C instead of 55°C. PCR products were assessed by electrophoresis using 1.5% (w/v) agarose gel and visualized by using an ultraviolet (UV) trans illuminator.

Statistical analysis: all data were analyzed using the Statistical Package for the Social sciences for Windows software package version 21.0 (SPSS-IBM, Armonk, NY).

Results were presented using frequency and percentages for qualitative variables. Categorical variables were compared by Chi-square test and all tests were two-sided, and differences with P-value <0.05 were considered statistically significant.

Table 1: Primers set used in the sequence and amplicon size (bp).

PCR name	Sequence (5´-3´)	Amplicon size (bp)
Acinetobacter species	F-CACGCCGTAAGAGTGCATTA	293
	R-AACGGAGCTTGTCAGGGTTA	
A.*baumannii* specific primers	F-CCTGAATCTTCTGGTAAAAC	500
	R-GTTTCTGGGCTGCCAAACATTAC	
Multiplex-1		
blaVIM	F-GATGGTGTTTGGTCGCATA	390
	R-CGAATGCGCAGCCCAG	
blaIMP	F-TTGACACTCCATTTACDG	139
	R-GATYGAGAATTAAGCCACYCT	
blaKPC	F-CATTCAAGGGCTTTCTTGCTGC	
	R-ACGACGGCATAGTCATTTGC	538
Multiplex-2		
blaGES	F-AGTCGGCTAGACCGGAAAG	399
	R-TTTGTCCGTGCTCAGGAT	
blaOXA	F-GCTTGATCGCCCTCGATT	281
	R- GATTTGCTCCGTGGCCGAAA	
blaNDM-1	F-ATGGAATTGCCCAATATTATGCAC	813
	R- TCAGCGCAGCTTGTCGGC	
Multiplex-3		
BlaOXA-51	F- TAA TGC TTT GATCGG CCT TG	353
	R- TGG ATT GCA CTT CAT CTT GG	
blaOXA-23	F-GAT CGG ATT GGA GAA CCA GA	501
	R-ATT TCT GAC CGC ATT TCC AT	

RESULTS

Detection of *A. baumanii:* A total of 39 *A. baumaniiout* of 100 gram-negative *coccobacilli* isolates were recovered from different clinical specimens; sputum (n=29), urine (n=4), blood, central line and tip (n=3) for each, wound and bed sore (n=1) for each, collected from the microbiology laboratory at Royal Care International Hospital (RCIH) and National Ribat Hospital (NRH) were included in the study (Table 2).

Antimicrobial susceptibility of *A. baumannii* **isolates:** 100% (39/39) of *A. baumannii* isolates from ICU patient's samples were resistant to ciprofloxacin, cefixime, ceftazidime, ceftriaxone, cefuroxime amoxacillin/clavulanic acid and gentamicin followed by 97.4% (38/39) meropenem. In other words, most of A. baumannii isolates were multidrug resistant. However, 59.0% (23/39) of the isolates were resistant to colistin.

Carbapenemase-encoding genes in *A. baumannii* **isolates:** 56.4% (22/39) of *A. baumannii* were positive for one or more carbapenemase blagenes. The most prevalent single blagenes detected were OXA (n=5) followed by NDM (n=4) and GES (n=1). Whereas twelve A. baumanii isolates were co-produced carbapenemase blagenes blaND +OXA(n=5)blaOXA-23/51(n=4), blaNDM-1+OXA-23/51/143(n=2), whileblaNDM-1+ blaOXA-51 was detected in only one (n=1) isolate (Figure 1).

Table 2: Distribution pattern of A. *baumanii* and CP-AB isolates by their respective sources of specimens from ICU patients at Khartoum state selected hospitals.

Source of specimens	*A. baumanii* (n=39)
	N (%)
Sputum (n=37)	29 (74.4%)
Urine (n=4)	3 (7.7%)
Wound (n=2)	1 (2.6%)
Blood (n=3)	3 (7.7%)
Bed sore (n=1)	1 (2.6%)
Central line (n=2)	1 (2.5%)
Tip (n=3)	2 (5.1%)

Table 3: Antimicrobial susceptibilities profiles of A. baumanii isolates and carbapenem resistant *A. baumaniifrom* ICU patients at Khartoum state selected hospitals.

Antibiotic disc µg/ml	*A.baumanii* (n=39)		CP- *A.baumanii* (n=22)		P value	X^2
	Resistance N (%)	Sensitive N (%)	Resistance N (%)	Sensitive N (%)		
Ciprofloxacin	39 (100%)	0 (0.0%)	22 (100%)	0 (0.0%)	0.000*	1
Cefixime	39 (100%)	0 (0.0%)	22 (100%)	0 (0.0%)	0.000*	1
Ceftazidime	39 (100%)	0 (0.0%)	22 (100%)	0 (0.0%)	0.000*	1
Gentamycin	39 (100%)	0 (0.0%)	22 (100%)	0 (0.0%)	0.000*	1
Ceftriaxone	39 (100%)	0 (0.0%)	22 (100%)	0 (0.0%)	0.000*	1
AMC*	39 (100%)	0 (0.0%)	22 (100%)	0 (0.0%)	0.000*	1
Cefuroxime	39 (100%)	0 (0.0%)	22 (100%)	0 (0.0%)	0.000*	1
Colistin	23 (59.0%)	16 (41.0%)	14 (63.6%)	8 (36.4%)	0.171	1.528
Meropenem	38 (97.4%)	1 (2.6%)	22 (100%)	0 (0.0%)	0.000*	1

*Antibiotic disc concentrations in µg/ml, AMC; Amoxacillin/Clavulanic Acid, *Sig. P value<0.05, CP- *A.baumanii*; Carbapenemase producing-*A.baumanii*.

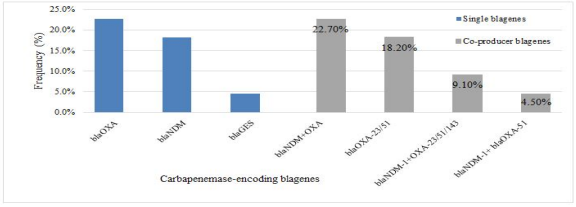

Figure 1: Distribution pattern of Carbapenemase producing *A. baumanii* (blagenes) from ICU patients at Khartoum State in selected hospitals.

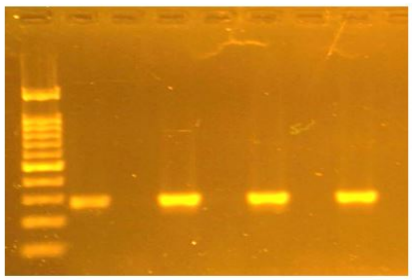

Figure 2: Gel-electrophoresis result of blaOXA amplification: lane 1: DNA ladder 100 bp; lane 2: OXA positive control 281 bp; lane 3: negative control; lanes 4, 6 &8: Positive OXA Acinetobacter isolates.

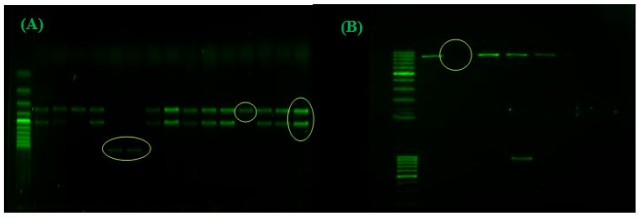

Figure 3: Gel-electrophoresis result of: (A) blaOXA specific amplification: lane 1: DNA ladder; lane 6: OXA-143 enzymes; lane 12: OXA-51 enzymes; lane 14: OXA-51/2. The molecular size marker (lane 1) is a 123 bp ladder (Invitrogen, Paisley, UK) and (B) blaNDM-1 amplification: lane 1: DNA ladder; lane 5: NDM-1 enzyme.

DISCUSSION

A. baumanii is an important opportunistic pathogen that is responsible for health-care infection specially the MDR. *A.baumannii* is highly resistant to commonly used antibiotics such as penicillins, cephalosporins, aminoglycosides and fluoroquinolones by intrinsic and acquired mechanisms. They are also gradually becoming resistant to carbapenems. The isolation of MDR *A. baumannii* from ICU samples had been reported earlier by researchers [12].

Hospitals have long served as reservoirs for the transmission of pathogenic bacteria, and. Among the source of the isolates in these study the vast majority of positive cultures were from respiratory specimens (74.4%) followed by urine and tip specimens, consistent with other studies [13,14,15]. Infections with *A. baumannii* affecting mainly the respiratory tract, urinary tract, wound infections and sometimes local infections may develop bacteraemia as almost all cases received (mechanical ventilation or endotracheal tube and catheters during their ICU stay, all these findings may support by [16].

The results of the present study show that there was an extreme increase in the resistance rate of *A. baumannii* to meropenem, from 89% in 2015 to 100% in 2019 [17]. In addition, the resistance rate of *A. baumannii* to colistin was 59%, which is higher than in previous reports in Khartoum state and other studies [18,19,20]. The present study showed 100% resistant rates of the most clinically applicable antibiotics for the treatment of infections caused by *A. baumannii*, except for colistin, which may be used as the final options in the management of infections caused by this bacterium. In this study, the high resistance rate of *A. baumannii* against carbapenems may indicate the outcome of overuse and misuse of carbapenems in our hospital.

Overall, blaOXA-51 genes were the most prevalent subgroup, which is consistent with the view that they are intrinsic to *A. baumannii* [21]. These genes were detected in 7 of 11 isolates, irrespective of levels of carbapenem susceptibility or resistance, these alleles does not correlate with the level of carbapenem resistance of the host isolate. Thus, resistance to carbapenems cannot be inferred from detection of blaOXA-51-like alleles. In contrast, alleles encoding OXA-23-like, OXA-24-like and OXA-58-like enzymes were consistently associated with resistance or, at least, with reduced susceptibility.

The blaOXA-23 carbapenemase-producing A. baumannii are becoming widespread globally in Europe, South America, and Asia [22]. In this study, blaOXA-23 carbapenemase was detected in 6 (15.4%) of the 39 carbapenem-resistant isolates and as in terms of carbapenem non-susceptibility, an alarmingly high rate of 75.0% over 2 years was detected, this high rate is similar to that reported by Perez et al [23] This rate, however; is much higher than that reported for other African countries [24] revealing a worrisome situation in this country. Alleles encoding OXA-24 (OXA-40)-like enzymes were not detected in any of the Sudanese clinical isolates; these enzymes are most often found in Portugal, Spain, Poland, Iran, the United States and Asia [15]. In Saudi Arabia, the blaOXA-24 gene was detected at a rate of 4–45% in Acinetobacter species isolates [25], we first report blaNDM-1-positive *A. baumanii* isolates in Sudan. In contrast to in other countries where blaNDM-1 was mostly carried by *Enterobacteriaceae*; all the blaNDM-1-positive *A. baumannii* isolates, which suggests that this species, which has a robust survival capability, can easily acquire foreign resistance genes such as blaNDM-1[26].

Recently the Ambler class A of the GES (carbapenemase) types has also been reported for *A. baumannii* [27]. The blaGES genes are usually carried on integrons found in various species, predominantly Klebsiella pneumoniae, Escherichia coli, and Pseudomonas aeruginosa, and these resistance determinants have been reported in several countries in Europe, Asia, South America, and South Africa [28]. Our data further point out the fact that one of CR-AB is producing GES gene, that might now be emerging independently in different areas in the world and indicate that, were also recently reported in an Acinetobacter isolate from Kuwait [29], as an additional mechanism of resistance to carbapenems in *A. baumannii*. Only GES-type carbapenemase was reported in Mediterranean countries [28].

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Ethical clearance: This study was approved by the ethics committee of Alribat national university-graduate collage.Bacterial isolates ethics approval and consent was not applicable as samples obtained from Microbiology Laboratory remaining samples and coded by Laboratory ID.

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