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Molecular Diagnosis and Identification of Carbapenemase Producing *Acinetobacter baumannii* among ICU Patients, in Khartoum State-Sudan

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Abstract

Background: Carbapenemase producing-*Acinetobacter baumannii* (CP-*A.baumanii*) has become a significant nosocomial pathogen because of its remarkable ability to acquire antibiotic resistance. The aim of this study was to investigate the molecular characterization of CP-*A.baumanii* isolated from intensive care unit (ICU), in Khartoum state sudan.

Methods: Hundred isolates of CP-*A.baumanii* were collected from ICU patients, from the Royal Care International Hospital and the National Ribbat Hospital. The disc diffusion of antimicrobial susceptibility testing of the isolates against common antibiotics were determined. The carbapenemase-encoding resistance genes of these isolates using the primer were detected by PCR.

Result: Thirty nine isolates were found to carry multiple drug resistance Among the 39 *A.baumanii* isolates, 22 were carbapenemase producing-*A.baumanii* (CP- *A.baumanii*), for an overall carbapenemase producing rate of 56.4%.

Conclusion: This is the first report of the molecular mechanisms of CRAB in Khartoum state. A very high level of carbapenem non-susceptibility was detected in these Sudanese hospitals over a period of two years form ICU patients. The predominant Carbapenemase in RCIH and NRH hospitals were NDM and GES and OXAs. As blaOXA-23, blaOXA-51, blaNDM-1 and blaGES producing CRAB isolates were prevalent in the ICU. The coexisted genes (OXA-23/51 and blaNDM-1+blaOXA-23/51/143) were also associated with increased virulence as compared to other OXAs. Here, we detected an emergent OXA subclass identified in two A*. baumannii* strains OXA-143 which reported as **High-Risk Clones** among MDR and XDR *A. baumannii*.

Introduction

Acinetobacter baumannii is an important opportunistic pathogen often involved in various nosocomial infections, such as bacteremia, urinary tract infection, secondary meningitis, surgical site infection, and ventilator-associated pneumonia, especially in patients admitted to intensive care and burn units [1]. *A. baumannii* is notorious for its remarkable innate and acquired resistance to multiple antimicrobial classes, including extended spectrum cephalosporins and carbapenems. The emergence of carbapenem-resistant *A. baumannii* has been described as the sentinel event of antimicrobials resistance [2,3].

Despite the high burden of antibiotic resistance in Sudan, there are very limited reports on the epidemiology of resistance among *A. baumanii* isolates in our region. Recent reports have indicated that carbapenem resistance mainly

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OXA-type genes may have their natural reservoirs and endemic in some countries (There is little known about the spread and clinical importance of *A.baumanii* antibiotic resistance and carbapenemase producing bla_{genes} at Khartoum state among hospitalized patients). A study on the epidemiology of *A.baumanii* in Egypt showed that 70% resistant isolates, with acquired the three OXA carbapenemases in different clones within one year [4]. Elsewhere; CP-AB in hospital settings ranged from 2.3% to 67.7% in North Africa and from 9% to 60% in sub-Saharan Africa and the major bla genes were OXA-23, OXA-58, OXA-48, NDM-1 and VIM-2 associated with *A.baumanii* isolates of hospitalized patients during the years between 2010-2018 [5,6]. More alarmingly, there was record of Extreme drug resistance *A.baumanii* with intermediate resistance to colistin. The lack of systematically collected data on the Sudan area contributes to a poor understanding of antimicrobial resistance and limits an effective response to the problem. Consequently, there is a critical need to conduct research to estimate the burden of carbapenemase genes underlying the attributed resistance.

Materials and Methods

One hundred *A. baumannii* isolates were collected during the period 2017 to June 2019 from Microbiology laboratory department at Royal Care International Hospital (RCIH) and National Ribat Hospital (NRH) as identified by both 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*

Were carried out based on cultural characteristics, Gram stains, oxidase test and conventional biochemical tests following standard assay of gram-negative rods at microbiology laboratory at both hospitals. Then genotypes identification of isolate was performed by amplification DNA-based testing PCR was used to confirm the identification of *Acinetobacter* species and *A. baumannii* from another gram negative.

Antimicrobial susceptibility was performed by disc diffusion method as per the (CLSI) guidelines [7], using Muller-Hinton agar (Hi-Media, Mumbai) and antimicrobial discs (bioanalyse, Turkey and Hi-Media, Mumbai). The following antimicrobial agents (µg/ml) were used: Ceftazidim (30), cefuroxime (30), gentamicin (10), cefixime (30), ciprofloxacin (5), amoxiclav (30), meropenem (10), ceftriaxone (30) and colistin (10). The diameter of inhibition zones was measured and reported as susceptible or resistant. Quality control of the disks were checked by using reference strains. For meropenem resistant strains the presence of the carbapenemases (bla_{NDM1}, bla_{VIM}, bla_{IMP}, bla_{OXA}, bla_{GES} and bla_{KPC} genes)was screened by Multiplex PCR.(On the other hand 11 samples of *A.baumanii* were identifying carbapenemase genes bla_{OXA} and bla_{NDM} sub-types by specific primers).

Genotypic characterization of AC-CP

The multiplex PCR assay (using eight primers) amplified fragments of bla_{NDM} [8] bla_{IMP}, bla_{KPC}, bla_{VIM}, bla_{OXA} and bla_{GES} [9] and for bla_{OXA-23}, bla_{OXA-24} , $bla_{OXA-143}$ and bla_{OXA-51} [10] and

Table 1: Primers specific to multiplex Carbapenemase (*blagene*) with sequence and amplicon size (bp):

PCR name	Sequence (5´-3´)	Amplicon size (bp)
Multiplex-1		
bla_{VIM}	F-GATGGTGTTTGGTCGCATA R-CGAATGCGCAGCCCAG	390
bla_{IMP}	F-TTGACACTCCATTTACDG R-GATYGAGAATTAAGCCACYCT	139
bla_{KPC}	F-CATTCAAGGGCTTTCTTGCTGC R-ACGACGGCATAGTCATTTGC	538
Multiplex-2		
bla_{GES}	F-AGTCGGCTAGACCGGAAAG R-TTTGTCCGTGCTCAGGAT	399
bla_{OXA}	F-GCTTGATCGCCCTCGATT R- GATTTGCTCCGTGGCCGAAA	281
bla_{NDM-1}	F-ATGGAATTGCCCAATATTATGCAC R- TCAGCGCAGCTTGTCGGC	813
Multiplex-3		
Bla_{OXA-51}	F- TAA TGC TTT GATCGG CCT TG R- TGG ATT GCA CTT CAT CTT GG	353
bla_{OXA-23}	F-GAT CGG ATT GGA GAA CCA GA R-ATT TCT GAC CGC ATT TCC AT	501

bla_{NDM-1} [11]; alleles encoding each of the three multiplex PCR to detect the carbapenemases genes, Table 1 and Table 2. 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 ng) in a total 25 µl. PCR thermal profile for NDM comprised of initial denaturation at 94 °C for 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. The PCR amplification 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. The PCR products were analyzed by gel electrophoresis.

Results

Collection of a total of 100 non-fermenting Gram-negative coccobacilli cultures that obtained from hospital microbiology laboratory was done and were re-identified as Acinetobacter spp. *A.baumannii* was identified in 39 isolates and *Acinetobacter* species in 13 isolates while the remaining 48 were identified as non-*Acinetobacter* species .antibiotic susceptibility results of the 39 isolates and the 22 carbapenem resistant isolates shown in Table 3.

Genotyping identification by restriction analysis of the 16s - 23s, served to identify the *Acinetobacter* species as well as confirm the *A. baumannii* isolates. similarities shared by isolates in the *A. baumannii* and non-*Acinetobacter* species as routine biochemical tests for identification Gram negative bacteria was poorly distinguish between them. Molecular methods; on the other hand, are specifically tailored for accurate identification. A total of thirty-nine non-duplicate *A. baumannii* isolates were used in the study and 13 *Acinetobacter* species were exclude. Among the 39 *A.baumanii* isolates, 22 were carbapenem resistant *A. baumanii* detection of the carbapenemase genes were confirmed by the produce of the carbapenemase resistant genes.

All 22 of the carbapenem-harbouring *A. baumannii* isolates carried either single bla_{genes} or more than one genes per (multiple bla_{genes} (12/22; 54.5%). The prevalent genes seen to be associated with the *A. baumannii* isolates is shown in Table 4. The common single bla_{genes} detected were OXA (5/22; 22.7%) followed by NDM (4/22; 18.2%) then NDM-1 and GES (1/22; 4.5%). Whereas Eleven *A. baumanii* isolates were re-identified by specific primers toward NDM-1, OXA-23

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 (%)	CP-*A.baumanii* (n = 22) N (%)	P value	X^2
Sputum (n = 37)	29 (74.4%)	17 (77.3%)	0.428	4.899
Urine (n = 4)	3 (7.7%)	0 (0.0%)		
Wound (n = 2)	1 (2.6%)	0 (0.0%)		
Blood (n = 3)	3 (7.7%)	1 (4.5%)		
Bed sore (n = 1)	1 (2.6%)	1 (4.5%)		
Central line (n = 2)	1 (2.5%)	1 (4.5%)		
Tip (n = 3)	2 (5.1%)	2 (9.1%)		

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

Antibiotic disc µg/ml	***A.baumanii* (n = 39)**		**CP- *A.baumanii* (n = 22)**			
	Resistance N (%)	**Sensitive N (%)**	**Resistance N (%)**	**Sensitive N (%)**	**P value**	**X^2**
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*.

and OXA-51. The majority (n = 17) of the 22 CP-AB isolates were from a sputum source (n = 5) produce both OXA and NDM + OXA followed by NDM (n = 4), then OXA-23/51 (n = 3). The triple gene CP-AB was NDM-1 + OXA-23/51/143 was encountered from sputum and catheter tips (Table 4) (Figure 1, Figure 2 and Figure 3).

Discussion

A. baumanii is an important opportunistic pathogen that is responsible for health-care infection specially the MDR. *A. baumannii* are 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 [13-15]. 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 [18-20]. 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, bla_{OXA-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.

Table 4: Distribution pattern of Carbapenemase producing-*A.baumanii* (bla_{genes}) from ICU patients at Khartoum State in selected hospitals.

CP *bla*$_{gene}$	***A.baumanii*** (n = 22) N (%)
bla_{OXA}	5 (22.7%)
bla_{NDM}	4 (18.2%)
bla_{GES}	1 (4.5%)
$bla_{NDM+OXA}$	5 (22.7%)
bla_{NDM-1+} bla_{OXA-51}	1 (4.5%)
$bla_{OXA-23/51}$	4 (18.2%)
$bla_{NDM-1+OXA-23/51/143}$	2 (9.1%)

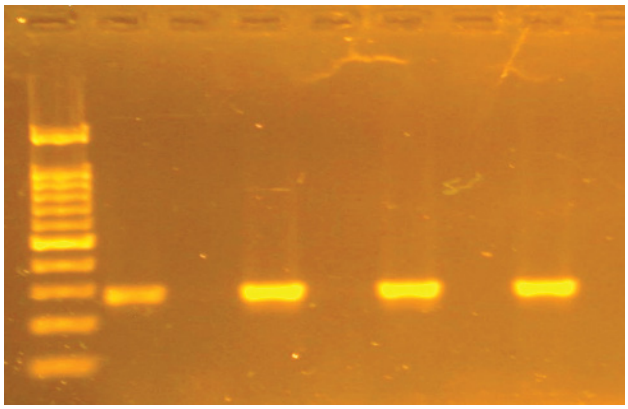

Figure 1: Gel-electrophoresis result of bla_{OXA} amplification: lane 1: DNA ladder 100bp; lane 2: OXA positive control 281 bp; lane 3: negative control; lanes 4, 6 &8: Positive OXA *Acinetobacter* isolates.

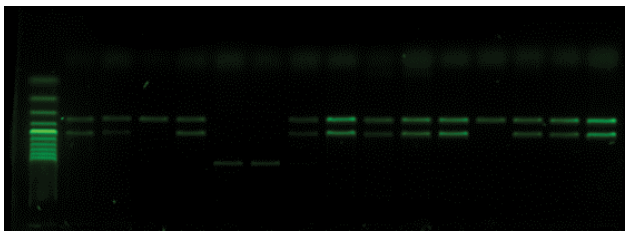

Figure 2: Gel-electrophoresis result of bla_{OXA} specific amplification: lane 1: DNA ladder; lane 6: OXA-143 enzymes; lane 12: OXA-51 enzymes; lane 14: OXA-51/2. The molecular size marker (lane 1) is a 123 bp ladder (Invitrogen, Paisley, UK).

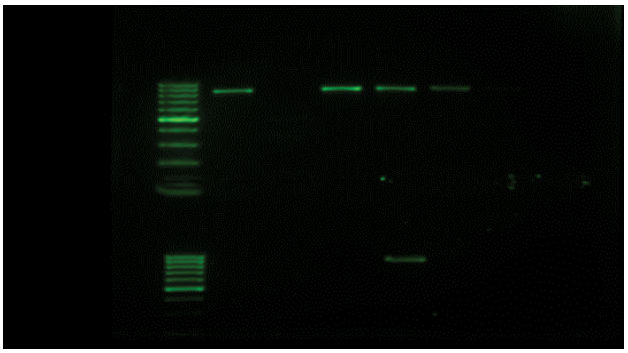

Figure 3: Gel-electrophoresis result of bla_{NDM-1} amplification: lane 1: DNA ladder; lane 5: NDM-1 enzyme.

The bla_{OXA-23} carbapenemase-producing *A. baumannii* are becoming widespread globally in Europe, South America, and Asia [22]. In this study, bla_{OXA-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 [13] 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 bla_{OXA-24} gene was detected at a rate of 4-45% in *Acinetobacter species* isolates [24], we first report bla_{NDM-1}-positive *A.baumanii* isolates in Sudan. In contrast to in other countries where bla_{NDM-1} was mostly carried by Enterobacteriaceae; all the bla_{NDM-1}-positive *A. baumannii* isolates, which suggests that this species, which has a robust survival capability, can easily acquire foreign resistance genes such as bla_{NDM-1} [25].

Recently the Ambler class A of the GES (carbapenemase) types have also been reported for *A. baumannii* [26]. The bla_{GES} 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 [27]. 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 [28], as an additional mechanism of resistance to carbapenems in *A. baumannii*. Only GES-type carbapenemase was reported in Mediterranean countries [27].

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Ethical Clearance

This study was approved by the ethics committee of Alribat national university-graduate collage. The informed consent was obtained from all the participants, and informed consent obtained was written.

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