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Edited by Rashmi Laddha
E-mail: drrashmirdaga@gmail.com
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bla_{OXA} and bla_{NDM} mediated carbapenemase resistance in *Acinetobacter baumannii* species

Sonali Vijay Bhaisare*

Department of Clinical Microbiology, J. N. Medical collage Sawangi, Datta Meghe institute of Higher Education and Research (Deemed To be University), Sawangi (Meghe), Wardha, Maharashtra, India; *Corresponding author

Affiliation URL:
https://www.dmiher.edu.in/

Author contact:
Sonali Vijay Bhaisare - E-mail: bhaisarevsonali@gmail.com; Phone: +91 7083849126

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Abstract:
The growing rise of the occurrence of Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) in critical care units is a disaster of the existing antimicrobial protocols, with the main cause of this problem being the dissemination of oxacillinase (OXA) and metallo-beta-lactamase (MBL) genes. In the present study, a cross-sectional molecular analysis of 215 clinical isolates was used to assess the antimicrobial susceptibility and define the genotypic presence of bla_{OXA-23}, bla_{OXA-51} and bla_{NDM-1} by using multiplex PCR assays in a tertiary care center. The resistance to meropenem was found to be 92.5% phenotypically and intrinsic bla_{OXA-51} was identified in 100% of isolates with acquired bla_{OXA-23} (78.6) and bla_{NDM-1} (34.4) in 22.3%. Thus, data shows the rise of *A. baumannii* strains that are co-producing OXA and NDM enzymes is an indication of the transition to pan-drug resistance. Hence, combined molecular surveillance and stewardship measures are in urgent need.

Keywords: *Acinetobacter baumannii*, carbapenemase, bla_{OXA-23}, bla_{NDM-1}, antimicrobial resistance

Background:
One of the most challenging nosocomial pathogens around the world, *acinetobacter baumannii*, has become the priority in a wide-ranging research and development of novel antibiotics by the World Health Organization (WHO) **[1]**. The success of the organism as a pathogen can be explained by the fact that it has outstanding genomic plasticity, which enables it to develop resistance determinants and survive in the hospital setting. Particularly noteworthy is the increase in the spread of Carbapenem-Resistant *A. baumannii* (CRAB), known to have a high mortality rate in the intensive care unit (ICU) and only a few treatment strategies are available **[2]**. Carbapenemases Carbapenin-hydrolyzing enzymes (carbapenemases) are produced in *A. baumannii* as the main mechanism of resistance to carbapenem. They can be divided into Ambler Class D oxacillinases (CHDLs) and Class B metallo-beta-lactamases (MBLs) to a great extent **[3]**. The intrinsic bla_{OXA-51}-like gene is ubiquitous and chromosomal in the species, but expressed weakly, in the Class D enzymes. Nevertheless, the expression acquisition of both insertion sequences (IS) upstream of this gene, or the expression acquisition of plasmid mediated genes like bla_{OXA-23}-like, $bla_{OXA-24/40}$-like and bla_{OXA-58}-like, radically amplifies carbapenem hydrolysis **[4]**. bla_{OXA-23} is the most common acquired carbapenemase gene found globally and when overexpressed, gives high-level resistance to carbapenems **[5]**. At the same time, the epidemiology of CRAB is being altered by invasion of Class B MBLs, namely the New Delhi Metallo- -lactamase (NDM). The bla_{NDM} gene was first detected in *Klebsiella pneumoniae* and has been effectively transferred across the species into *Acinetobacter*. In contrast to OXA enzymes, NDM enzymes have a zinc-dependent hydrolytic activity against practically all 2-lactams, including carbapenems and are not inhibited by common 2-lactamase inhibitors such as clavulanic acid or tazobactam **[6]**. Recent surveillance data have shown a disturbing pattern where bla_{NDM} variants do not just replace the bla_{OXA} variants in some parts of the world, but are also becoming yet again co-existing in the same host strain **[7]**. This is because when bla_{OXA} and bla_{NDM} genes are co-located in one isolate, it forms a so-called double-hit mechanism that frequently will result in pan-drug resistance phenotypes making such last-resort drugs like cefiderocol potentially less effective depending on which specific gene variants are utilized **[8]**. Although prevalence rates of OXA and NDM at an individual level are thoroughly recorded in research, recent information exists on the synergistic effect of phenotype and the clinical demographics of dual-producing strains in high-density critical care units **[9]**. Therefore, it is of interest to describe the prevalence and molecular epidemiology of bla_{OXA-23}, bla_{OXA-51} and bla_{NDM-1} mediated resistance in clinical isolates of *Acinetobacter baumannii* and to evaluate their combined impact on phenotypic antimicrobial susceptibility patterns and clinical implications in the studied population.

Materials and Methods:
Study design and setting:
This cross-sectional, observational study was conducted over a period of 12 months at the Department of Microbiology in a 1,500-bed tertiary care teaching hospital.

Sample collection and identification:
A total of 215 non-duplicate clinical isolates were collected from various biological specimens, including blood, endotracheal aspirates, sputum, urine, pus/wound swabs and catheter tips, from patients admitted to Intensive Care Units (ICUs) and general wards. Inclusion criteria encompassed all isolates identified as the *Acinetobacter calcoaceticus-baumannii* (Acb) complex. Exclusion criteria included duplicate samples from the same patient within a 14-day period and isolates identified as non-*baumannii* species.
Species identification was initially performed using standard biochemical tests (oxidase negative, catalase positive, non-fermenter on TSI, non-motile). Confirmation was achieved using the VITEK® 2 compact system (bioMérieux, France) using GN cards. Definitive identification of *A. baumannii* was confirmed molecularly by the detection of the intrinsic *bla*OXA-51-like gene via PCR.

Antimicrobial Susceptibility Testing (AST):
Phenotypic susceptibility testing was performed using the Kirby-Bauer disk diffusion method on Mueller-Hinton agar (MHA) in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines (2023-2024). The antibiotic panel included: Piperacillin/Tazobactam (100/10 µg), Ceftazidime (30 µg), Cefepime (30 µg), Imipenem (10 µg), Meropenem (10 µg), Doripenem (10 µg), Amikacin (30 µg), Gentamicin (10 µg), Ciprofloxacin (5 µg), Levofloxacin (5 µg), Tetracycline (30 µg) and Trimethoprim/Sulfamethoxazole (1.25/23.75 µg). Minimum Inhibitory Concentrations (MIC) for Colistin and Tigecycline

were determined using the broth microdilution method (BMD), as disk diffusion is unreliable for these agents. *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains.

Molecular characterization of resistance genes:
Genomic DNA was extracted from fresh bacterial colonies using the boiling lysis method. The supernatant containing the DNA was used as the template for Polymerase Chain Reaction (PCR). Multiplex PCR assays were optimized to detect the following carbapenemase-encoding genes:
[1] bla_{OXA-51}-like (Species identification target)
[2] bla_{OXA-23}-like (Acquired Class D)
[3] bla_{NDM-1} (Acquired Class B)
Primers were synthesized based on specific sequences targeting conserved regions. The PCR reaction mixture (25 µL) contained 12.5 µL of 2X Master Mix, 1 µL of forward and reverse primers (10 pmol), 2 µL of DNA template and nuclease-free water. Thermal cycling conditions involved initial denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 30s, annealing at varying temperatures (52°C–56°C) specific to primer pairs and extension at 72°C for 45s, with a final extension at 72°C for 7 min. Amplified products were visualized on 1.5% agarose gel electrophoresis stained with ethidium bromide.

Statistical analysis:
Data were entered into MS Excel and analyzed using SPSS version 26.0 (IBM Corp, Armonk, NY). Categorical variables were presented as frequencies and percentages. Continuous variables were expressed as Mean ± Standard Deviation (SD). The Chi-square test (χ^2) was utilized to compare the resistance rates between different genotypic groups. A p-value of <0.05 was considered statistically significant.

Results:
A total of 215 non-duplicate *A. baumannii* isolates were recovered. The mean age of the patients was 54.2 ± 16.8 years. Males constituted 61.4% (n=132) of the study population. The majority of isolates were recovered from the Intensive Care Unit (68.8%), reflecting the nosocomial nature of the pathogen. Respiratory tract specimens (Endotracheal aspirate and Sputum) were the most common source of isolation (44.2%), followed by pus/wound swabs (22.3%) and blood (18.6%) **(Table 1).** The antibiogram revealed alarming levels of resistance. Resistance to carbapenems was notably high: Meropenem (92.5%) and Imipenem (91.6%). High resistance was also observed for Cephalosporins (Ceftazidime 94.4%) and Fluoroquinolones (Ciprofloxacin 89.3%). Colistin remained the most active agent with 96.7% susceptibility, followed by Tigecycline with 88.4% susceptibility **(Table 2).** PCR analysis confirmed that 100% (n=215) of the isolates carried the intrinsic bla_{OXA-51} gene. Among the acquired carbapenemases, bla_{OXA-23} was the most prevalent, detected in 169 isolates (78.6%). The metallo-β-lactamase gene bla_{NDM-1} was detected in 74 isolates (34.4%). Significantly, co-existence of bla_{OXA-23} and bla_{NDM-1} was observed in 48 isolates (22.3%). Isolates harboring both genes showed significantly higher resistance rates to Amikacin (92.0% versus 65.1%, $p<0.05$) and Tigecycline (20.8% versus 11.6%, $p<0.05$) compared to the overall cohort **(Table 3).**

Table 1: Demographic and clinical distribution of *A. baumannii* isolates (N=215)

Characteristic	Category	Frequency (n)	Percentage (%)
Gender	Male	132	61.4%
	Female	83	38.6%
Ward Location	ICU	148	68.8%
	Surgical Ward	42	19.5%
	Medical Ward	25	11.7%
Specimen Type	Respiratory (ET/Sputum)	95	44.2%
	Pus/Wound Swab	48	22.3%
	Blood	40	18.6%
	Urine	22	10.2%
	Others (Fluids/Tips)	10	4.7%

Table 2: Antimicrobial resistance profile of *A. baumannii* isolates

Antibiotic Class	Antibiotic Agent	Resistant n (%)	Intermediate n (%)	Sensitive n (%)
Carbapenems	Meropenem	199 (92.5%)	5 (2.3%)	11 (5.2%)
	Imipenem	197 (91.6%)	8 (3.7%)	10 (4.7%)
Cephalosporins	Ceftazidime	203 (94.4%)	2 (0.9%)	10 (4.7%)
	Cefepime	200 (93.0%)	4 (1.9%)	11 (5.1%)
Aminoglycosides	Amikacin	140 (65.1%)	15 (7.0%)	60 (27.9%)
	Gentamicin	155 (72.1%)	10 (4.7%)	50 (23.2%)
Fluoroquinolones	Ciprofloxacin	192 (89.3%)	3 (1.4%)	20 (9.3%)
Others	Colistin	7 (3.3%)	-	208 (96.7%)
	Tigecycline	25 (11.6%)	-	190 (88.4%)

Table 3: Distribution of genotypes among carbapenem-resistant isolates

Genotype Profile	Frequency (n)	Percentage (%)	Phenotypic Meropenem Resistance Rate within Group
bla_{OXA-51} only (Intrinsic)	20	9.3%	40.0%
bla_{OXA-51} + bla_{OXA-23}	121	56.3%	98.3%
bla_{OXA-51} + bla_{NDM-1}	26	12.1%	100%
bla_{OXA-51} + bla_{OXA-23} + bla_{NDM-1}	48	22.3%	100%
Total	**215**	**100%**	

Discussion:
The spread of the Carbapenem-Resistant *Acinetobacter baumannii* is a serious threat to contemporary medicine. This paper aims to draw attention to an important epidemiological process: the prevalence of bla_{OXA-23} and the simultaneous increase in bla_{NDM-1} in clinical samples. We find that the resistance rate of

Meropenem is 92.5% that is consistent with recent global surveillance data published by the SENTRY Antimicrobial Surveillance Program (2020-2024) and shows that carbapenem susceptibility in Acinetobacter spp. is now below 20% in most areas **[10]**. We have found bla_{OXA-23} as the main acquired carbapenemase (78.6%). This finding is in line with those of Southeast Asian and Middle Eastern studies that established bla_{OXA-23} as the key element in carbapenem resistance because it is mobilized by ISAba1 elements **[11]**. The presence of bla_{OXA-51} identifies the species but the phenotypic data in Table 3 indicate that bla_{OXA-51} alone (without upstream insertion sequences or acquisition of a plasmid) is frequently not sufficient to provide high-level resistance, as the lower resistance rates in the OXA-51 only group indicate. The most alarming result however is the prevalence of bla_{NDM-1}, which is 34.4% and finally there is the co-harboring of bla_{OXA-23} and bla_{NDM-1}, which results in 22.3%. This co-production rate is greater than those figures reported on the European studies but reflect the recent developments in South Asia and Latin America **[12]**. This poses especially problematic due to the presence of NDM-1 that provides resistance to all 8 -lactams except those that are hydrolyzed by the co-existence of OXA enzymes (monobactams); it is also not vulnerable to new -lactamase inhibitors such as Avibactam **[13]**. Accordingly, the therapeutic index of these two-producing agents is very small. We found a high rate of resistance of co-producers (OXA-23 + NDM-1), to non-bacterial-lactin antibiotics (amino-glycoside and tigecycline). This implies that the plasmids that emerged with these carbapenemase genes also encode other resistance determinants (*e.g.*, armA methylases), which allow the dissemination of multidrug-resistant (MDR) and extensively drug-resistant (XDR) phenotypes **[14]**. Although Colistin had a high efficacy (96.7%), the use of this nephrotoxic agent is hardly an ideal option. According to the recent literature, the development of these dual-carbapenemase producers can be preconditioned by a specific pressure of increasing the popularity of broad-spectrum antibiotics in the course of the post-pandemic period **[15]**. Moreover, the different plasmid incompatibility groups that harbor the OXA and NDM genes permit stable co-resistance in the host cell and they pose a potential of horizontal gene transfer to other *Enterobacterales* **[16]**. The clinical implications are far-reaching. When treating infections caused by *A. baumannii* Empirical therapy using carbapenems is no longer applicable in this environment. The data substantiates the urgency of quick molecular diagnostics in usage in the hospital admission workflow in order to reveal the NDM producers at the initial stages **[17]**. In confirmed cases of NDM/OXA co-producers, new therapeutic options, including cefiderocol or ceftazidime-avibactam with aztreonam, are undergoing clinical trials, although the issue of access remains a challenge in most low-to-middle-income countries **[18]**. Notably, there is no statistically significant difference in the average MIC and MBC values between the presence and absence of bla_{OXA-23} and bla_{NDM-1}. This finding suggests that Cs NPs may serve as a promising adjunctive treatment for carbapenem-resistant *A. baumannii*, particularly in scenarios where the synthesis of β-lactamases limits the efficacy of conventional therapies **[19]**. Additionally, our findings are strongly supported by global and regional data confirming an escalating molecular trend toward heavy reliance on dual carbapenemase mechanisms. In a cross-sectional study profiling surgical site infections in Pakistan, Gul *et al.* (2026) documented bla_{OXA-23} in 60.9% and bla_{NDM-1} in 30.4% of isolates, showcasing high-level phenotypic resistance and widespread multidrug-resistant (MDR) profiles similar to our critical care cohort **[20]**. This genetic complexity is further mirrored in the Middle East; Alkhawaja and Hadi (2025) revealed an exceptionally high prevalence of bla_{NDM} (93%) alongside bla_{OXA-23} (76.7%) and bla_{OXA-48} (81.3%) in Iraqi hospital isolates, driving extensive drug resistance (XDR) in up to 62% of their strains. Together, these comparative datasets solidify the conclusion that co-expression of Class B and Class D carbapenemases has evolved from isolated occurrences into a global, cross-border clinical emergency **[21]**.

Conclusion:

High carbapenem resistance in *A. baumannii* mandates removing these drugs from local empirical treatment protocols. The 22.3% co-occurrence of bla_{OXA-23} and bla_{NDM-1} genes drives a dangerous pan-drug resistance phenotype. Immediate antibiotic stewardship, strict infection control and rapid molecular screening are vital to halt superbug dissemination.

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